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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

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associated with the aforementioned anxiety and depression characteristics in NESDA (van Reedt Dortland et al., 2010a, 2010b). HDL, LDL cholesterol and triglyceride levels were determined from fasting blood samples using routine standardized laboratorial methods. To account for medication use, HDL cholesterol, LDL cholesterol and triglyceride values were adjusted according to medication effects observed in trials, as previously performed (Vogelzangs et al., 2007). Medication use within the past month was registered by observation of drug containers brought in, and ATC coded (WHO, 2008). For persons using fibrates, 0.10 mmol/l was subtracted from HDL cholesterol, and 0.67 mmol/l was added to triglycerides (Bays et al., 2003; Grundy et al., 2005). For persons using nicotid acid, 0.15 mmol/l was subtracted from HDL cholesterol, and 0.19 mmol/l was added to triglycerides. For persons using LDL-lowering medication, 0.74 mmol/l was added to LDL cholesterol (Ray et al., 2007). Height and weight were measured to calculate BMI (=weight(kg)/height(m)^2). WC was measured with a measuring tape at the central point between the lowest front rib and the highest front point of the pelvis, upon light clothing. The distribution of residuals was normalized by natural log-transformation of HDL and LDL cholesterol, triglyceride, BMI and WC values.

2.2.3. Biological stress systems

The four *HPA axis* measures included area under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg), mean evening cortisol and a cortisol suppression ratio after 0.5 mg dexamethasone intake. HPA axis measures were based on seven saliva samples taken by subjects at home. Details of assessment and analyses of HPA axis measures have been described in detail elsewhere (Vreeburg et al., 2009b). The AUCg is an estimate of total cortisol secretion over the first hour after awakening, and the AUCi is a measure of the dynamic of the cortisol awakening response, more related to the sensitivity of the system, emphasizing changes over time (Edwards et al., 2001).

The five *ANS* measures included heart rate (HR), pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA). Assessment and analyses of ANS measures are described in detail elsewhere (Licht et al., 2010b). HR is an indicator of combined sympathetic (SNS) and parasympathetic (PNS) nervous system activity; high PEP reflects low SNS activity; RSA reflects cardiac PNS activity.

The three *inflammation* markers included CRP, IL-6 and TNF-α. CRP, IL-6 and TNF-α were determined from initially frozen (at $-80\,^{\circ}C$) serum. High-sensitivity plasma levels of CRP were measured in duplicate by an in-house ELISA based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). Plasma IL-6 levels were measured in duplicate by a high-sensitivity enzyme-linked immunosorbent assay (PeliKine Compact™ ELISA, Sanquin, Amsterdam). Plasma TNF-α levels were assayed in duplicate at Good Biomarker Science, Leiden, The Netherlands, using a high-sensitivity solid phase ELISA (Quantikine® HS Human TNF-α Immunoassay, R&D Systems Inc., Minneapolis, MN, United States).

2.2.4. Lifestyle

Number of *tobacco* (i.e., cigarette, cigar or pipe) and *alcohol consumptions* (i.e., glasses) a day were assessed through standardized questionnaires. *Physical activity* was assessed using the International Physical Activity Questionnaire (Booth, 2000), and expressed in 1000 Metabolic Equivalent of Task (MET)-minutes in the past week. MET-minutes reflect the ratio of the associated metabolic rate for specific activities divided by the resting metabolic rate, multiplied by minutes performed activity.

2.2.5. Covariates

Sociodemographic variables included age and sex. Use of corticosteroids (i.e., ATC code H02, R03BA, R03AK and D07, used more than 50% of the time), beta-blockers (i.e., ATC code C07, used more than 50% of the time), other heart medication (i.e., ATC-codes C01, C02, C03, C04, C05, C08 or C09) and anti-inflammatory (i.e., ATC-codes M01A, M01B, A07EB and A07EC) medication (no/yes) in the past month was identified.

2.2.6. Statistical analyses

Data were missing completely at random (MCAR: Little's MCAR test Chi-square = 140.709, df = 334, $p = 1.0$) on ANS ($n = 146$; 5.2%), HPA axis ($n = 936$; 33.1%), inflammation ($n = 21$; 0.7%) and lifestyle ($n = 151$; 5.4%) variables. Multiple imputation by the iterative Markov chain method was therefore an appropriate way to impute missing data (Donders et al., 2006). Age, sex, anxiety severity, depression severity, medication adjusted HDL, LDL cholesterol and triglyceride values, BMI, WC, use of TCAs, corticosteroids, beta-blockers, other heart medication and anti-inflammatory medication were considered as predictors.

