Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use

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ABSTRACT

Introduction
The metabolic syndrome predisposes to cardiovascular disease and diabetes mellitus. There might also be an association between the metabolic syndrome and anxiety and depression, but its nature is unclear. We aimed to investigate whether diagnosis, symptom severity and antidepressant use are associated with the metabolic syndrome.

Methods
We addressed the odds for the metabolic syndrome and its components among 1217 depressed and/or anxious subjects and 629 controls, and their associations with symptom severity and antidepressant use.

Results
Symptom severity was positively associated with prevalence of the metabolic syndrome (adjusted odds ratio [OR] = 2.21 for very severe depression: 95% confidence interval [CI]: 1.06–4.64, $p = .04$), which could be attributed to abdominal obesity and dyslipidemia. Tricyclic antidepressant (TCA) use also increased odds for the metabolic syndrome (OR = 2.30, 95% CI: 1.21–4.36, $p = .01$), independent of depression severity.

Conclusion
The most severely depressed people and TCA users more often have the metabolic syndrome, which is driven by abdominal adiposity and dyslipidemia.

2.1 INTRODUCTION

The metabolic syndrome is defined as a cluster of metabolic abnormalities, including abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension and hyperglycemia. The metabolic syndrome thereby predisposes to cardiovascular disease (CVD) and diabetes mellitus.[17,97] Mapping risk factors for the metabolic syndrome is important given the high global risk and burden of CVD and diabetes,[98] plus the increasing prevalence of obesity and the metabolic syndrome worldwide.[99] There is a growing interest in whether anxious or depressed people are at higher risk for the metabolic syndrome, since depression as well as anxiety show high co-morbidity with CVD.[100,101]

In most studies investigating the link between depressive symptoms and the metabolic syndrome,[23,24,26-29,32,46-49,73,74,132-140] a positive association was reported,[24,26-29,32,46,48,49,73,74,132-137,139,140] while some described none.[20,44,45,102,103] Only few studies focused on the association between anxiety and the metabolic syndrome,[20,23,44,49,103-105] of which only two confirmed a positive association,[103,104] and others did not confirm a link. In studies considering the metabolic syndrome and its components, mainly abdominal obesity,[23,24,26-29,46-48,134,138] hypertriglyceridemia [23,24,26,27,133,134,140,142] and a low HDL cholesterol[20,21,25,26,32,102,106,107] were found to be associated with depressive symptoms, while associations with hypertension[23,24,138] or hyperglycemia[24,47,73,138,140] have rarely been reported. In the few studies on anxiety and metabolic syndrome components,[23,26,47,137] only an association with hypertriglyceridemia[137] and high blood pressure[20] was found. This raises the question whether anxiety or depression are risk factors for several individual metabolic syndrome components, rather than for the whole metabolic syndrome cluster.

It is not only important to study whether metabolic syndrome prevalence differs among DSM-IV diagnoses groups, but also simultaneously its association with symptom severity, as this latter approach focuses on a separate psychopathological aspect, namely dimensionality of disease. Vogelzangs et al.[28] for example, reported an association of the metabolic syndrome with depression severity, while no association was present with the dichotomous depression classification. Another point of interest is whether antidepressant use influences the odds for having the metabolic syndrome. Previous studies have scarcely addressed this topic. Nevertheless, the use of TCAs is known to induce side effects like hypertension,[62] hyperglycemia,[78] and weight gain,[75,76] which may consequently promote dyslipidemia.[143] To a lesser extent, the commonly prescribed selective serotonin re-uptake inhibitors (SSRIs) also tend to induce weight gain[59] and thereby dyslipidemia[143] in some patients, but they do not cause hyperglycemia.[61]

The present study is the first to analyze clinical anxiety and depression diagnoses, as well as symptom severity and antidepressant use, as potential predictors of the metabolic syndrome. We also aimed to

elucidate which of the individual metabolic syndrome components are most strongly associated with these predictors.

