DEPRESSION AND ANXIETY 33:754–764 (2016)

Research Article

BIDIRECTIONAL PROSPECTIVE ASSOCIATIONS OF METABOLIC SYNDROME COMPONENTS WITH DEPRESSION, ANXIETY, AND ANTIDEPRESSANT USE

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Background: *Metabolic syndrome components—waist circumference, high-density lipoprotein cholesterol (HDL-C), triglycerides, systolic blood pressure and fasting glucose—are cross-sectionally associated with depression and anxiety with differing strength. Few studies examine the relationships over time or whether antidepressants have independent effects.* **Methods:** *Participants were from the Netherlands Study of Depression and Anxiety (NESDA; N = 2,776; 18–65 years; 66% female). At baseline, 2- and 6-year follow-up, participants completed diagnostic interviews, depression and anxiety symptom inventories, antidepressant use assessment, and measurements of the five metabolic syndrome components. Data were analyzed for the consistency of associations between psychopathology indicators and metabolic syndrome components across the three assessment waves, and whether psychopathology or antidepressant use at one assessment predicts metabolic dysregulation at the next and vice versa.* **Results:** *Consistently across waves, psychopathology was associated with generally poorer values of metabolic syndrome components, particularly waist circumference and triglycerides. Stronger associations were observed for psychopathology symptom severity than diagnosis. Antidepressant use was independently associated with higher waist circumference, triglycerides and number of metabolic syndrome abnormalities, and lower HDL-C. Symptom severity and antidepressant use were associated with subsequently increased number of abnormalities, waist circumference, and glucose after 2 but not 4 years. Conversely, there was little evidence that metabolic syndrome components were associated with subsequent psychopathology outcomes.* **Conclusions:** *Symptom severity and antidepressant use were independently associated with metabolic dysregulation consistently over time and also had negative consequences for short-term metabolic health. This is of concern given the chronicity of depression and anxiety and prevalence of*

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Contract grant sponsor: The Netherlands Organisation for Health Research and Development; Contract grant number: 10-000-1002; Contract grant sponsor: European Union Horizon 2020 Marie Skłodowska-Curie Programme; Contract grant number: 658897; Contract grant sponsor: European Union Seventh Framework Programme (FP7/2007-2013); Contract grant number: PCIG12-GA-2012-334065; Contract grant sponsor: NWO-VICI; Contract grant number: 91811602.

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Received for publication 10 December 2015; Revised 29 March 2016; Accepted 29 March 2016

DOI 10.1002/da.22512
Published online 27 April 2016 in Wiley Online Library (wileyonlinelibrary.com).

antidepressant treatment. Depression and Anxiety 33:754–764, 2016.

Key words: *depression; anxiety; antidepressive agents; metabolic syndrome; obesity; dyslipidemia; longitudinal studies; comorbidity*

INTRODUCTION

Metabolic syndrome is a cluster of conditions—abdominal obesity, dyslipidemia, elevated fasting glucose, and hypertension—with serious consequences for physical health, such as increased risk of atherosclerotic cardiovascular disease, type 2 diabetes, and all-cause mortality.[1–4] Metabolic syndrome and its components are also associated with a range of psychological characteristics, including depression, anxiety, anger, hostility, and impaired cognitive functioning.[5–8] These associations may in part explain why people with psychopathology are at high risk of developing a range of chronic illnesses.[9] Metabolic syndrome has been defined as a discrete, binary entity; however, previous research indicates that some components are more strongly associated with psychopathology than others, particularly obesity and dyslipdemia.[10–12] Given these discrepancies between components in the context of psychiatric illness, using a dichotomous definition of metabolic syndrome may not be the strongest way of identifying the nature of associations between psychopathology and metabolic dysregulation. Rather, describing components on their own is warranted to investigate uniformities across the components.

Although there is much evidence for cross-sectional associations between metabolic syndrome dysregulations and psychopathology, few longitudinal studies assess temporal relationships, with even fewer examining both directions of the relationship simultaneously.[6] Furthermore, most of the current evidence involves depressive symptoms, whereas associations for anxiety symptoms or diagnosis of depression and anxiety have been infrequently reported, and results have been inconsistent.[13–15] Consequently, it remains unclear as to whether, over time, psychopathology impairs components of the metabolic syndrome, or vice versa. Each direction is biologically plausible, since the development and progression of both psychopathology and metabolic dysregulation are associated with a range of detrimental biological processes, including altered autonomic and neuroendocrine stress functioning, low grade inflammation, cellular aging, and oxidative and nitrosative damage.[16–18] Thus, the pathophysiology of psychopathology may increase the risk of metabolic dysregulation, and vice versa. The unhealthy lifestyle of people with psychopathology and metabolic dysregulation may also contribute, since smoking, physical inactivity and alcohol use are frequently observed in people with psychopathology[19,20] and may also drive impairments in metabolic indicators, particularly obesity.[21,22]