Sample characteristics were summarized using means and standard deviations for quantitative variables and percentages for categorical variables. Linear regression analyses, basically adjusted for age, sex and medication use (see Section 2.2.5) were conducted to assess the basic associations of anxiety severity, depression severity and TCA use (all independent variables) with lipid (i.e., HDL and LDL cholesterol and triglycerides) and obesity measures (i.e., BMI and WC: all dependent variables). This resulted in basically adjusted beta-coefficients (β^as). Factors that could explain such an association should be associated with both the independent and the dependent variable (Miettinen and Cook, 1981). Within the NESDA study we previously found that certain biological stress systems and lifestyle factors relate to anxiety, depression and TCA use (Licht et al., 2008, 2009; Vreeburg et al., 2009a, 2010; de Wit et al., 2010), as well as to lipids and obesity (Licht et al., 2010b). It is therefore feasible that biological stress systems and lifestyle factors (partially) explain associations of anxiety severity, depression severity and TCA use with lipids and obesity. To study this hypothesis, linear regression analyses were repeated, in turn including biological stress system (i.e., HPA axis, ANS or inflammation) and lifestyle measures (i.e., alcohol or tobacco consumption, or physical activity). When biological stress systems or lifestyle influenced β^as substantially (defined as a change = $[\beta^b \times 100\%]/\beta^a$ of more than 10%, i.e., $\%\Delta > 10$), the impact of their separate components was additionally studied. Then, the joint impact of all significant biological stress system and lifestyle mechanisms was studied by including them collectively. In order to more thoroughly evaluate the influence of CVD and diabetes, all 262 subjects with prevalent medicated CVD (i.e., stroke, myocardial infarction, angina pectoris or coronary heart

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disease, as assessed by standardized questionnaires and observation of drug containers brought in (Vogelzangs et al., 2010) or diabetes (a glucose value of $\geq$7.0 mmol/l or anti-diabetic medication use) were excluded in a sensitivity analysis. To more thoroughly exclude the possible effects of medication, all 698 (=24.5%) subjects using corticosteroids, anti-inflammatory drugs, beta-blockers, other heart medication or lipid-lowering medication were excluded in a second sensitivity analysis. In a third sensitivity analysis on anxiety and depression severity, all 78 subjects who used TCAs were excluded. All statistical analyses were undertaken with SPSS 18.0.

3. Results

Table 1 shows the sample characteristics. The mean age of the sample was 42.0 years (SD 13.0) and 33.4% were male. 2.7% used TCAs, whereas 75.0% used no antidepressant at all.

Tables 2–4 show the basically adjusted associations of anxiety or depression severity and TCA use with lipid and obesity measures (i.e., basically adjusted beta-coefficient [β^a]), their associations adjusted for every biological stress system and lifestyle factor, and the relative change of these adjusted βs with respect to β^a (i.e., %Δ).

The associations of anxiety severity with lipid and especially obesity measures (Table 2) were significantly diminished when inflammation was taken into account, with a significant individual contribution of mainly CRP (%Δ ranged from 14.0 concerning LDL to 33.7 concerning BMI). HPA axis and ANS measures did not influence associations significantly. Tobacco use significantly influenced the associations of anxiety severity with lipids (%Δ ranged from 33.7 to 41.5). Alcohol use and physical activity did not explain these associations substantially. All significant mechanisms jointly reduced associations from 29.2 (for WC) to 53.7% (for HDL cholesterol). However, these mechanisms did not sufficiently explain the associations of anxiety severity with HDL cholesterol, triglycerides, BMI and WC: solely the association of anxiety severity with LDL cholesterol lost statistical significance.

The associations of depression severity with lipid and especially obesity measures (Table 3) were significantly diminished by inflammation, CRP (by 14.0% concerning LDL to 31.6% concerning BMI) in particular. HPA axis and ANS measures did not influence these associations significantly. Tobacco use significantly influenced the associations of depression severity with lipids (%Δ ranged from 24.6 to 42.6). Alcohol use and physical activity did not influence these associations substantially. All significant mechanisms jointly reduced associations from 27.4 (for WC) to 69.1% (for HDL cholesterol), but only the association of depression severity with HDL cholesterol lost statistical significance.