2.2 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 18–65 years. Subjects were recruited from community, primary care, and mental health care in the Netherlands. The baseline assessment comprised of a face-to-face interview, written questionnaires, and biological measurements. The study design is described in detail elsewhere.[95] 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, four study groups were constructed, i.e., subjects with an anxiety disorder within the past 6 months but no lifetime major depressive disorder (MDD) (i.e., 'current pure anxiety', n=276), subjects with an MDD within the past 6 months but no lifetime anxiety disorder (i.e., 'current pure MDD', n=272), subjects with both MDD and anxiety disorder within the past 6 months (i.e., 'current anxiety and MDD', n=731), and those who never had a MDD or anxiety disorder (i.e., 'controls', n=652), resulting in a preliminary sample size of 1931. Then, 84 subjects with missing values on metabolic syndrome components or on anxiety or depression severity (see below) were excluded, resulting in the current sample of 1846 subjects (i.e., n=266 current pure anxiety, n=261 current pure MDD, n=690 current anxiety and MDD, and n=629 controls).

Indicators of psychopathology

The presence of an anxiety disorder (i.e., panic disorder with or without agoraphobia, social phobia or generalized anxiety disorder) or MDD within the past 6 months was diagnosed according to the fourth edition of the Diagnostic and Statistical Manual for mental disorders (DSM-IV) criteria using the Composite International Diagnostic Interview (CIDI).[108]

Anxiety severity was assessed by the 21-item self-report Beck Anxiety Inventory (BAI) ranging from 0 to 63. Beck Anxiety Inventory total scores were subdivided into four severity groups, i.e., normal (total score 0–9), mild (10–18), moderate (19–29), and severe (30–63), as described before.[109] Depression severity was assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR) ranging from 0 to 84. IDS-SR total scores were, as before,[110] subdivided into five severity groups, i.e., low (total score 0–13), mild (14–25), moderate (26–38), severe (39–48), and very severe (49–84).

Antidepressant medication use within the past month, as registered by observation of drug containers brought in, was subdivided into selective serotonin re-uptake inhibitors (SSRI, ATC code N06AB), tricyclic antidepressants (TCA, ATC code N06AA) and other antidepressants (mainly

consisting of serotonergic and noradrenergic working antidepressants N06AF and N06AX). Subjects who used more than one kind of antidepressant (n=15) were classified according to the category with the strongest assumed metabolic side effects (TCAs > SSRIs > other).

The metabolic syndrome

The metabolic syndrome was defined according to the American Heart Association & National Heart, Lung and Blood Institute's update of the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) definition.[17] It requires the presence of three or more of the following criteria: i) abdominal obesity, i.e., waist circumference ≥ 102 cm in men and ≥ 88 cm in women; ii) hypertriglyceridemia, i.e., elevated triglyceride level (≥ 1.70 mmol/L) or drug treatment for elevated triglycerides; iii) low high-density lipoprotein (HDL) cholesterol (< 1.03 mmol/L in men and < 1.30 mmol/L in women) or drug treatment for reduced HDL cholesterol; iv) hypertension, i.e., elevated blood pressure (≥ 130/85 mmHg) or use of antihypertensive medication and v) hyperglycemia, i.e., elevated fasting glucose level (≥ 5.6 mmol/L) or use of antidiabetic medication.

Waist circumference 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. Triglyceride, HDL cholesterol and glucose levels were determined using routine standardized laboratory methods after a mean of 11:16 h (SD = 1:50 h) overnight fast. Systolic and diastolic blood pressure were measured twice during supine rest on the right arm by the OMRON M4 IntelliSense (HEM-752A; Omron Healthcare, Inc., Bannockburn, IL, USA), and were averaged over the two measurements. ATC coded[111] use of HDL increasing or triglyceride lowering (ATC codes C10AB, C10AD, C10BA01), antihypertensive (ATC codes C02, C03, C07, C08, C09) or antidiabetic medication (ATC code A10) within the past month was registered by observation of drug containers brought in.

In line with previous research,[137,148] the number of metabolic syndrome components was used as an indicator of severity of metabolic abnormalities.

