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# Longitudinal relationship of depressive and anxiety symptoms with dyslipidemia and abdominal obesity

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## ABSTRACT

### Introduction

Previous research indicates that patients with severe symptoms of depression or anxiety are prone towards the development of dyslipidemia and abdominal obesity. We aimed to study these associations longitudinally.

### Methods

Among 2126 Netherlands Study of Depression and Anxiety (NESDA) participants, we studied whether severity of depressive (Inventory of Depressive Symptoms) or anxiety (Beck Anxiety Inventory) symptoms at baseline was associated with changes in lipids (i.e., total, high or low-density [HDL or LDL] cholesterol and triglycerides) or waist circumference (WC) during a 2-year follow-up period. We also examined whether changes in severity of symptoms were associated with changes in lipid or WC levels over these 2 years. Analyses were adjusted for age, sex, education and tobacco consumption in multivariate linear regression analyses.

### Results

Baseline symptoms of depression or anxiety predicted a decrease in HDL cholesterol (adjusted  $\beta = -.062$ ,  $p = .003$  and  $\beta = -.050$ ,  $p = .02$ , respectively) and an increase in WC (adjusted  $\beta = .060$ ,  $p = .01$  and  $\beta = .053$ ,  $p = .02$ , respectively) over 2 years. Reduction of symptoms of depression or anxiety over time did not coincide with an amelioration of lipid or WC values.

### Conclusions

People with initially severe symptoms of depression or anxiety showed a subsequent decrease in HDL cholesterol levels and an increase in abdominal obesity over time, independent of a potential reduction in symptom severity in this time period. Therefore, those people are at elongated and increasing risk of dyslipidemia and obesity, predisposing them to cardiovascular disease.

## 5.1 INTRODUCTION

Patients with depression and anxiety are prone to the cardiovascular disease (CVD) risk factors dyslipidemia (i.e., increased total cholesterol, low-density lipoprotein [LDL] cholesterol and triglyceride levels and lower high-density lipoprotein [HDL] cholesterol) and abdominal obesity (i.e., increased waist circumference [WC]).<sup>23-26,43,45,106,107</sup> Associations of depression or anxiety with the other classic cardiovascular risk factors hyperglycemia and hypertension are less consistent and strong: most studies on hyperglycemia<sup>20,21,23-30,44,46</sup> or hypertension<sup>22-26,28-30,43-46,47-49</sup> did not find significant associations, while only some did (See for hyperglycemia:<sup>22,43,45</sup> and for hypertension:<sup>21,27,44</sup>). Previously we also reported an increased prevalence of dyslipidemia and obesity and not of hyperglycemia and hypertension in patients with depression or anxiety. These prominent associations of depression and anxiety with dyslipidemia and abdominal obesity may contribute to the generally increased risk of CVD in patients with depressive<sup>100</sup> and anxiety disorders.<sup>189</sup> Therefore, we aimed to further explore the associations of depression and anxiety with dyslipidemia and obesity.

Most previous studies on dyslipidemia and obesity in depression and anxiety had cross-sectional designs. To further disentangle these relationships, it is important to also study associations over time. This may reveal whether or not depression or anxiety are associated with sustained dyslipidemia and obesity, and whether changes in depression or anxiety status over time go together with changes in lipid or obesity levels.

Most existing longitudinal studies focused on depression diagnoses,<sup>35,41,190</sup> while scales for severity of symptoms are likely to detect the more subtle differences and changes in depressive or anxiety state. Because of their continuous nature,<sup>312,313</sup> severity scales allow more precise (longitudinal) associations of depression or anxiety with lipid or obesity values than associations based on dichotomous diagnoses. In line with this thought, it was found in several cross-sectional analyses that the severity of symptoms is more strongly related to lipid levels and abdominal obesity than diagnostic categories.<sup>25,117,150</sup>

Despite the importance, only a few longitudinal studies explored associations of depression severity with lipids and/or obesity,<sup>28,191,192</sup> and no studies reported on severity of anxiety. Concerning severity of depression, Pulkki-Raback et al.<sup>28</sup> found that baseline severity of depression predicted WC but not HDL cholesterol or triglyceride levels 9 years later. Vogelzangs et al.<sup>192</sup> reported that among 2088 elderly, baseline depression severity did not predict changes in WC over 5 years. Deisenhammer et al.<sup>191</sup> found that change in depression severity score over a 4 week period was not accompanied by changes in total, LDL and HDL cholesterol or in triglycerides among 50 patients with MDD.