The associations of TCA use with lipid and especially obesity measures (Table 4) were significantly diminished (by 11.0–52.9%) by CRP. Associations were not significantly influenced by HPA axis measures. By addition of ANS measures, a significant reduction was established in the associations of TCA use with HDL cholesterol (%Δ = 42.2), LDL cholesterol (%Δ = 31.5), triglycerides (%Δ = 60.9), BMI (%Δ = 58.8) and WC (%Δ = 34.9). All individual ANS elements (i.e., HR, PEP and RSA) had significant impact. Tobacco use

Table 1 Sample characteristics among 2850 subjects with and without anxiety and depressive disorders.

Anxiety and depression severity and TCA use	
Anxiety severity (BAI score)	12.1 (10.7)
Depression severity (IDS-SR score)	21.5 (14.1)
Use of tricyclic antidepressants (%)	2.7
No use of antidepressants (%)	75.0
Lipid and obesity measures	
High-density lipoprotein (HDL) cholesterol (mmol/l)	1.6 (0.4)
Low-density lipoprotein (LDL) cholesterol (mmol/l)	3.2 (1.0)
Triglycerides (mmol/l)	1.3 (0.8)
Lipid lowering medication use (%)	7.1
Body mass index (kg/m^2)	25.6 (5.0)
Waist circumference (cm)	89.1 (14.0)
Biological stress systems	
Hypothalamic–Pituitary–Adrenal (HPA) axis	
AUCg (nmol/l/h)	18.8 (7.2)
AUCi (nmol/l/h)	2.3 (6.4)
Mean evening level (nmol/l)	5.6 (3.4)
Cortisol suppression ratio[a]	2.8 (1.7)
Autonomic nervous system (ANS)	
Heart rate (HR, bpm)	72.0 (9.7)
Pre-ejection period (PEP, ms)	119.5 (18.3)
Respiratory sinus arrhythmia (RSA, ms)	44.4 (25.9)
Inflammation	
C-reactive protein (CRP, mg/l)	2.8 (5.0)
Interleukin (IL)-6 (pg/ml)	1.3 (3.1)
Tumor necrosis factor-alpha (TNF-α, pg/ml)	1.1 (1.4)
Lifestyle	
Tobacco consumptions (*n* per day)	5.1 (8.8)
Alcohol consumptions (glasses per day)	0.9 (1.5)
Physical activity (in 1000 MET-minutes last week)	3.5 (3.1)
Covariates	
Age (years)	42.0 (13.0)
Sex (% men)	33.4
Use of corticosteroids (%)	5.5
Use of anti-inflammatory medication (%)	4.5
Use of beta-blockers (%)	7.9
Use of other heart medication (%)	11.5
Cardiovascular disease (%)	5.7
Diabetes (%)	4.9

Abbreviations: AUCg, area under the curve with respect to the ground; AUCi, area under the curve with respect to the increase; BAI, Beck anxiety inventory; IDS-SR, inventory of depressive symptoms-self report; MET, metabolic equivalent. Means (standard deviations) are given for quantitative variables. Percentages are given for categorical variables.

[a] Cortisol at awakening divided by cortisol at awakening the next day after 0.5 mg dexamethasone ingestion.

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Table 2 Influence of biological stress systems and lifestyle factors on the relationship of anxiety severity with lipids and obesity (n = 2850).