Covariates

Sociodemographic variables included age, sex (male/female) and years of education. Oral contraceptive use (no/yes) was identified through self-report. Clinic site (five sites) was added as a covariate as well. We also included lifestyle characteristics previously associated with anxiety, depression and the metabolic syndrome: smoking status (never/former/current) and alcohol use (<1/1–2/>2 drinks per day) were assessed by standardized 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 reflects the ratio of the associated metabolic rate for specific activities

divided by the resting metabolic rate, multiplied by the minutes performed activity. Prevalent medicated CVD or diabetes mellitus were assessed by standardized questionnaires.

Statistical analyses

Characteristics of DSM-IV diagnosis groups were compared by Kruskal–Wallis test (Monte Carlo method with 95% confidence intervals) for (non-normally distributed) quantitative variables, and by x^2 statistics for categorical variables. To evaluate which group differences accounted for significant overall *p* values, post hoc tests were done by Mann–Whitney U-tests with Bonferroni correction. Mann–Whitney U-tests were performed only between controls and the three psychopathology groups (and not between all groups) to reduce the type I error rate. Multivariate logistic regression analyses were conducted to assess the association between DSM-IV diagnosis (controls [i.e., reference group]/current pure anxiety/current pure MDD/current anxiety and MDD), anxiety (BAI) or depression severity (IDS-SR) group or antidepressant use group (none [i.e., reference group]/SSRI/TCA/other; all independent variables) and the presence of the metabolic syndrome (absent [i.e., reference group]/present; dependent variable). We adjusted for basic covariates (i.e., age, sex, years of education, clinic site and oral contraceptive use) in model 1, and additionally for lifestyle-related covariates (i.e., smoking status, alcohol use, and physical activity) in model 2. Since sex differences in the association between anxiety, depression and the metabolic syndrome have been observed before,[21, 43, 105] sex × DSM-IV diagnosis/anxiety severity/depression severity interaction terms were examined in model 2. Furthermore, CVD / diabetes × DSM-IV diagnosis / anxiety severity / depression severity interaction terms were tested within model 2. Differences in the mean number of prevalent metabolic components per DSM-IV diagnosis group, anxiety or depression severity group, and per antidepressant use group were assessed by x^2 statistics (using linear-by-linear tests for anxiety and depression severity). In multivariate logistic regression analyses, the associations were assessed between DSM-IV diagnosis, anxiety or depression severity or antidepressant use group (independent variables) and the presence of each single component of the metabolic syndrome (absent [i.e., reference group]/present; dependent variables). In analyses on symptom severity or antidepressant use, only those subjects with psychopathology were included. Statistical significance was inferred at $p < 0.05$. All statistical analyses were undertaken with SPSS 16.0 (IBM company, Chicago, Illinois, USA).

2.3 RESULTS

Table 1 shows the characteristics of the DSM-IV diagnosis groups. The mean age of the sample was 41.1 years (SD 13.2) and 35.5% were male.

Table 1. Characteristics according to DSM-IV diagnosis in 1846 subjects

Characteristics	Controls	Current pure anxiety	Current pure MDD	Current anxiety and MDD	*p* *
n	629	266	261	690	
Age	43.0 (27.0-55.0)	42.0 (29.8-53.0)	41.0 (30.0-51.0)	42.0 (31.0-51.0)	.58
Sex (% men)	38.3	38.0	39.1	30.6	.009
Years of education	12.0[a] (10.0-15.0)	11.0[b] (10.0-15.0)	11.0[b] (10.0-15.0)	11.0[b] (9.0-15.0)	<.001
Oral contraceptive use (%)	18.9	16.2	20.7	19.7	.55
Smoking status (%)					<.001
Never	36.7	25.6	26.8	27.0	
Former	36.2	31.6	31.0	26.1	
Current	27.0	42.9	42.1	47.0	
Alcohol use (%)					.009
<1 glasses/day	57.6	60.9	65.9	67.5	
1-2 glasses/day	23.7	23.7	18.8	17.2	
> 2 glasses/day	18.8	15.4	15.3	15.2	
Physical activity (in 1000 MET-minutes last week)	3.2[a] (1.6-4.9)	2.8[a] (1.4-4.8)	2.9[a] (1.2-4.6)	2.7[b] (1.2-4.8)	.02
Antidepressant use (%)					
Selective serotonin re-uptake inhibitors	0.6	14.7	24.9	32.9	<.001
Tricyclic antidepressants	0.2	2.6	3.1	4.9	<.001
Other antidepressants	0.2	4.5	9.6	12.3	<.001
Anxiety severity (BAI; %)					<.001
Normal	87.9	32.3	46.0	15.9	
Mild	10.5	35.3	32.6	29.1	
Moderate	1.4	24.4	17.6	32.6	
Severe	0.2	7.9	3.8	22.3	
Depression severity (IDS-SR; %)					<.001
None	80.3	21.8	9.6	4.2	
Mild	16.4	43.6	30.3	17.8	
Moderate	2.9	26.7	40.2	40.6	
Severe	0.5	6.4	15.7	24.8	
Very severe	0.0	1.5	4.2	12.6	

