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

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ABSTRACT

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 % Δ >10.

Results

The inflammatory marker C-reactive protein had the most consistent impact (explaining 14 to 53% of the associations of anxiety and depression severity and TCA use with lipid and obesity levels), followed by tobacco use (explaining 34 to 43% of the associations with lipids). The ANS mediated all associations with TCA use (explaining 32 to 61%). The HPA axis measures did not explain any of the associations.

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.

7.1 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.^{23-26,43,45,106,107,200} 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,¹¹⁷ and in users of tricyclic antidepressants (TCAs).¹⁵⁰ 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^{100,101} and diabetes mellitus²⁴³ 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^{67,69} as well as decreased parasympathetic and increased sympathetic autonomic nervous system (ANS) activity^{200,227,244} and elevated inflammatory markers such as C-reactive protein (CRP), interleukin(IL)-6^{72,73,200} and tumor necrosis factor-alpha (TNF- α)¹⁹⁹ have been detected in anxiety and depression and among TCA users.^{227,245} Also, unfavourable lifestyle habits such as increased tobacco and alcohol use and decreased physical activity^{74,118,128,246-248} have been observed in patients with mood disorders. In turn, these HPA axis,^{120,209,249} ANS,²⁵⁰ inflammatory⁵¹ and lifestyle^{75,97,130} 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.

7.2 METHODS

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 to 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.⁹⁵ The study protocol was approved by the Ethical Review Board of each participating centre, 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).

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 63.¹⁷¹ Depression severity was assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR) ranging from 0 to 84.¹¹⁰ TCA use (Anatomical Therapeutic Chemical [ATC]¹¹¹ code N06AA) within the past month was registered by observation of drug containers brought in.

Lipid and obesity measures

HDL and LDL cholesterol, triglycerides, body mass index (BMI) and waist circumference (WC) were previously found to be associated with the aforementioned anxiety and depression characteristics in NESDA.^{117, 150} HDL, LDL cholesterol and triglyceride levels were determined from fasting blood samples using routine standardised laboratory 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.²⁵ Medication use within the past month was registered by observation of drug containers brought in, and ATC coded.¹¹¹ For persons using fibrates, 0.10 mmol/L was subtracted from HDL cholesterol, and 0.67 mmol/L was added to triglycerides. For persons using nicotid acid, 0.15 mmol/L was subtracted from HDL cholesterol, and 0.19 mmol/L was added to triglycerides.^{167,168} For persons using LDL-lowering medication, 0.74 mmol/L was added to LDL cholesterol.¹⁹⁴ Height and weight were measured to calculate BMI ($=\text{weight}(\text{kg})/\text{height}(\text{m})^2$). 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.

Biological stress systems

The four *HPA axis* measures included area under the curve with respect to the increase (AUC_i) and with respect to the ground (AUC_g), 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.²³¹ The AUC_g is an estimate of total cortisol secretion over the first hour after awakening, and the AUC_i is a measure of the dynamic of the cortisol awakening response, more related to the sensitivity of the system, emphasizing changes over time.²³⁴

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.¹⁷⁶ 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°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).

Lifestyle

Number of *tobacco* (i.e., cigarette, cigar or pipe) and *alcohol consumptions* (i.e., glasses) a day were assessed through standardised questionnaires. *Physical activity* was assessed using the International Physical Activity Questionnaire,¹¹² 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.

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.

Statistical analyses

Data were missing completely at random (MCAR: Little's MCAR test $\chi^2 = 140.709$, $df = 334$, $p = 1.0$) 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.²⁵¹ 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 Covariates) 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^a s). Factors that could explain such an association should be associated with both the independent and the dependent variable.²⁵² Within the NESDA study we previously found that certain biological stress systems and lifestyle factors relate to anxiety, depression and TCA use,^{62,68,69,227,253} as well as to lipids and obesity.¹⁷⁶ 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^a s substantially (defined as a change = $[\beta^b * 100\%]/\beta^a$ 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 disease, as assessed by standardized questionnaires and observation of drug containers brought in) or diabetes (a glucose value of ≥ 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 (IBM Company, Chicago, Illinois, USA).

7.3 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.

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 antidepressant use (%)	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		
<i>Hypothalamic-Pituitary-Adrenal (HPA) axis</i>		
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*	2.8	(1.7)
<i>Autonomic Nervous System (ANS)</i>		
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)
<i>Inflammation</i>		
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 of task.

Means (standard deviations) are given for quantitative variables. Percentages are given for categorical variables.

*: cortisol at awakening divided by cortisol at awakening the next day after 0.5 mg dexamethasone ingestion.

Tables 2 to 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 β s 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 to 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 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 imputed data. Sensitivity analyses in which all 262 subjects with CVD or diabetes were excluded, sensitivity analyses in which

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	B	% Δ^b	β	% Δ^b	B	% 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^a s 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	B	% 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^a s 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 4. Influence of biological stress systems and lifestyle factors on the relationship of TCA use with lipids and obesity (n=2203)

	n [^]	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
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.

^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.

[^]: number of subjects that used TCAs.

*: statistically significant β at the *p*<.05 level.

** : statistically significant β at the *p*<.001 level.

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.

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).

7.4 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 the inflammatory marker CRP among the anxious and depressed. Higher levels of inflammation have been observed in persons with anxiety⁷³ and depression.^{72,199,200,254} This is supported by an overrepresentation of inflammation genes in depression²⁵⁵ and a higher risk of depression in users of pro-inflammatory medication like interferon-alpha.²⁵⁶ In turn, inflammation may 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.⁵¹ Adipose tissue cells are highly sensitive to inflammatory signals, and release inflammatory markers themselves,²⁵⁷ 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,²⁵⁴ and because CRP is the most accurate and stable marker of systemic inflammation.²⁵⁸ 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.¹¹⁸ This is possibly due to an increased risk of smoking initiation, decreased cessation motivation, self-medication by nicotine¹⁹⁷ or shared (e.g., genetic) etiological factors.²⁵⁹ Smoking is well known to detrimentally influence lipid levels.⁷⁵⁻⁹⁷ 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.²⁶⁰ 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.⁶⁰ Also, persons with depressive symptomatology who smoke, more often use antidepressants than depressed non- or former smokers.²⁶¹ As to the ANS, TCAs might reduce parasympathetic activity while increasing sympathetic activity,²²⁷⁻²⁴⁴ which may also lead to metabolic alterations like dyslipidemia and obesity.¹⁷⁶

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,⁶⁷⁻⁶⁸⁻²⁶² and with TCA use.²⁶³ HPA axis deregulations have also been associated with visceral adipose tissue accumulation as well as with (subsequent) dyslipidemia.^{209,120,249} Yet, several former studies on the association of HPA axis activity with psychopathology²⁶⁴ or with dyslipidemia and obesity^{221,176} 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.²⁵ 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.¹²²

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,¹¹⁸ might (partly) account for residual associations. Also, insomnia and hypersomnia in patients with depression may have promoted obesity and dyslipidemia,²⁶⁵⁻²⁶⁷ possibly through altered neuroendocrine processes such as insulin resistance.²⁶⁸

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 an influential 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.