Given the limited research so far, longitudinally studying severity of depression and anxiety in relation to dyslipidemia and abdominal obesity importantly adds to this research field. Furthermore, depression and

anxiety are highly co-morbid, with co-morbidity rates of over 60 percent.<sup>12,13</sup> Therefore, it is valuable to examine how depression and anxiety independently relate to dyslipidemia and abdominal obesity.

The present study examined within the Netherlands Study of Depression and Anxiety (NESDA) whether depressive or anxiety symptoms at baseline predicted an increase in abdominal obesity or dyslipidemia over a 2-year follow-up period. We also intended to study whether 2-year changes of depressive or anxiety symptoms over time coincided with 2-year changes in lipid and abdominal obesity values. Because severity of depressive and anxiety symptoms have been found to be related to dyslipidemia and obesity, we expected that symptoms of depression and anxiety predicted an aggravation of dyslipidemia and abdominal obesity, and we also hypothesized that changes in severity of depression or anxiety went together with lipid and abdominal obesity changes. Finally, as relatively more studies found depression to be related to dyslipidemia<sup>20-30</sup> (versus<sup>45-49</sup> finding no association) or abdominal obesity<sup>20,23-28,43-46</sup> (versus<sup>49</sup> finding no association) than anxiety (<sup>20</sup>found anxiety to be related to dyslipidemia while<sup>26,29,47</sup> found no association, and none<sup>23,26,29,47</sup> found anxiety to be related to abdominal obesity), we expected that depression severity dominates anxiety severity in relation to dyslipidemia and abdominal obesity.

## 5.2 METHODS

### Subjects

Subjects participated in the baseline (data collection from September 2004 to February 2007) and 2-year follow-up (data collection from September 2006 to February 2009) assessment of the Netherlands Study of Depression and Anxiety (NESDA), a cohort study including 2981 persons aged 18 to 65 years. Subjects were recruited from community (n=564, 18.9%), primary care (n=1610, 54%, of which 373, 12.5% subjects had never had a depressive or anxiety disorder), and mental health care settings (n=807, 27.1%) in the Netherlands. Subjects with personal or family history of depression and anxiety as well as healthy controls that never had experienced any depressive or anxiety disorder were recruited in order to reflect a range of settings and stages of psychopathology. See for further details:<sup>95</sup> The baseline and 2-year follow-up assessment both comprised a face-to-face interview, written questionnaires and biological measurements, as described in detail elsewhere.<sup>95,96</sup> According to the Composite Interview Diagnostic Instrument (CIDI, version 2.1), at baseline 2329 subjects had a lifetime depressive or anxiety disorder (i.e., social phobia, panic disorder with or without agoraphobia or generalized anxiety disorder) of which 1701 during the 6 months prior to the baseline interview, and 652 subjects had never had a depressive or anxiety disorder.<sup>95</sup> The response rate at 2-year follow-up was 87.1%.<sup>193</sup> The study protocol was approved by the Ethical Review Board of each participating centre, and all subjects signed informed consent.

Subjects who did not attend the 2-year follow-up assessment (n=385) or who otherwise lacked data on severity of depression or anxiety or on lipid or WC measures either at baseline or at the 2-year follow-up assessment (n=470) were excluded from analyses. This resulted in the current sample of 2126 subjects, aged 18-65 years at baseline. Subjects who were excluded due to missing data were younger (mean age 40.1 [SD 12.9] versus 42.6 [SD 13.1],  $p < .001$ ), more often female (69.9 versus 65.0%,  $p = .01$ ) and had less years of education (mean 11.7 [SD 3.3] versus 12.4 [SD 3.3],  $p < .001$ ) than those without missing data. Also, excluded subjects more often had an MDD (43.5 versus 34.9%,  $p < .001$ ) or an anxiety disorder (50.5 versus 41.1%,  $p < .001$ ) in the 6 months preceding the baseline assessment.

### **Severity of depression and anxiety**

Because we previously found no cross-sectional associations of obesity and lipid measures with MDD or anxiety disorder diagnoses but only with severity scales for depression and anxiety, we now examine longitudinal associations of severity of depression and anxiety with lipids and abdominal obesity. *Depression severity* was assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR) ranging from 0 to 84.<sup>133</sup> *Anxiety severity* was assessed by the 21-item self-report Beck Anxiety Inventory (BAI) ranging from 0 to 63.<sup>171</sup>

Cronbach's alphas were .90 at baseline and .89 at 2-year follow-up for the IDS-SR. Cronbach's alphas were .92 at both time points for the BAI. Those values are considered acceptable.<sup>287</sup> Test-retest reliability correlation coefficients were .72 for the IDS-SR and .69 for the BAI, which mark a high to moderate test-retest reliability.