Table 1. Continued

Characteristics	Controls	Current pure anxiety	Current pure MDD	Current anxiety and MDD	*p**
n	629	266	261	690	
Metabolic syndrome (%)	19.4	22.2	21.8	22.5	.56
Abdominal obesity (≥ 88/102 cm, %)	28.6	29.3	32.6	36.7	.01
Hypertriglyceridemia (≥ 1.7 mmol/L, %)	18.6	21.8	21.5	21.3	.68
Low HDL-cholesterol (< 1.03/1.3 mmol/L, %)	11.1	14.3	15.7	15.9	.18
Triglyceride lowering or HDL cholesterol increasing medication use (%)	0.3	0.4	0.4	0.1	.88
Hypertension (≥ 130/85 mmHg, %)	61.9	57.5	54.8	57.0	.15
Antihypertensive medication use, %)	14.5	15.8	11.9	14.1	.63
Hyperglycemia (≥ 5.6 mmol/L, %)	21.3	23.4	21.5	21.3	.90
Antidiabetic medication use (%)	3.7	2.6	3.1	3.6	.85

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; DSM-IV, Diagnostic and Statistical Manual of mental disorders – fourth edition; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; MET, metabolic equivalent of task.

Medians (interquartile ranges) or percentages are given, when appropriate.

**: p* by Kruskal-Wallis test for quantitative variables or x^2 statistics for categorical variables.

[abc]: Superscript letters that differ from the superscript letter of the control group indicate that the post hoc *p* values of those groups differ significantly ($p<0.05$ by Mann-Whitney test after Bonferroni correction).

Control subjects had more years of education, tended to use more alcohol and to smoke less than the anxiety or MDD groups. The prevalence of abdominal obesity tended to be higher among depressed or anxious subjects. There were no statistically significant differences in the prevalence of the metabolic syndrome or its components between diagnosis groups.

As shown in Table 2, no statistically significant associations between diagnosis group and the metabolic syndrome were found. Although the moderate and severe anxiety groups were associated with the presence of the metabolic syndrome in unadjusted analyses, no statistically significant associations were found in models 1 and 2. The odds for presence of the metabolic syndrome increased with increasing levels of depression severity, which was statistically significant for very severe depression as compared to the reference group (OR = 2.21, 95% CI: 1.06–4.64, $p = .04$ in model 2). Additional adjustment for antidepressant use did not alter these results (OR = 2.18, 95% CI: 1.04–4.60, $p = .04$). Prevalence of the metabolic syndrome was also significantly increased in TCA users as compared to the group not using antidepressants (OR = 2.30, 95% CI: 1.21–4.36, $p = .01$ in model 2), which was not affected by additional adjustment for depression severity (OR = 2.18, 95% CI: 1.15–4.15, $p = .02$). In Table 2, repeated analyses of model 2 including sex × DSM-IV diagnosis/anxiety severity/depression severity interaction terms, showed no statistically significant interaction (all $p > 0.6$). This suggests that associations do not significantly differ for men or women. CVD/diabetes × DSM-IV diagnosis/anxiety severity/depression severity interaction terms were also non-significant (all $p > 0.20$), suggesting similar associations among subjects with or without CVD or diabetes. Figure 1 shows that the mean number of metabolic syndrome components did not differ between DSM-IV diagnosis groups. The number of metabolic syndrome components increased over increased severity of both anxiety ($p < 0.001$) and depression ($p < 0.001$). Moreover, antidepressant use, and TCA use in particular, was associated with a higher mean number of metabolic syndrome components.