Independent of psychiatric disorder, antidepressants may also directly influence metabolic syndrome components. The use of tricyclic antidepressants (TCA) has been associated with metabolic dysregulation, particularly abdominal obesity.[10,23] However, the effects of selective serotonin reuptake inhibitors (SSRIs) on metabolic syndrome components are less clear.[24–26] For instance, SSRI use has been associated with weight gain, loss and no change, as well as both impaired and improved glucose and lipid profiles.[23,26] SSRI use is also associated with positive impacts on biological correlates of metabolic dysregulation, such as inflammation,[27,28] which may in part explain why their metabolic effects are diverse. Thus it is uncertain, particularly in the longitudinal context, the effect of antidepressants on metabolic syndrome components independent of psychopathology.

The current study contributes to the understanding of three issues that remain largely unclear regarding associations between psychopathology and metabolic dysregulation: (1) is psychopathology associated across all the metabolic syndrome components? (2) How are psychopathology indicators and metabolic syndrome components associated longitudinally? (3) Are antidepressants independently associated with metabolic dysregulation over time? We addressed these issues using baseline, 2- and 6-year data from a large-scale, longitudinal cohort study of depression and anxiety. First, we examined the consistency of associations of five metabolic syndrome components with depression, anxiety and antidepressant use across the three data waves. Second, to investigate prospective associations we examined whether psychopathology at one assessment predicted metabolic dysregulation at the next, and vice versa.

MATERIALS AND METHODS

PARTICIPANTS AND PROCEDURES

Participants were drawn from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing prospective cohort study of 2,981 adults with and without depression and anxiety (18–65 years). Detailed study rationale, design, and methods have been published elsewhere.[29] Briefly, between September 2004 and February 2007, participants were recruited from the community, primary care, and specialized mental health care. Exclusion criteria were a primary diagnosis of psychosis, obsessive compulsive disorder, bipolar disorder or severe addiction disorder or a lack of fluency in Dutch. Informed consent was obtained after the nature of the procedures was explained and all procedures were approved by institutional ethical review boards.

Participants completed a detailed interview, self-report questionnaires, and a medical examination involving physical assessments and fasting blood draw. Metabolic syndrome components and psychopathology were assessed at baseline, 2- and 6-year follow-up assessments. Retention of participants across follow-up assessments was high (87% of baseline sample at 2-year follow-up and 76% of baseline sample at 6-year follow-up). Participants who did not contribute to the 2- or 6-year follow-up were relatively similar to participants in demographic characteristics and antidepressant use, although they had higher depression and anxiety symptoms at baseline as well as poorer metabolic syndrome components (including lower HDL-C and greater waist circumference, glucose, and triglycerides and number of abnormalities), compared to participants. Participants were included in analyses when they had data for at least one metabolic syndrome component, psychopathology, and covariates for at least one assessment (baseline assessment: $N = 2{,}776$, 93% of available sample; 2-year assessment: $N = 2{,}203$, 85% of available sample; 6-year assessment: $N = 1{,}899$, 84% of available sample).

MEASURES

Psychopathology indicators, metabolic syndrome components, and covariates were assessed at baseline, 2- and 6-year assessment waves.

Psychopathology. Participants completed the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI, version 2.1) to derive lifetime and 6-month DSM-IV diagnoses of major depressive disorder, dysthymia, social phobia, panic disorder, agoraphobia, and generalized anxiety disorder. From these diagnoses, participants were classified at each wave as having: (1) any current depressive or anxiety disorder in the previous 6 months; (2) remitted depression and/or anxiety disorder (disorder > 6 months prior); or (3) no lifetime history of depression or anxiety.

Participants also completed validated self-report measures for the severity of psychopathology symptoms: the 30-item inventory of depressive symptomatology (IDS)[30,31] for depressive symptoms, the 21-item Beck Anxiety Inventory (BAI)[32] for measuring the psychological and arousal components of anxiety, and the 24-item fear questionnaire (FQ)[33] for measuring fear avoidance symptoms.

Medication use was derived from medication container inspection and interview, and coded with the WHO anatomical therapeutic chemical (ATC) classification system. Antidepressant use was defined as frequent use (≥50% of the time) of a TCA (N06AA), SSRI (N06AB), or other antidepressant (remaining NA06) in the previous month.

Metabolic Syndrome Components. Waist circumference was measured with a measuring tape at the central point between the lowest front rib and highest point of the pelvis over light clothing. Pregnant women were excluded from waist measurements. High-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose levels were determined from fasting blood samples using routine methods. Supine resting systolic blood pressure (SBP) was taken using OMRON M4 IntelliSense digital blood pressure monitor, as an average of two right-arm measurements.