### **Lipid and abdominal obesity measures**

HDL cholesterol, LDL cholesterol, triglycerides and WC were previously found to be cross-sectionally associated with severity of depressive and anxiety symptoms in NESDA.<sup>117-150</sup> Total, HDL and LDL cholesterol as well as triglyceride levels were determined using routine standardised laboratory methods. To account for medication use, HDL cholesterol, LDL cholesterol and triglyceride values were adjusted according to changes observed in clinical trials, as previously performed.<sup>25</sup> Medication use within the past month was registered by observation of drug containers brought in, and ATC coded.<sup>111</sup> For persons using fibrates, 0.10 mmol/L was subtracted from HDL cholesterol, and 0.67 mmol/L was added to triglycerides.<sup>167-168</sup> 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.<sup>194</sup> A sensitivity analysis including the original lipid values, and lipid affecting medication use as a covariate, yielded largely similar results to the original findings reported in this paper. 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.

### **Covariates**

Sociodemographic variables included age, sex and years of education at baseline. Since tobacco use likely is a confounder, number of tobacco (i.e., cigarette, cigar or pipe) consumptions a day - as assessed through standardised questionnaires - was taken into account.

Exercise was not taken into account as a covariate as in a recently published article<sup>340</sup> we reported that exercise did not play a significant role in the associations of dyslipidemia or obesity with depression or anxiety. For certainty, we did additional analyses including physical activity as a covariate, and indeed physical activity did not affect associations significantly (data not shown).

### **Statistical analyses**

Baseline, 2-year follow-up and 2-year change characteristics of the sample were expressed in percentages for categorical variables, and in means (95% confidence intervals, CIs) for continuous variables. Paired-sample T tests were performed to explore whether mean 2-year changes were statistically significant; McNemar's test was used for paired dichotomous variables. 2-year changes in lipid or obesity, and in severity of depression or anxiety were computed as follow-up values minus baseline values. Linear regression analyses were conducted 1) to confirm associations of baseline severity of depression and anxiety with baseline lipid and obesity values that we previously reported,<sup>117,150</sup> and to further examine 2) whether baseline severity of depression or anxiety predicted 2-year changes in lipid or WC values (while adjusting for baseline lipid or WC values), 3) and if 2-year change in severity of depression or anxiety was accompanied by 2-year changes in lipid or WC levels (while adjusting for baseline depression or anxiety severity and the concerning lipid or WC values). All analyses were then adjusted for age, sex, years of education and tobacco consumption. Because of the co-morbidity of depression and anxiety, analyses on depression severity were additionally adjusted for anxiety severity scores and vice versa in order to understand how depression and anxiety collaborate in relation to dyslipidemia and obesity.<sup>341</sup> Since sex differences in the association between anxiety, depression and cardiovascular risk factors have been observed before,<sup>21,43,105</sup> sex × depression severity / anxiety severity interaction terms were examined in adjusted models. To ensure that associations were not due to CVD, all 118 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) at baseline were excluded in a sensitivity analysis. Previously, we found subjects who used tricyclic antidepressants (TCAs) but not those on other kinds of antidepressants to be prone to dyslipidemia and obesity.<sup>150</sup> Therefore, an additional sensitivity analysis

was performed by excluding subjects who used TCAs at baseline (n=10), at 2-year follow-up (n=13) or at both time points (n=42). TCA use within the past month was registered by observation of drug containers brought in and ATC coded.<sup>111</sup> All statistical analyses were done with SPSS 18.0 (IBM company, Chicago, Illinois, USA).

### 5.3 RESULTS

Sample characteristics at baseline and 2-year follow-up as well as changes between these time points are presented in Table 1. Mean age at baseline was 42.6 years (95% confidence interval [CI] 42.0-43.2), and 35.1% were male. The mean depression severity score significantly diminished over time, as did the mean anxiety severity score. HDL cholesterol levels decreased during 2 years of follow-up. Triglyceride levels and WC significantly increased over time. Associations of baseline severity of depression and anxiety with baseline lipid and obesity values (data not shown) were similar to the results we reported earlier.<sup>117,150</sup> At baseline, severity of depression was associated with higher triglycerides and WC (adjusted  $\beta = .061$ ,  $p = .003$  and  $\beta = .093$ ,  $p < .001$ , respectively); baseline severity of anxiety was associated with lower HDL cholesterol (adjusted  $\beta = -.048$ ,  $p = .02$ ) and higher triglyceride and WC levels (adjusted  $\beta = .066$ ,  $p = .002$  and  $\beta = .077$ ,  $p < .001$ , respectively).