Table 3 shows the odds for the presence of each single metabolic syndrome component across DSM-IV diagnoses, anxiety or depression severity and antidepressant use groups in model 2. The unadjusted higher odds for having abdominal obesity in co-morbid current MDD and anxiety (OR = 1.44, 95% CI: 1.15–1.82, $p = .002$), as compared to controls, was no longer statistically significant in model 2. Nevertheless, the odds for abdominal obesity increased with increasing severity of anxiety symptoms. However, its association with low HDL cholesterol in model 1 (OR = 1.88, 95% CI: 1.14–3.10, $p = .01$) was reduced in model 2. In model 1, very severe depression was associated with abdominal obesity (OR = 2.37, 95% CI: 1.27–4.41, $p = .007$) and hypertriglyceridemia (OR = 2.11, 95% CI: 1.05–4.24, $p = .04$), but only the association with abdominal obesity

Table 2. The associations between DSM-IV diagnosis, severity, antidepressant use and the presence of the metabolic syndrome

		Crude			**Model 1**			**Model 2**		
	n	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
DSM-IV diagnosis										
Controls*	629	1.00			1.00			1.00		
Current pure anxiety	266	1.18	0.83-1.68	.34	1.10	0.75-1.60	.64	1.04	0.71-1.54	.83
Current pure MDD	261	1.16	0.82-1.65	.41	1.19	0.81-1.75	.37	1.12	0.76-1.66	.57
Current anxiety and MDD	690	1.20	0.92-1.57	.17	1.14	0.85-1.53	.39	1.08	0.80-1.46	.62
Anxiety severity (BAI)°										
Normal*	316	1.00			1.00			1.00		
Mild	380	1.21	0.82-1.77	.34	1.11	0.73-1.67	.63	1.09	0.72-1.66	.68
Moderate	336	1.68	1.15-2.46	.007	1.38	0.92-2.07	.12	1.37	0.90-2.07	.14
Severe	185	1.81	1.17-2.79	.008	1.46	0.91-2.33	.12	1.38	0.85-2.23	.19
Depression severity (IDS-SR)°										
None*	112	1.00			1.00			1.00		
Mild	318	1.51	0.83-2.74	.17	1.21	0.64-2.29	.55	1.24	0.65-2.35	.52
Moderate	456	1.44	0.81-2.56	.22	1.11	0.60-2.06	.74	1.09	0.58-2.04	.79
Severe	229	2.48	1.36-4.53	.003	1.65	0.87-3.14	.13	1.51	0.78-2.91	.22
Very severe	102	3.27	1.68-6.38	<.001	2.55	1.24-5.25	.01	2.21	1.06-4.64	.04
Antidepressant use°										
None*	730	1.00			1.00			1.00		
SSRI	328	1.35	0.99-1.84	.06	1.30	0.93-1.82	.13	1.22	0.87-1.72	.25
TCA	49	3.35	1.85-6.05	<.001	2.56	1.36-4.82	.004	2.30	1.21-4.36	.01
Other	110	1.21	0.75-1.96	.44	0.97	0.59-1.61	.92	0.97	0.58-1.63	.91

Abbreviations: BAI, Beck Anxiety Inventory; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of mental disorders– fourth edition; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; OR, odds ratio by multivariate logistic regression analysis; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.
Model 1: adjusted for age, sex, years of education, clinic site and oral contraceptive use.
Model 2: additionally adjusted for smoking status, alcohol use and physical activity.
*: Reference group to the subsequent groups.
°: Controls (n=629) were excluded from these analyses.