The number of metabolic syndrome abnormalities present was defined as a count of the number of ATP-III criteria[34] present: (1) abdominal obesity: waist circumference > 102 cm in men, >88 cm in women; (2) low HDL-C: HDL-C < 1.03 mmol/L in men, <1.30 mmol/L in women; (3) hypertriglyceridemia: triglycerides ≥ 1.7 mmol/L; (4) hypertension: blood pressure ≥ 130/85 mmHg or using antihypertensive medication; (5) hyperglycemia: fasting plasma glucose ≥ 6.1 mmol/L or using antidiabetic medication.

For analyses using continuous values of metabolic syndrome components, raw values were adjusted for use of medication as previously described.[14,18,35] Specifically, for HDL-C 0.10 mmol/L was subtracted for use of fibrates (C10AB); for triglycerides 0.67 mmol/L was added for use of fibrates; for SBP 10 mmHg was added for use of antihypertensive medication (C02, C03, C07-09); and for glucose a value of 7 mmol/L was given for those on antidiabetic medication (A10) with glucose level below 7 mmol/L.

Covariates. Covariates were self-reported age, sex, years of education, smoking status (current, not current), alcohol use, and physical activity. Categories of alcohol use were derived from responses on the AUDIT[36] by calculating the average number of drinks per week: no use (0), moderate use (1–21 for males, 1–14 for females), and heavy use (>21 for males, >14 for females). Physical activity was calculated from response to the International Physical Activity Questionnaire (IPAQ), which uses the weekly duration of self-reported vigorous, moderate, walking, and sitting activity to calculate Metabolic Equivalent Total (MET) minutes of activity per week (MET level × minutes of activity × events per week).[37,38]

STATISTICAL ANALYSIS

Analyses were conducted using IBM SPSS Statistics Version 20.0 (IBM Corp. Armonk, NY). Values for triglycerides and glucose were log-transformed to account for nonnormality. Descriptive statistics were calculated at baseline, 2- and 6-year assessments. To examine the consistency of the associations between psychopathology or antidepressant use and metabolic dysregulation across the baseline, 2- and 6-year follow-up assessments, generalized estimating equations (GEE) were performed with an exchangeable correlation structure. Time (0, 2, 6) and psychopathology (diagnosis or symptom severity) or antidepressant use (none, TCAs, SSRIs, other antidepressants) were entered as main effects, with metabolic syndrome components as the outcome (normal distribution model for continuous outcomes and Poisson distribution for count outcomes). Time was entered as a continuous variable for ease of reporting, since results were identical when time was treated categorically. Analyses were adjusted for sociodemographic and lifestyle characteristics. Covariates of age and sex were held at baseline values, whereas years of education, smoking status, alcohol use, and physical activity could vary over time. Missing values were considered missing completely at random.

To examine whether the effects of psychopathology on metabolic syndrome components were the same across the three waves, analyses were repeated including an interaction term between psychopathology indicators and time.

To further examine longitudinal relationships, autoregression models were tested, which essentially "remove" the cross-sectional components of the relationship. Autoregression GEE models were applied to examine whether levels of psychopathology symptom severity or antidepressant use at one time point (t) predicted levels of metabolic syndrome components at the next time point ($t + 1$), controlling for covariates and metabolic syndrome components at t. Thus, there were two comparisons made: between baseline and 2-year follow-up assessment, and between 2- and 6-year follow-up assessment. Given the differential time gap between the two assessments (2 vs. 4 years), a binary variable coding the assessment comparison group was tested as an independent variable and also in interaction with psychopathology. Most of these interactions were significant, indicating that the effect of psychopathology on subsequent metabolic syndrome components differed in the two assessment comparisons. Consequently, stratified analyses were conducted and are reported in the results. Analyses were repeated with metabolic syndrome components as predictor and psychopathology as outcome. In these autoregression analyses, since the pattern across antidepressant classes were relatively consistent and to retain sufficient group size, antidepressant use was coded as a binary variable (use vs. no use).