	HDL cholesterol		LDL cholesterol		Triglycerides		Body mass index		Waist circumference	
	β	%Δ [b]	β	%Δ [b]	β	%Δ [b]	β	%Δ [b]	β	%Δ [b]
Anxiety severity [a]	−.082**		.050*		.098**		.089**		.096**	
Adjusted for all biological stress systems	−.057*	**−30.5**	.043*	**−14.0**	.065**	**−33.7**	.067**	**−24.7**	.073**	**−24.0**
HPA axis	−.079**	−3.7	.049*	−2.0	.093**	−5.1	.092**	+3.4	.099**	+3.1
ANS	−.080**	−2.4	.050*	+0.0	.090**	−8.2	.093**	+4.5	.097**	+1.0
Inflammation [c]	−.059**	**−28.0**	.043*	**−14.0**	.072**	**−26.5**	.056*	**−37.1**	.065**	**−32.3**
CRP	−.064**	**−21.9**	.043*	**−14.0**	.075**	**−23.5**	.059**	**−33.7**	.068**	**−29.2**
IL-6	−.075**	−8.5	.048*	−4.0	.092**	−6.1	.080**	**−10.1**	.087**	−9.4
TNF-α	−.076**	−7.3	.050*	+0.0	.093**	−5.1	.085**	−4.5	.092**	−4.2
Adjusted for lifestyle [c]	−.038*	**−53.7**	.031	**−38.0**	.062**	**−36.7**	.093**	+4.5	.092**	−4.2
Tobacco use	−.048*	**−41.5**	.033	**−34.0**	.065**	**−33.7**	.097**	+9.0	.094**	−2.1
Alcohol use	−.081**	−1.2	.050*	−0.0	.098**	−0.0	.089**	−0.0	.096**	−0.0
Physical activity	−.080**	−2.4	.050*	−0.0	.094**	−4.1	.087**	−2.2	.094**	−2.1
Adjusted for significant mechanisms	−.038*	**−53.7**	.029	**−42.0**	.052*	**−46.9**	.057**	**−35.9**	.068**	**−29.2**

Abbreviations: ANS, autonomic nervous system; β, standardized beta by multivariate linear regression analysis; CRP, c-reactive protein; HDL, high-density lipoprotein; HPA, hypothalamic pituitary adrenal; IL-6, interleukin-6; LDL, low-density lipoprotein; TNF-α, tumor necrosis factor-alpha.

[a] Basically adjusted for age, sex and medication use.

[b] Percent change (%Δ) of β with respect to basically adjusted β^a as an effect size of the magnitude of influence. Percentages >10% have been marked bold and are considered as significant.

[c] When a biological stress system or lifestyle influenced β^as substantially (i.e., %Δ > 10), the impact of their separate components was additionally studied.

* Statistically significant β at the $p < .05$ level.

** Statistically significant β at the $p < .001$ level.

Table 3 Influence of biological stress systems and lifestyle factors on the relationship of depression severity with lipids and obesity (n = 2850).

	HDL cholesterol		LDL cholesterol		Triglycerides		Body mass index		Waist circumference	
	β	%Δ [b]	β	%Δ [b]	β	%Δ [b]	β	%Δ [b]	β	%Δ [b]
Depression severity [a]	−.068**		.057*		.085**		.098**		.102**	
Adjusted for all biological stress systems	−.041*	**−39.7**	.049*	**−14.0**	.054*	**−36.5**	.073**	**−25.5**	.077**	**−24.5**
HPA axis	−.065**	−4.4	.056*	−1.7	.081**	−4.7	.101**	+3.1	.106**	+3.9
ANS	−.067**	−1.5	.057*	+0.0	.081**	−4.7	.103**	+5.1	.105**	+2.9
Inflammation [c]	−.043*	**−36.8**	.049*	**−14.0**	.057**	**−32.9**	.062**	**−36.7**	.069**	**−32.3**
CRP	−.049*	**−27.9**	.049*	**−14.0**	.061**	**−28.2**	.067**	**−31.6**	.074**	**−27.4**
IL-6	−.060**	**−11.8**	.054*	−5.3	.078**	−8.2	.087**	**−11.2**	.092**	−9.8
TNF-α	−.061**	**−10.3**	.057**	−0.0	.080**	−5.9	.093**	−5.1	.098**	−3.9
Adjusted for lifestyle [c]	−.028	**−58.8**	.040*	**−29.8**	.053*	**−37.6**	.099**	+1.0	.097**	−4.9
Tobacco use	−.039*	**−42.6**	.043*	**−24.6**	.057*	**−32.9**	.104**	+6.1	.101**	−1.0
Alcohol use	−.066**	−2.9	.057*	+0.0	.086**	+1.2	.097**	−1.0	.102**	−0.0
Physical activity	−.066**	−2.9	.057*	+0.0	.079**	−7.1	.096**	−2.0	.099**	−2.9
Adjusted for significant mechanisms	−.021	**−69.1**	.038*	**−33.3**	.041*	**−51.8**	.064**	**34.7**	.074**	**−27.4**

Abbreviations: ANS, autonomic nervous system; β, standardized beta by multivariate linear regression analysis; CRP, c-reactive protein; HDL, high-density lipoprotein; HPA, hypothalamic pituitary adrenal; IL-6, interleukin-6; LDL, low-density lipoprotein; TNF-α, tumor necrosis factor-alpha.