Table 3. The association between DSM-IV diagnosis, severity, antidepressant use and the presence of individual metabolic syndrome components

		Abdominal obesity			Hypertriglyceridemia			Low HDL cholesterol		
	n	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Model 2										
DSM-IV diagnosis										
Controls*	629	1.00			1.00			1.00		
Current pure anxiety	266	0.96	0.68-1.35	.80	1.10	0.76-1.61	.61	1.06	0.68-1.64	.81
Current pure MDD	261	1.23	0.88-1.72	.22	1.07	0.73-1.57	.72	1.12	0.73-1.72	.61
Current MDD and anxiety	690	1.28	0.99-1.66	.06	1.08	0.80-1.45	.62	1.00	0.71-1.40	.98
Anxiety severity (BAI)°										
Normal*	316	1.00			1.00			1.00		
Mild	380	1.16	0.82-1.66	.41	1.07	0.71-1.61	.75	1.12	0.70-1.79	.64
Moderate	336	1.40	0.97-2.00	.07	1.43	0.96-2.14	.08	1.47	0.92-2.33	.11
Severe	185	1.74	1.14-2.65	.01	1.33	0.83-2.13	.24	1.57	0.94-2.64	.09
Depression severity (IDS-SR)°										
Low*	112	1.00			1.00			1.00		
Mild	318	0.92	0.54-1.57	.76	1.06	0.57-1.94	.86	1.26	0.62-2.53	.52
Moderate	456	0.96	0.57-1.60	.87	1.09	0.61-1.97	.77	0.99	0.50-1.97	.98
Severe	229	1.52	0.88-2.63	.13	1.37	0.73-2.57	.32	1.34	0.65-2.75	.43
Very severe	102	2.30	1.22-4.34	.01	1.72	0.85-3.52	.14	1.20	0.53-2.67	.67
Antidepressant use°										
None*	730	1.00			1.00			1.00		
SSRI	328	1.12	0.83-1.51	.45	1.27	0.91-1.78	.17	1.06	0.74-1.53	.75
TCA	49	1.88	1.00-3.54	.05	2.57	1.36-4.84	.004	1.40	0.68-2.89	.36
Other	110	1.27	0.81-1.97	.30	1.27	0.78-2.08	.33	0.85	0.46-1.57	.60

Abbreviations: BAI, Beck Anxiety Inventory; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of mental disorders – fourth edition; HDL, high-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; OR, odds ratio by multivariate logistic regression analysis; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.
Model 2: adjusted for age, sex, years of education, clinic site, oral contraceptive use, smoking status, alcohol use and physical activity.
*: Reference group to the subsequent groups.
°: Controls (n=629) were excluded from these analyses.

Table 3. Continued

	n	Hypertension OR	95% CI	*p*	Hyperglycemia OR	95% CI	*p*
Model 2							
DSM-IV diagnosis							
Controls*	629	1.00			1.00		
Current pure anxiety	266	0.97	0.69-1.36	.86	1.09	0.74-1.59	.68
Current pure MDD	261	0.75	0.54-1.05	.10	1.12	0.76-1.66	.57
Current MDD and anxiety	690	0.90	0.69-1.17	.43	1.09	0.81-1.47	.58
Anxiety severity (BAI)°							
Normal*	316	1.00			1.00		
Mild	380	0.97	0.69-1.37	.87	0.87	0.58-1.30	.49
Moderate	336	1.06	0.74-1.51	.77	1.04	0.69-1.55	.86
Severe	185	1.41	0.91-2.18	.12	1.09	0.67-1.76	.73
Depression severity (IDS-SR)°							
Low*	112	1.00			1.00		
Mild	318	1.00	0.61-1.66	1.00	0.91	0.50-1.66	.76
Moderate	456	0.90	0.55-1.46	.66	0.96	0.54-1.71	.89
Severe	229	0.86	0.50-1.47	.57	0.99	0.53-1.84	.97
Very severe	102	0.94	0.50-1.77	.84	1.65	0.80-3.37	.17
Antidepressant use°							
None*	730	1.00			1.00		
SSRI	328	0.96	0.71-1.30	.78	1.01	0.71-1.42	.98
TCA	49	2.29	1.07-4.91	.03	1.38	0.70-2.71	.35
Other	110	1.35	0.83-2.21	.23	0.69	0.40-1.18	.18

Abbreviations: BAI, Beck Anxiety Inventory; CI, confidence interval; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; OR, odds ratio by multivariate logistic regression analysis; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.