TABLE 1. Baseline, 2- and 6-year characteristics of the sample

Characteristic	Baseline (total $N = 2,776$)	2-Year follow-up (total $N = 2,203$)	6-Year follow-up (total $N = 1,899$)
Sociodemographic and lifestyle characteristics			
Age (years; mean, *SD*)	41.8 (13.1)	44.3 (13.1)	48.20 (13.2)
Male (*N*, %)	946 (34.1)	756 (34.3)	654 (34.4)
Education (years; mean, *SD*)	12.2 (3.3)	12.6 (3.3)	13.0 (3.3)
Physical activity (total MET-minutes/week; mean, *SD*)	3,674.1 (3,120.3)	4,050.5 (3,416.5)	3,905.9 (3,415.2)
Current smoking (*N*, %)	1,065 (38.4)	667 (30.3)	625 (21.0)
Alcohol use (*N*, %)			
None	885 (31.9)	694 (31.5)	535 (28.2)
Moderate	1,573 (56.7)	1,276 (57.9)	1,198 (63.1)
Heavy	318 (11.5)	233 (10.6)	166 (8.7)
Body mass index (mean, *SD*)	25.6 (5.0)	25.8 (4.9)	26.2 (5.1)
Body mass categories (*N*, %)			
Underweight	65 (2.3)	39 (1.8)	32 (1.7)
Normal weight	1,405 (50.6)	1,084 (49.2)	860 (45.3)
Overweight	840 (30.2)	687 (31.2)	635 (33.4)
Obese	466 (16.8)	393 (17.8)	372 (19.6)
Metabolic syndrome			
Metabolic syndrome present (*N*, %)	505 (17.2)	454 (20.0)	454 (22.8)
Number of metabolic syndrome abnormalities (mean, *SD*)	1.4 (1.2)	1.4 (1.3)	1.5 (1.3)
Waist circumference (cm; mean, *SD*)	89.0 (14.0)	89.7 (14.3)	92.2 (13.8)
HDL cholesterol (mmol/L; mean, *SD*)[a]	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)
Triglycerides (mmol/L; median, IQR)[a]	1.1 (0.8)	1.1 (0.8)	1.1 (0.8)
SBP (mmHg; mean, *SD*)[a]	128.3 (17.5)	132.1 (18.1)	133.0 (18.3)
Glucose (mmol/L; median, IQR)[a]	5.0 (0.9)	5.2 (0.8)	5.3 (0.8)
Psychopathology			
Diagnoses in previous 6 months (*N*, %)			
Current disorder	1,572 (56.6)	808 (36.7)	538 (28.3)
Depression	1,066 (38.4)	519 (23.6)	346 (18.2)
Anxiety	1,202 (43.3)	593 (26.9)	373 (19.6)
Remitted disorder	589 (21.2)	922 (41.9)	954 (50.2)
Healthy controls	615 (22.1)	473 (21.5)	407 (21.4)
IDS (mean, *SD*)			
Overall	21.4 (14.1)	15.6 (11.8)	15.1 (11.8)
Among those with current disorder	29.2 (12.5)	25.0 (12.1)	26.1 (12.2)
Among those with remitted disorder	14.2 (8.9)	12.6 (8.3)	13.0 (8.8)
Among healthy controls	8.6 (7.5)	6.2 (5.4)	5.9 (5.3)
BAI (mean, *SD*)			
Overall	12.0 (10.6)	8.6 (8.6)	8.4 (8.5)
Among those with current disorder	17.1 (10.8)	14.5 (9.6)	15.7 (10.0)
Among those with remitted disorder	7.2 (6.5)	6.4 (6.2)	6.7 (6.1)
Among healthy controls	4.1 (4.8)	3.0 (3.8)	3.0 (3.8)
Fear questionnaire (mean, *SD*)			
Overall	24.7 (19.9)	19.1 (17.5)	17.3 (17.1)
Among those with current disorder	32.8 (20.6)	30.6 (19.9)	30.5 (19.8)
Among those with remitted disorder	16.7 (13.2)	14.7 (13.1)	14.1 (13.6)
Among healthy controls	12.0 (12.2)	9.2 (9.0)	8.0 (9.3)
Antidepressants (*N*, %)			
Tricyclic antidepressants	73 (2.6)	64 (3.0)	60 (3.2)
SSRIs	467 (16.8)	307 (14.5)	221 (11.6)
Other antidepressants	157 (5.7)	112 (5.3)	92 (4.8)
No antidepressants	2,054 (74.0)	1,631 (77.2)	1,521 (80.1)

[a]Adjusted for use of medications with metabolic effects.

RESULTS

SAMPLE CHARACTERISTICS

Table 1 shows the descriptive statistics of the sample. At baseline, 66% of the participants were female and were on average 42 years old with 12 years of education. Physical activity was relatively stable across the three assessment waves, whereas smoking rates and the proportion of heavy drinkers and nondrinkers declined. Depression and anxiety symptoms and the frequency

of current diagnoses significantly decreased over time, whereas components of metabolic syndrome generally worsened over time.

CONSISTENCY OF ASSOCIATIONS ACROSS ASSESSMENT WAVES

Table 2 shows the main effects of time and psychopathology indicators on metabolic syndrome components. There were significant main effects of time on metabolic syndrome components, indicating that levels of HDL-C decreased across assessment waves, whereas number of metabolic syndrome abnormalities, waist circumference, triglycerides, SBP, and fasting glucose increased (Table 2). Across the three assessments, current and remitted anxiety or depressive disorders were associated with lower SBP, although associations with other components were not significant. In contrast, the results for continuous symptom severity measures were much stronger. Across all assessment waves, higher IDS was associated with higher number of metabolic syndrome abnormalities, waist circumference, HDL-C and triglycerides, and lower SBP. The pattern of results between the two anxiety scales differed. BAI scores were significantly and strongly associated with higher values for number of metabolic syndrome components, waist circumference, triglycerides, and glucose, whereas FQ scores were only weakly associated with higher HDL-C.