[a] Basically adjusted for age, sex and medication use.

[b] Percent change (%Δ) of β with respect to basically adjusted β^a as an effect size of the magnitude of influence. Percentages >10% have been marked bold and are considered as significant.

[c] When a biological stress system or lifestyle influenced β^as substantially (i.e., %Δ > 10), the impact of their separate components was additionally studied.

* Statistically significant β at the $p < .05$ level.

** Statistically significant β at the $p < .001$ level.

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Table 4 Influence of biological stress systems and lifestyle factors on the relationship of TCA use with lipids and obesity (n = 2203).

		HDL cholesterol		LDL cholesterol		Triglycerides		Body mass index		Waist circumference	
	n[d]	β	%Δ[b]	β	%Δ[b]	β	%Δ[b]	β	%Δ[b]	β	%Δ[b]
TCA use[a]	78	−.045*		.073**		.069*		.051*		.083**	
Adjusted for all biological stress systems		−.019	**−57.8**	.050*	**−31.5**	.017	**−75.4**	.013	**−74.5**	.046*	**−44.6**
HPA axis		−.046*	+2.2	.073**	+0.0	.066*	−4.3	.052*	+2.2	.083**	+0.0
ANS[c]		−.026	**−42.2**	.050*	**−31.5**	.027	**−60.9**	.021	**−58.8**	.054*	**−34.9**
HR		−.029	**−35.6**	.057*	**−21.9**	.030	**−56.5**	.030	**−41.2**	.062**	**−25.3**
PEP		−.040*	**−11.1**	.062*	**−15.1**	.059*	**−14.5**	.033	**−35.3**	.068**	**−18.1**
RSA		−.039*	**−13.3**	.063*	**−13.7**	.057*	**−17.4**	.043	**−15.7**	.074**	**−10.8**
Inflammation[c]		−.025	**−44.4**	.066*	−9.6	.046*	**−33.3**	.023	**−54.9**	.057*	**−31.3**
CRP		−.029	**−35.6**	.065*	**−11.0**	.048*	**−30.4**	.024	**−52.9**	.059**	**−28.9**
IL-6		−.042*	−6.7	.072**	−1.4	.066**	−4.3	.047*	−7.8	.079**	−4.8
TNF-α		−.039*	**−13.3**	.073**	−0.0	.065**	−5.8	.048*	−5.9	.080**	−3.6
Adjusted for lifestyle[c]		−.020	**−55.6**	.065*	**−11.0**	.054*	**−21.7**	.047*	−7.8	.079**	−4.8
Tobacco use		−.034	**−24.4**	.067**	−8.2	.056*	**−18.8**	.052*	+2.2	.081**	−2.4
Alcohol use		−.037*	**−17.8**	.072**	−1.4	.071**	+2.9	.048*	−5.9	.083**	+0.0
Physical activity		−.044*	−2.2	.073**	−0.0	.066**	−4.3	.051*	+0.0	.082**	−1.2
Adjusted for significant mechanisms		.003	**−93.3**	.048*	**−34.2**	.012	**−82.6**	.013	**−74.5**	.046*	**−44.6**

Abbreviations: ANS, autonomic nervous system; β, standardized beta by multivariate linear regression analysis; CRP, c-reactive protein; HDL, high-density lipoprotein; HPA, hypothalamic pituitary adrenal; HR, heart rate; IL-6, interleukin-6; LDL, low-density lipoprotein; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; TCA, tricyclic antidepressant; TNF-α, tumor necrosis factor-alpha. Subjects who used TCAs (n = 78) were compared with subjects who did not use antidepressants at all (n = 2138). Subjects that used other antidepressants were not included in these analyses.

[a] Basically adjusted for age, sex and medication use.

[b] Percent change (%Δ) of β with respect to basically adjusted β^a as an effect size of the magnitude of influence. Percentages >10% have been marked bold and are considered as significant.

[c] When a biological stress system or lifestyle influenced β^as substantially (i.e., %Δ > 10), the impact of their separate components was additionally studied.

[d] Number of subjects that used TCAs.

* Statistically significant β at the $p < .05$ level.