**Table 1.** Baseline, 2 year follow-up and 2 year change characteristics of 2126 subjects

Characteristics	Baseline	2 year follow-up	$p^*$	2 year changes
Age (years, at baseline)	42.6 (42.0-43.2)			
Sex (% men)	35.1			
Years of education	12.4 (12.2-12.5)			
Tobacco consumptions a day	4.6 (4.3-5.0)	4.1 (3.8-4.5)	<.001	-0.5 (-0.7- -0.3)
Depression severity (IDS-SR)	20.5 (19.9-21.1)	16.0 (15.4-16.5)	<.001	-4.5 (-5.0- -4.1)
Anxiety severity (BAI)	11.3 (10.9-11.8)	8.8 (8.4-9.1)	<.001	-2.6 (-2.9- -2.3)
Waist circumference (cm)	89.0 (88.5-89.7)	89.8 (89.2-90.4)	<.001	0.7 (0.5-1.0)
Total cholesterol (mmol/L)	5.2 (5.1-5.2)	5.1 (5.1-5.2)	.051	-0.03 (-0.1-0.0)
LDL cholesterol (mmol/L)	3.2 (3.2-3.3)	3.2 (3.2-3.3)	.14	0.02 (-0.01-0.05)
HDL cholesterol (mmol/L)	1.6 (1.6-1.7)	1.6 (1.5-1.6)	<.001	-0.10 (-0.11- -0.9)
Triglycerides (mmol/L)	1.3 (1.25-1.32)	1.3 (1.3-1.4)	.003	0.05 (0.02-0.08)
Lipid affecting medication use (%)	7.3	8.1	.054	0.8

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report.

Means (95% confidence intervals) or percentages are given, when appropriate.

\*:  $p$  by paired-sample  $t$  test for means, and McNemar's test statistics for lipid medication use.

Table 2 shows crude and adjusted associations of severity of baseline depression and anxiety with 2-year changes in lipid and obesity values. Baseline severity of depression was associated with a significant increase in WC over 2 years (basically adjusted  $\beta = 0.60$ ,  $p = .01$ , respectively) and a decline in HDL cholesterol (basically adjusted  $\beta = -.062$ ,  $p = .003$ ). Baseline severity of anxiety was also associated with a significant increase in WC (adjusted  $\beta = .053$ ,  $p = .02$ ) and a decline in HDL cholesterol over 2 years (adjusted  $\beta = -.050$ ,  $p = .02$ ) and an. The associations of more severe symptoms of anxiety at baseline with increasing waist circumference ( $\beta =$



.053 to .017, i.e.,  $\Delta$  -67.9%) and with lowering of HDL cholesterol levels ( $\beta$  = -.050 to -.002, i.e.,  $\Delta$  -95.0%) were significantly explained by co-morbid symptoms of depression. Associations of depression severity with increasing waist circumference ( $\beta$  .060 to .047, i.e.,  $\Delta$  -21.7%) and with lowering of HDL cholesterol levels ( $\beta$  -.062 to -.061, i.e.,  $\Delta$  -1.6%) were less substantially explained by co-morbid symptoms of anxiety. There was no considerable multicollinearity in these models (variance inflation factors were all 2.5). Adjustment for tobacco use did not affect the associations. No associations were found of baseline depression or anxiety severity with changes in total or LDL cholesterol or in triglyceride levels.

Table 3 shows crude and adjusted associations of 2-year change in severity of depressive and anxiety symptoms with 2-year changes in lipids and WC. Changes in depression or anxiety severity were not accompanied by significant changes in lipid or WC values. Adjustment for tobacco consumption did not affect these findings.

Repeated analyses including sex  $\times$  depression severity / anxiety severity interaction terms showed no statistically significant interaction ( $p$  ranged from .11 to .99). This suggests that associations do not significantly differ for men or women. Sensitivity analyses in which 118 subjects with CVD or 65 subjects who were using TCAs at either time point were excluded, yielded similar results.