Model 2: adjusted for age, sex, years of education, clinic site, oral contraceptive use, smoking status, alcohol use and physical activity.

*: Reference group to the subsequent groups.

°: Controls (n=629) were excluded from these analyses.

persisted in model 2. These results were not significantly altered by additional adjustment for antidepressant use (data not shown). TCA users demonstrated higher odds for having abdominal obesity, hypertriglyceridemia and hypertension, as compared to non-users of antidepressants. Additional adjustment for depression severity did not alter these results significantly (data not shown).

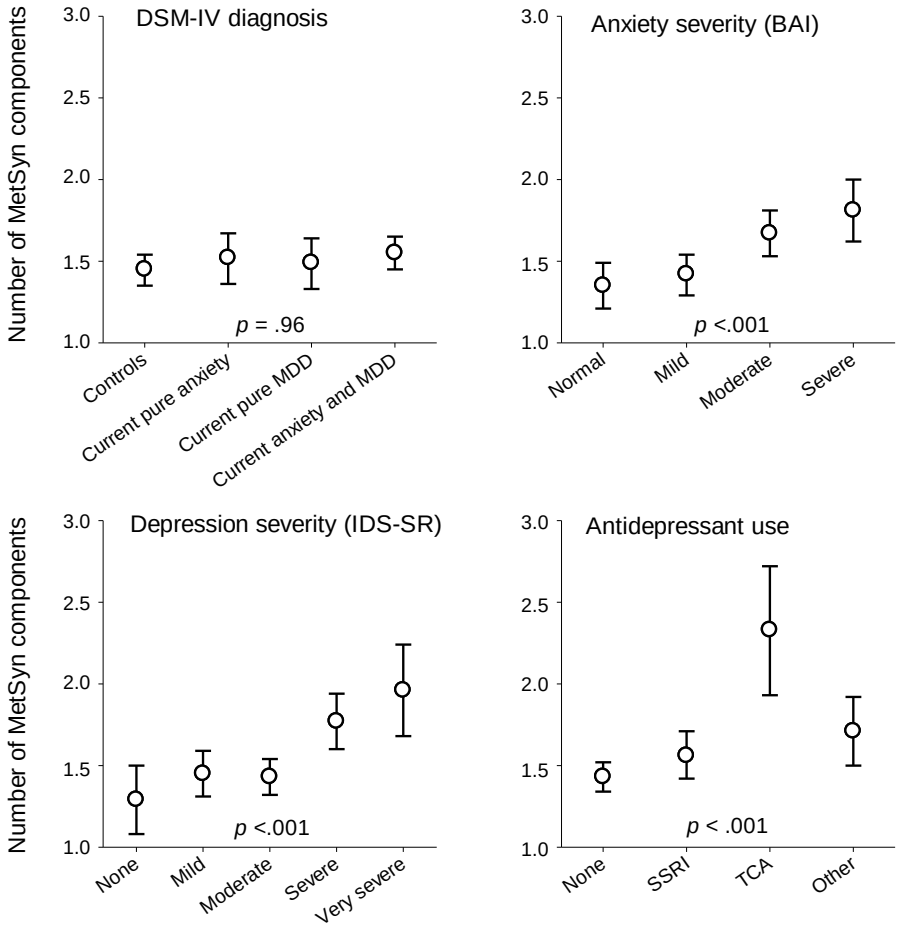

Figure 1. Dots indicate mean number of metabolic syndrome (MetSyn) components; bars indicate 95% confidence intervals. Analyses on DSM-IV diagnosis are based on the complete sample (n=1846). Analyses on anxiety severity group, depression severity group or antidepressant use are based on the sample excluding controls (n=1217). *p* by x^2 statistics. x^2 linear-by-linear test was applied for anxiety and depression severity.

2.4 DISCUSSION

In this large cohort study, the prevalence of the metabolic syndrome was uniformly not increased in subjects with either MDD or an anxiety disorder, as compared to controls. However, subjects with more severe depressive symptoms did have increased metabolic syndrome odds, which were mainly driven by increased abdominal adiposity, lower HDL cholesterol levels and hypertriglyceridemia. TCA users were also at increased odds for the metabolic syndrome, which was not only determined by the increased prevalence of abdominal obesity and hypertriglyceridemia, but also that of hypertension.