** Statistically significant β at the $p < .001$ level.

significantly influenced the associations of TCA use with HDL cholesterol (%Δ = 24.4) and triglycerides (%Δ = 18.8). Alcohol use and physical activity did not considerably affect associations. These mechanisms sufficiently explained the associations of TCA use with HDL cholesterol, triglycerides and BMI, although the associations of TCA use with LDL cholesterol and WC did not lose statistical significance.

Analyses on the original data (i.e., excluding subjects with imputed data; data not shown) showed largely similar results as compared to the analyses on multiple imputated data. Sensitivity analyses in which all 262 subjects with CVD or diabetes were excluded, sensitivity analyses in which all 698 subjects using corticosteroids, anti-inflammatory drugs, beta-blockers, other heart medication or lipid-lowering medication were excluded, and sensitivity analyses on anxiety and depression severity in which all 78 subjects who used TCAs were excluded, also gave largely similar results (data not shown).

4. Discussion

In this large study, we investigated the impact of biological stress systems (i.e., HPA axis, ANS and inflammation) and lifestyle factors (i.e., tobacco or alcohol use, and physical activity) on the associations of anxiety and depression severity and TCA use with dyslipidemia and obesity. The increased risk of dyslipidemia and especially of obesity among persons with more severe anxiety and depression symptoms may have been mediated by low-grade inflammation as marked by higher levels of CRP. Our data also suggest that lipid levels in persons with more severe symptoms of depression or anxiety were adversely affected by current smoking, which was more common among this group. We also found support for the hypothesis that TCA users are prone to obesity and dyslipidemia through the combined effects of inflammation, tobacco use and ANS alterations. HPA axis functioning did not explain increased dyslipidemia and obesity risk among those with severe anxiety or depression symptoms and in TCA users.

The higher risk of dyslipidemia and obesity among persons with more severe anxiety and depression symptoms may have been mediated by low-grade inflammation as defined by higher serum levels of the inflammatory marker CRP among the anxious and depressed. Higher levels of inflammation have been observed in persons with anxiety (Bankier et al., 2009) and depression (Penninx et al., 2003; Pizzi et al., 2008; Howren et al., 2009; Vogelzangs et al., 2012). This is supported by an overrepresentation of inflammation genes in depression (Dowlati et al., 2010) and a higher risk of depression in users of pro-inflammatory medication like interferon-alpha (Capuron and Miller, 2004). In turn, inflammation may

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induce dyslipidemia, by stimulating lipid release into the blood stream to fuel host defense and to block cytotoxic effects of inflammogens by binding to them (Esteve et al., 2005). Adipose tissue cells are highly sensitive to inflammatory signals, and release inflammatory markers themselves (Rajala and Scherer, 2003). Thereby further stimulating dyslipidemia. So, complex and bidirectional associations exist between inflammation, psychopathology, dyslipidemia and obesity. Consequently, increased inflammation among the severely anxious and depressed may induce dyslipidemia and obesity. The fact that we found CRP and not the cytokines IL-6 or TNF-α to be important, might be explained by the fact that CRP is the strongest inflammatory correlate of at least depression (Vogelzangs et al., 2012), and because CRP is the most accurate and stable marker of systemic inflammation (Pepys and Hirschfield, 2003). This probably made the results on CRP more cohesive.

The lifestyle factor tobacco use, and not alcohol use or physical activity, may also elucidate part of the association of depression and anxiety severity with dyslipidemia. Persons with anxiety disorders, and to a greater extent those with depression, smoke much more often than those without psychopathology (Bonnet et al., 2005). This is possibly due to an increased risk of smoking initiation, decreased cessation motivation, self-medication by nicotine (Breslau et al., 1998) or shared (e.g., genetic) etiological factors (Kendler et al., 1993). Smoking is well known to detrimentally influence lipid levels (Craig et al., 1989; NCEP, 2002). It thus is a feasible mechanism in the association between psychopathology and dyslipidemia, and smoking cessation may be of great benefit.

The joint impact of CRP and tobacco use on the associations of anxiety and depression severity and TCA use with lipid measures was generally lower than the sum of their separate influences. This suggests some mechanistic overlap. Smoking is a major environmental factor that raises CRP levels (Bakhru and Erlinger, 2005). Tobacco use might therefore have induced part of the increased CRP levels in psychopathology, which successively triggered dyslipidemia. Smoking cessation might therefore additionally reduce dyslipidemic effects through a diminution of inflammatory reactions.