Antidepressant use was also associated with metabolic syndrome components (Table 2). Compared with antidepressant nonusers, TCA use was associated with lower HDL-C and the use any type of antidepressant (TCA, SSRI, or others) was associated with higher waist circumference, triglycerides, and number of metabolic syndrome abnormalities. The effect sizes observed were somewhat stronger for TCA use compared with use of SSRIs and other antidepressants, particularly for waist circumference.

To see whether the effects of antidepressant use were independent of symptom severity, both were included as main effects predicting metabolic syndrome components. The effects were largely the same magnitude as those reported in Table 2, indicating independent effects (detailed in Supporting InformationTable S1).

We did not observe consistent interactions between psychopathology indicators and time, indicating that the relationship between psychopathology indicators and metabolic syndrome components did not differ over time (data not shown).

PROSPECTIVE, AUTOREGRESSIVE RELATIONSHIPS

In the prospective analyses, several psychopathology indicators at baseline significantly predicted levels of metabolic syndrome components at 2-year assessment, taking into account covariates and baseline metabolic syndrome component values (Table 3). In contrast, there was little evidence that psychopathology indicators at the 2-year assessment predicted levels of metabolic dysregulation at 6-year assessment. Higher IDS or BAI scores and antidepressant use at baseline were all associated with an increasing or a higher number of metabolic syndrome abnormalities at 2-year follow-up. Higher IDS and BAI scores at baseline were associated with increasing waist circumference by 2-year follow-up. A contrasting pattern emerged for antidepressant use. Antidepressant use at baseline was associated with increasing waist circumference by 2-year follow-up, whereas antidepressant use at 2-year follow-up was associated with decreasing waist circumference by 6-year follow-up. To explore this effect, an additional within-subject ANCOVA was conducted on waist circumference change between 2- and 6-years, comparing groups according to antidepressant use pattern, adjusting for baseline waist circumference and covariates. Participants using antidepressants at both 2- and 6-year assessments had similar waist gain (marginal mean [m] = 2.2 cm, SE = 0.4) to those who had no use (m = 3.0 cm, SE = 0.2, pairwise contrast P = .108) or commenced use at the 6-year assessment (m = 2.6 cm, SE = 0.8, pairwise contrast P = .622), whereas those who stopped using antidepressants at 6-year assessment had, on average, a slight waist reduction (m = −0.1 cm, SE = 0.7, pairwise contrast P = .006). These differences were less pronounced between baseline and 2 years, rendering a discrepant average effect. These effects indicate that current antidepressant use has strongest influence on waist, which aligns with findings of Table 2.

Fewer consistent patterns across symptom severity and antidepressant use were observed for the other components. Higher IDS score at baseline were weakly associated with lower HDL-C by 2-year follow-up. Antidepressant use, but not severity measures, at baseline was also associated with higher fasting triglycerides and glucose by 2-year follow-up. Psychopathology indicators did not significantly predict subsequent levels of SBP.

Finally, we examined the opposite predictive relationship to see whether metabolic syndrome component values at t were associated with psychopathology scores at $t + 1$, controlling for psychopathology at t and covariates (Table 4). There was only one weak effect (at P = .025), suggesting that metabolic syndrome components do not consistently predict subsequent psychopathology in this sample.

DISCUSSION

Elevated depressive or anxiety symptoms and antidepressant use were independently associated with generally poorer metabolic syndrome component outcomes, consistently across three assessment waves. Waist circumference and triglycerides were most consistently affected. The association was stronger for symptom severity and antidepressant use, as compared to the clinical diagnosis. Although all antidepressant medication types were associated with negative outcomes, as expected the deleterious effects on metabolic syndrome components were stronger for TCAs compared to

TABLE 2. Associations of psychopathology diagnosis, symptoms, and antidepressant use with metabolic syndrome components across baseline, 2 and 6 year assessments