**Table 2.** Associations of baseline depression and anxiety severity with 2 year changes in lipid and obesity values

	2 year changes in lipid and obesity values									
	Total cholesterol		LDL cholesterol		HDL cholesterol		Triglycerides		Waist circumference	
Baseline depression severity (IDS-SR)	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>
Crude	-.003	.90	-.004	.85	<b>-.046</b>	.04	-.001	.95	.026	.23
Adjusted <sup>a</sup>	-.003	.87	.001	.95	<b>-.062</b>	.003	-.008	.71	<b>.060</b>	.01
Baseline anxiety severity (BAI)	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>
Crude	.013	.54	.006	.77	-.022	.31	.012	.57	.026	.24
Adjusted <sup>a</sup>	.006	.79	.008	.69	<b>-.050</b>	.02	.024	.29	<b>.053</b>	.02

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report.

$\beta$  coefficients indicate the standardised beta by linear regression analysis. Statistically significant ( $p < .05$ ) associations are marked bold.

All analyses are adjusted for the concerning baseline lipid or obesity values.

<sup>a</sup>: Adjusted for age, sex, years of education, and baseline as well as 2 year change in tobacco consumption.

**Table 3.** Associations of 2 year change in depression and anxiety severity with 2 year changes in lipid and obesity values

	2 year changes in lipid and obesity values									
	Total cholesterol		LDL cholesterol		HDL cholesterol		Triglycerides		Waist circumference	
2 year changes in depression severity (IDS-SR)	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>
Crude	.014	.53	.013	.56	<b>.049</b>	.03	.004	.87	.008	.73
Adjusted <sup>a</sup>	.017	.46	.008	.73	.045	.06	-.002	.95	.025	.32
2 year changes in anxiety severity (BAI)	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>
Crude	.012	.60	.017	.42	.032	.14	-.023	.30	-.016	.47
Adjusted <sup>a</sup>	.008	.71	.018	.46	.032	.18	-.026	.30	.003	.90

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report.

$\beta$  coefficients indicate the standardised beta by linear regression analysis. Statistically significant ( $p < .05$ ) associations are marked bold.

All analyses are adjusted for the concerning baseline depression or anxiety severity and lipid or obesity values.

<sup>a</sup>: Adjusted for age, sex, years of education, and baseline as well as 2 year change in tobacco consumption.

## 5.4 DISCUSSION

Earlier we reported that more severe symptoms of depression and also of anxiety made people prone to dyslipidemia and abdominal obesity.<sup>117, 150</sup> In this longitudinal follow-up study, we observed that people who had more severe symptoms of depression or anxiety at baseline displayed a further decline in HDL cholesterol levels and an increase in abdominal obesity over the subsequent 2 years. These associations were driven by depression severity: anxiety severity seemed to be related to increasing dyslipidemia and abdominal obesity mainly through its close relationship with depression.<sup>341</sup> Finally, a reduction of symptoms of depression or anxiety over this time period did not go together with amelioration of lipid or abdominal obesity values.

So far no comparable studies concerning symptoms of anxiety have been reported. Moreover, we were to our knowledge the first to study the relative contribution of depression and anxiety to the development of dyslipidemia and abdominal obesity. Our results showed that anxiety severity rather is a proxy risk factor for depression severity in aggravating dyslipidemia and abdominal obesity.<sup>341</sup>

Our finding that baseline severity of depression predicted progressive abdominal obesity over the subsequent 2 years corresponds to another study that reported that baseline severity of depression predicted an increased abdominal obesity value after 9 years.<sup>28</sup> Our finding is also in line with a meta-analysis which revealed that baseline depression was associated with an increased odds ratio for developing overall obesity over time (47). Yet another study found no predictive relationship over 5 years.<sup>192</sup> Our finding that symptoms of depression predicted a decline in HDL cholesterol levels was not replicated over 9 years.<sup>28</sup> Conversely, our result that a reduction of depressive symptoms did not coincide with changes in HDL cholesterol was largely comparable to an earlier study over a period of 1 month in which a reduction in depression score did not coincide with changes in HDL cholesterol.<sup>191</sup> Our findings are also in line with the observation that patients with severe depressive symptoms after myocardial infarction who were successfully treated for their depression showed no improvement in their high risk of cardiac mortality.<sup>75</sup>

The fact that a reduction in severity of depression or anxiety did not go together with changes in HDL cholesterol or abdominal obesity, indicates that reductions of depressive or anxiety symptoms do not manifest themselves as improved dyslipidemia or obesity, at least over a rather short term of 2 years. This finding, together with the observed worsening of dyslipidemia and abdominal obesity independent of an improved mental state, indicates that probably multiple relatively stable etiological factors connect a liability to depression and anxiety to lower HDL cholesterol and to abdominal obesity. Among these possible mechanisms are lifestyle, biological, and genetic factors. A first possible lifestyle mechanism is smoking. Smoking lowers HDL cholesterol,<sup>19,75</sup> and people with depressive or anxiety disorders smoke more regularly.<sup>118</sup>