Dyslipidemia and obesity in TCA users may have been partly mediated by increased CRP levels and smoking, but also by ANS alterations among TCA users. TCA use has already been associated with increased CRP levels (Hamer et al., 2011). Also, persons with depressive symptomatology who smoke, more often use antidepressants than depressed non- or former smokers (Gravely-Witte et al., 2009). As to the ANS, TCAs might reduce parasympathetic activity while increasing sympathetic activity (Licht et al., 2008, 2010a), which may also lead to metabolic alterations like dyslipidemia and obesity (Licht et al., 2010b).

Dyslipidemia and obesity among persons with severe anxiety and depression symptoms and in TCA users were not explained by HPA axis alterations. HPA axis deregulations have been associated though with anxiety and depressive disorders (Holsboer, 2000; Gold et al., 2002; Vreeburg et al., 2009a), and with TCA use (Manthey et al., 2011). HPA axis deregulations have also been associated with visceral adipose tissue accumulation as well as with (subsequent) dyslipidemia (Bjorntorp and Rosmond, 2000; Anagnostis et al., 2009; Veen et al., 2009). Yet, several former studies on the association of HPA axis activity with psychopathology (Brouwer et al., 2005) or with dyslipidemia and obesity (Kajantie et al., 2004; Licht et al., 2010b) did not report any association. The inconsistencies in earlier research in addition to our null finding might indicate that HPA axis alterations only play a role in certain subgroups (Vogelzangs et al., 2007). It is also possible that the HPA axis only relates anxiety and depression to dyslipidemia and obesity in acute stress situations and not under basal conditions, such as in our study. Otherwise, urinary rather than salivary cortisol might play a role (Brunner et al., 2002).

Generally, no combination of putative pathways wholly seemed to explain the associations under study, since most associations of anxiety and depression severity and TCA use with lipid and most strongly with obesity measures remained statistically significant after adjustment for all influential mechanisms. Other mechanisms, such as poor diet rich in carbohydrates and saturated fat among those with anxiety and depression (Bonnet et al., 2005), might have (partly) accounted for residual associations. Also, insomnia and hypersomnia in patients with depression may have promoted obesity and dyslipidemia (Wolk and Somers, 2007; Gangwisch et al., 2010; Katano et al., 2011), possibly through altered neuroendocrine processes such as insulin resistance (Broussard and Brady, 2010).

There are some limitations of our study that need to be discussed. A first limitation is the cross-sectional design, which did not allow us to make causal inferences on how psychopathology, dyslipidemia, obesity and biological stress systems or lifestyle are temporarily intertwined. Second, the variable concentration of some biological stress markers may have distorted our results. Third, we were unable to take all known biological stress parameters into account. Lastly, we did not have information on other possible mechanisms such as dietary factors. Strengths of our study are the large, psychopathology-based sample, and the assessment of various psychopathological characteristics as well as lipid and obesity measures. HPA axis, ANS and inflammatory factors were measured through well-validated methods. Moreover, we were the first to assess the role of various biological stress systems and lifestyle factors in concert.

In conclusion, the current study provides evidence for a role of low-grade inflammation (as defined by increased CRP levels) in the associations of anxiety and depression and TCA use with (abdominal) obesity and dyslipidemia, and of tobacco use in the association of psychopathology with dyslipidemia. ANS alterations may have played an additional role in dyslipidemia and obesity among TCA users. HPA axis functioning was not a significant mediator. Although our findings need to be confirmed, they increase our understanding of the possible mechanisms behind the increased dyslipidemia and obesity risk in mood disorders. If these mechanisms are indeed fundamental, interventions that dampen inflammation (e.g., smoking cessation, physical activity or antioxidant supplementation) and normalize ANS function (e.g., discontinue TCA use) could beneficially affect serum lipids and obesity.

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Conflicts of interest

None declared.

Contributions

Brenda Penninx designed the NESDA study and wrote the protocol. Arianne van Reedt Dortland managed the literature searches, undertook the statistical analyses, and wrote the main drafts of the manuscript. Erik Giltay reviewed the statistical analyses. Sophie Vreeburg, Erik Giltay, Carmilla Licht, Nicole Vogelzangs, Tineke van Veen, Eco de Geus, Brenda Penninx and Frans Zitman regularly reviewed the manuscript. All authors contributed to and have approved the final manuscript.

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