	Outcomes																	
	Number of metabolic syndrome abnormalities			Waist circumference			HDL cholesterol			Log triglycerides			SBP			Log glucose		
Predictors	*B*	*SE*	*P*	*B*	*SE*	*P*	*B*	*SE*	*P*	*B*	*SE*	*P*	*B*	*SE*	*P*	*B*	*SE*	*P*
Disorder category																		
Time	0.0242	0.0027	<.001	0.5845	0.0317	<.001	−0.0118	0.0011	<.001	0.0026	0.0008	.001	0.7923	0.0601	<.001	0.0049	0.0002	<.001
Disorder																		
Healthy controls (reference)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Current disorder	0.0116	0.0311	.709	0.7643	0.4463	.087	0.0140	0.0143	.327	0.0049	0.0084	.558	−1.6659	0.6238	.008	0.0031	0.0023	.163
Remitted disorder	0.0078	0.0314	.803	0.8230	0.4622	.075	−0.0095	0.0145	.511	0.0072	0.0086	.401	−1.3645	0.6366	.032	0.0040	0.0022	.074
IDS																		
Time	0.0255	0.0027	<.001	0.6110	0.0313	<.001	−0.0120	0.0011	<.001	0.0032	0.0007	<.001	0.7607	0.0580	<.001	0.0050	0.0002	<.001
IDS	0.0019	0.0008	.021	0.0315	0.0107	.003	0.0011	0.0004	.003	0.0006	0.0002	.007	−0.0471	0.0170	.005	0.0001	0.0001	.378
BAI																		
Time	0.0253	0.0026	<.001	0.6067	0.0307	<.001	−0.0126	0.0011	<.001	0.0030	0.0007	<.001	0.7892	0.0573	<.001	0.0050	0.0002	<.001
BAI	0.0036	0.0011	.001	0.0455	0.0156	.003	0.0003	0.0005	.541	0.0010	0.0003	.001	−0.0148	0.0236	.532	0.0003	0.0001	.006
FQ																		
Time	0.0238	0.0027	<.001	0.6035	0.0311	<.001	−0.0121	0.0011	<.001	0.0027	0.0008	<.001	0.7869	0.0590	<.001	0.0050	0.0002	<.001
FQ	0.0000	0.0006	.969	0.0126	0.0081	.119	0.0006	0.0003	.026	0.0001	0.0002	.668	−0.0154	0.0124	.214	0.0001	0.0000	.176
Antidepressant																		
Time	0.0241	0.0026	<.001	0.5962	0.0304	<.001	−0.0127	0.0011	<.001	0.0028	0.0007	<.001	0.7878	0.0572	<.001	0.0049	0.0002	<.001
Antidepressants																		
No antidepressants (reference)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TCA	0.2806	0.0421	<.001	3.2672	0.7795	<.001	−0.0795	0.0248	.001	0.0581	0.0177	.001	1.7370	1.5402	.259	0.0082	0.0065	.210
SSRI	0.0603	0.0278	.030	1.4224	0.3567	<.001	−0.0078	0.0115	.497	0.0204	0.0078	.009	−0.8352	0.5683	.142	0.0001	0.0023	.961
Other antidepressant	0.1120	0.0376	.003	1.9581	0.5034	<.001	−0.0079	0.0184	.667	0.0470	0.0125	<.001	1.8746	0.9836	.057	0.0007	0.0030	.804

Notes: Estimates were obtained from generalized estimating equations. Analyses were adjusted for age, sex, education, smoking status, alcohol use, and physical activity. Analyses were conducted with the maximum number of cases for each outcome. *N* ranges of cases: number of components: 6,611–6,633; waist: 6,824–6,847; HDL: 6,611–6,633; triglycerides: 6,614–6,636; SBP: 6,849–6,872; glucose: 6,607–6,629.

TABLE 3. Prospective association of baseline psychopathology (t) with metabolic syndrome components at the next assessment ($t + 1$)

Predictor (t)	Outcome ($t + 1$)	0→2 Years			2→6 Years		
		B	*SE*	*P*	*B*	*SE*	*P*
IDS	Number of components	0.0027	0.0010	.006	−0.0009	0.0013	.513
BAI	Number of components	0.0030	0.0013	.026	−0.0006	0.0018	.758
Antidepressant use (vs. none)	Number of components	0.0731	0.0308	.017	0.0086	0.0378	.820
IDS	Waist	0.0251	0.0103	.015	−0.0003	0.0159	.985
BAI	Waist	0.0293	0.0142	.039	−0.0030	0.0232	.898
Antidepressant use (vs. none)	Waist	1.2098	0.3120	<.001	−1.4736	0.4298	.001
IDS	HDL	−0.0008	0.0004	.032	0.0001	0.0006	.843
BAI	HDL	−0.0008	0.0005	.137	−0.0002	0.0008	.837
Antidepressant use (vs. none)	HDL	−0.0147	0.0123	.229	−0.0067	0.0165	.685
IDS	Triglycerides	0.0004	0.0003	.133	0.0004	0.0004	.279
BAI	Triglycerides	0.0005	0.0004	.151	0.0008	0.0005	.137
Antidepressant use (vs. none)	Triglycerides	0.0272	0.0086	.002	0.0169	0.0108	.119
IDS	SBP	−0.0121	0.0189	.523	0.0024	0.0267	.928
BAI	SBP	−0.0251	0.0277	.365	0.0300	0.0381	.431
Antidepressant use (vs. none)	SBP	0.4676	0.6468	.470	−0.2191	0.7495	.770
IDS	Glucose	0.0000	0.0001	.598	0.0002	0.0001	.153
BAI	Glucose	0.0000	0.0001	.850	0.0002	0.0002	.195
Antidepressant use (vs. none)	Glucose	0.0095	0.0026	<.001	−0.0007	0.0028	.800