Moreover, they often have difficulty with smoking cessation after mood improvement, possibly due to antidepressant effects of nicotine.<sup>145,197</sup> Sustained smoking could thus have led to decreased HDL cholesterol levels in people with initially more severe symptoms of depression or anxiety. Smoking did however not explain our results. A second underlying lifestyle factor could be that people who are vulnerable to depression or anxiety, independent of their current mental state, continue to eat more carbohydrates and (saturated) fat.<sup>118</sup> Persistent unhealthy dietary habits may have led to increases in dyslipidemia and abdominal obesity. A biological mechanism may be low-grade inflammation. People with depressive<sup>200,72,199</sup> or anxiety disorders<sup>73</sup> display higher levels of inflammation than controls. At the same time, inflammation causes a reduction in HDL lipoproteins<sup>51</sup> and also induces obesity through leptin resistance.<sup>201,202</sup> As baseline symptoms of depression predict augmentation of inflammation<sup>203</sup> and inflammation may not decline after recovery from depression,<sup>204</sup> chronic inflammation in people who are vulnerable to depression or anxiety might cause progressive dyslipidemia and abdominal obesity. This may be independent of an improved mood. Lastly, it is possible that symptoms of depression and anxiety share genetic and complex biological etiological substrates with HDL cholesterol and abdominal obesity. For instance, gene-environment interactions may have activated the hypothalamic-pituitary-adrenal axis, which subsequently has led to depression as well as to aggravation of obesity.<sup>205</sup> Mechanistic factors may however normalize in the longer term. Our previous observation that HDL cholesterol values in people with a remitted depression during lifetime were similar to those of controls<sup>117</sup> supports this premise.

In addition, it is noteworthy that depressive and anxiety symptoms declined significantly over the 2-year follow-up period. Due to our recruitment method, a large proportion of our subjects had prevalent depressive or anxiety disorders at baseline. Although residual symptoms of depression and anxiety are common, it is estimated that over half of patients with depression show clinical recovery after two years,<sup>342</sup> and also anxiety disorders seem to decline over time.<sup>343,344</sup> This common decline in symptoms of depression and anxiety may have explained the significant decrease of depression and anxiety symptoms in our general sample. Moreover, part of the improvement may be ascribed to regression to the mean effects.

A first important limitation of our study is that changes in depression and anxiety severity and in lipid and obesity values over time showed relatively low variability. This might be caused by the high proportion of subjects from mental health care, who are more likely to have longstanding disorders<sup>9</sup> which may have caused a slower improvement in symptoms of depression and anxiety in the general group. This may have limited the power to detect longitudinal associations. Second, the 2-year time interval between assessments might have been too short to establish

a degree of relieve in depression or anxiety symptoms that was able to account for considerable lipid or obesity changes. A major strength of our study is the prospective design, through which we were able to extensively explore the longitudinal associations of depression and anxiety severity with lipid and obesity patterns. Strength of our recruitment procedures was that because we oversampled subjects in different stages of psychopathology, we could analyse the impact of current and prolonged symptomatology of depression and anxiety with relatively high precision. Another main strength is the assessment of the severity of depression and anxiety using validated scales as well as the assessment of lipid and obesity values at both time points in a large cohort. Furthermore, severity of anxiety symptoms had not yet been prospectively studied in relation to metabolic risk factors. Exploration of this association adds importantly to the existing longitudinal literature, as symptoms of anxiety have been found to be almost as strong markers for dyslipidemia and abdominal obesity as symptoms of depression.

In conclusion, we found that people with more severe symptoms of depression or anxiety showed a decrease in HDL cholesterol levels and an increase in abdominal obesity over the subsequent 2 years, independent of a reduction in symptoms of depression or anxiety. These findings could be of clinical importance. As low HDL cholesterol as well as abdominal obesity are important risk factors for CVD,<sup>17</sup> those people are at elongated and increasing risk of CVD. It is important for clinicians to be aware of an increased CVD risk in patients with depressive and anxiety disorders, that does not seem to fade after remission of symptoms. These patients should therefore be continuously evaluated for the presence of metabolic risk factors as targets for prevention and treatment.