The finding that metabolic syndrome prevalence was increased in subjects with severe psychopathology, but not among diagnosis groups, indicates that symptom severity is more differentiating than diagnostic DSM-IV categories. The high co-morbidity between depression and anxiety[113,114] supports this indication. This implies that the use of dimensional instruments is a more sensitive approach, and therefore may be more helpful in the understanding of the complex relationship between psychopathology and the metabolic syndrome. This is supported by a study by Vogelzangs et al.,[25] in which they did not find an association between the metabolic syndrome and a dichotomous depression standard, but did report an association with a severity scale.

Abdominal adiposity, hypertriglyceridemia and low HDL cholesterol were the components that were increased in subjects with psychopathology. Previous studies also found these three components,[23,24,26-29,35,46-48,133,134,138,140,142] but rarely hypertension[20,21,102] or hyperglycemia,[24,47,73,138,140] to be more prevalent in subjects with anxiety or depression. This suggests that abdominal adiposity and dyslipidemia largely account for the increased metabolic syndrome odds in anxiety and depression, which is in line with a factor analytical study that demonstrated that lipids and abdominal adiposity form a distinct cluster within the metabolic syndrome.[115] These findings add to the general debate on whether the whole metabolic syndrome is more than the sum of its parts, and consequently on its usefulness as an unambiguous cluster in research and clinical practice,[116] at least in affective disorders.

Several possible explanations exist for the increased odds for abdominal obesity and dyslipidemia in subjects with more severe psychopathology. First, this might be a reflection of unfavorable lifestyle habits that are associated with anxiety and depression.[117] However, the lifestyle factors smoking, alcohol use and physical activity that were adjusted for in the present study, could only partly explain the associations. Unfortunately, we were unable to take dietary factors into account, while depression is associated with poor diets rich in carbohydrates and saturated fat.[118] A second -common causal- pathway might be the upregulation of the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis perturbations may lead to psychopathology[67,119] and to visceral adipose tissue accumulation, which subsequently, through

inflammatory factor secretion by adipose tissue, might induce dyslipidemia.[120] Depression-related inflammation,[155,156] which might be enhanced by reduced levels of anti-inflammatory factors such as adiponectin in depression,[121] could also aggravate metabolic alterations in psychopathology. Finally, hyperactivity of the autonomic nervous system,[122] or another third factor, might underlie the metabolic dysregulation in severe psychopathology.

Tricyclic antidepressant users demonstrated a distinct metabolic pattern, likely induced by TCA side effects. Next to the antihistaminergic effects that induce weight gain[75,76] and subsequently dyslipidemia,[143] TCA use is also associated with hypertension[62] through peripheral α1 adrenergic receptor agonism.[63] As metabolic syndrome disturbances in TCA users and that in subjects with severe psychopathology overlap, these findings may be linked: TCA users are, at least before starting medication, more severely depressed than current SSRI users. However, TCA use remained an independent predictor of metabolic syndrome alterations after adjustment for depression severity.

The first limitation of our study is the cross-sectional design, which does not allow us to make causal inferences on whether psychopathology precedes metabolic alterations or vice versa. Second, the number of TCA users was relatively small, which could have led to some imprecision of effect estimates of the actual associations between TCA use and metabolic syndrome alterations. Strengths of our study are the large, psychopathology-based sample, the assessment of both DSM-IV diagnoses and disease severity scores, and the possibility to reliably illuminate the role of antidepressant use and individual metabolic syndrome components.

In conclusion, prevalence of the metabolic syndrome was not generally increased in large groups of subjects with anxiety and depressive disorders. However, the most severely depressed persons and TCA users had increased odds for the metabolic syndrome, which was driven by the abdominal adiposity and dyslipidemia components. To prevent CVD and diabetes mellitus, we recommend to screen for these metabolic syndrome components, especially in severely depressed patients, or when considering the start or continuation of TCA pharmacotherapy.