Notes: Estimates were obtained from generalized estimating equations. Analyses were adjusted for baseline values of the outcome, age, sex, education, smoking, alcohol use, and physical activity.

other antidepressants. The differences between classes were observed after controlling for sociodemographic characteristics, health, and symptom severity. In terms of prospective relationships, there was some evidence that more severe depression and anxiety symptoms and antidepressant use were associated with poorer metabolic syndrome component outcomes at follow-up, at least in the short-term, whereas there was no evidence that baseline metabolic syndrome components predicted psychopathology outcomes at follow-up.

The cross-sectional relationship between psychopathology and metabolic dysregulation has been relatively well-established, and the current study adds to this in highlighting the consistency of the

TABLE 4. Prospective association of baseline metabolic syndrome components (t) with psychopathology at the next assessment ($t + 1$)

Predictor (t)	Outcome ($t + 1$)	0→2 Years			2→6 Years		
		B	*SE*	*P*	*B*	*SE*	*P*
Number of components	IDS	−0.0168	0.0106	.112	0.0230	0.0126	.068
Number of components	BAI	0.0002	0.0152	.991	0.0253	0.0191	.185
Number of components	Antidepressant use (vs. none)	−0.0535	0.0555	.335	0.0642	0.0707	.364
Waist	IDS	−0.0226	0.0158	.152	0.0237	0.0175	.176
Waist	BAI	0.0018	0.0114	.874	0.0106	0.0135	.432
Waist	Antidepressant use (vs. none)	0.0023	0.0052	.660	−0.0003	0.0068	.970
HDL	IDS	0.1553	0.4951	.754	−0.5917	0.5323	.266
HDL	BAI	−0.0500	0.3582	.889	−0.6080	0.3903	.119
HDL	Antidepressant use (vs. none)	0.1223	0.1603	.445	−0.5069	0.2265	.025
Triglycerides	IDS	0.4046	0.8218	.623	0.6401	0.9383	.495
Triglycerides	BAI	0.4294	0.6186	.488	0.6835	0.6775	.313
Triglycerides	Antidepressant use (vs. none)	0.0730	0.0652	.263	0.1116	0.0872	.200
SBP	IDS	−0.0132	0.0104	.202	−0.0096	0.0117	.409
SBP	BAI	−0.0132	0.0076	.085	−0.0088	0.0084	.294
SBP	Antidepressant use (vs. none)	−0.0006	0.0037	.878	0.0042	0.0055	.448
Glucose	IDS	1.3291	2.8651	.643	−1.5277	3.3214	.646
Glucose	BAI	0.7495	2.1295	.725	0.2202	2.3306	.925
Glucose	Antidepressant use (vs. none)	−0.1252	0.0746	.093	0.0641	0.0809	.428

Notes: Estimates were obtained from generalized estimating equations. Analyses were adjusted for baseline values of the outcome, age, sex, education, smoking, alcohol use, and physical activity.

relationship with repeated measurement over time. Most of effects were in the expected direction, whereby psychopathology severity and antidepressant use were associated with poorer metabolic outcomes across the three assessment waves. However, in contrast to the other components, results for SBP and HDL-C were unexpected, whereby greater depressive and anxiety symptom severity were associated with lower SBP and higher HDL-C. Although a relationship between depression and hypertension is often observed,[39,40] a negative association between psychopathology and SBP has been reported previously in NESDA and other cohorts.[41–44] The effect does not seem to be driven by medication use. Lowered blood pressure in psychopathology may be a consequence of shared risk factors, such as levels of neuropeptide Y, which is associated with suppressed parasympathetic activity and stress, depression and anxiety.[45] The reason for the positive association between symptom severity and HDL-C is unclear, particularly since HDL-C has anti-inflammatory properties [46] and recent evidence suggests that use of cholesterol improving medication is associated with improved mental health.[47] Nevertheless, the findings are consistent with previous research demonstrating that depressive symptoms and suicidality are associated with lowered total cholesterol and higher HDL-C,[48,49] although heterogeneity between studies is high and the effect is not always observed.[50,51] Overall, people with psychopathology may have a more nuanced risk pattern across metabolic syndrome components, rather than increased risk of metabolic abnormalities across the board.

We also observed contrasting effects for the two anxiety scales used in this study, which is important to note since anxiety symptoms are less frequently reported in relation to metabolic dysregulation than depressive symptoms. In the current study, the general anxiety arousal symptoms measured with the BAI were significantly associated with higher waist circumference, glucose, triglycerides, and number of metabolic syndrome abnormalities, rather than phobic/avoidance symptoms measured in the FQ, which was only weakly associated with higher HDL-C. The operational definition and nature of anxious symptoms appears to substantially influence results. Anxiety symptoms related to somatic arousal may be a stronger correlate of metabolic syndrome components than those related to fear.[52]

Regarding prospective relationships, higher psychopathology severity and antidepressant use at baseline were associated with poorer metabolic syndrome component outcomes at 2-year follow-up. This was particularly true for use of antidepressants, which compared with depressive and anxiety symptoms, negatively influenced a range of metabolic syndrome components after 2-years. Antidepressants have pleiotropic effects across biological systems, including effects on autonomic nervous system, immune and inflammatory processes, oxidation, and cellular aging.[53–55] These systems are all associated with negative consequences for cardiometabolic health and the development and maintenance cardiometabolic diseases.[56–58] The effects of antidepressants were largely independent of psychopathology, highlighting antidepressants as important risk factors in their own right.

In an extended examination from 2- to 6-year follow-up, the effects of psychopathology on subsequent metabolic dysregulation were no longer significant. Indeed, one of the observed effects was that antidepressant users at 2 years had on average waist reduction at 6-year follow-up; an effect explained by waist reduction or a lack of gain in those who had stopped using antidepressants by the 6-year assessment. Around 30% of antidepressant users at 2 years were no longer users at 6 years, allowing a four-year window to normalize waist after cessation of antidepressant use. The findings indicate that it is the current use of antidepressants that has the strongest influence on waist circumference.

The limited evidence of prospective relationships in the longer term indicates that effects of psychopathology and antidepressants on metabolic dysregulation may be diluted over time, or better explained by lifestyle or another enduring behavioral or biological factor. Several studies indicate that presence of depression or anxiety or more severe baseline levels of psychopathology are associated with poor metabolic outcomes over time, particularly obesity and dyslipidemia,[6,14] and sometimes over extended periods, up to 15 years later.[59] Other studies indicate effects in the opposite direction.[13,60] However, many of these previous studies by nature of their study design are unable to test both directions of the prospective relationship, or are unable to take into account current psychological functioning or confounding from unhealthy lifestyle as a possible explanations for effects. For instance, one explanation for significant prospective associations in previous studies may involve unhealthy lifestyle, in particular smoking and heavy alcohol use, which often remain present in people with depression and anxiety even though their other symptoms resolve.[19] The current study controls for such factors. Nevertheless, in the current study, longitudinal effects of psychopathology on metabolic syndrome components 2 years later were present after adjusting for several key lifestyle factors. This may indicate that possible shared pathophysiological aspects involved. For instance, higher baseline parasympathetic nervous system activity and shortened telomere length have been associated with worsening metabolic dysregulation after 2 years in NESDA participants.[18,61]

We did not observe evidence supporting the opposite prospective relationship; levels of metabolic syndrome components were not associated with psychopathology at the next assessment. Thus, if there is a prospective relationship among people with psychopathology, the direction from psychopathology to metabolic dysregulation may be stronger. It is possible that the lack of association may be partly due to the overall good health of the sample, with previous findings demonstrating stronger associations between obesity and depression

than overweight and depression.[62,63] It may also be partly due to the sample composition, which at baseline largely consisted of people with high psychopathology symptoms who decrease in their symptoms over time as a consequence of treatment or naturalistic change. Nevertheless, a large majority of participants enrolled at baseline did not have a current diagnosis (see symptom levels in remitted and healthy controls in Table 1), and since the focus of analyses was on change in symptom severity, it is likely that there was sufficient range in psychopathology scores to detect change in psychopathology in either direction.

The major limitation of this study is the lack of assessments at finer time gradations, which may have provided a better understanding of the reciprocal relationship between psychopathology and metabolic dysregulation. Another limitation is that although many participants with severe psychopathology were retained in NESDA, there is evidence that participants with higher psychopathology symptom severity and current diagnosis were more likely to drop out. Maximum likelihood analyses showed largely similar patterns to those reported here, indicating low risk of selective bias. Nevertheless, the findings may be less generalizable to more severe psychopathology cases and people with more severe metabolic dysregulation, and may underestimate the true effect. A final consideration is the influence of multiple testing on the interpretation of findings. Numerous tests were conducted to examine the hypotheses, yet these analyses were expected to be largely correlated so *P*-value adjustment methods that assume independence between tests would be too conservative. The results of this study were instead interpreted based on the consistency of patterns across the results, rather than statistical significance. However, calculating a Benjamini–Yekutieli false-discovery rate,[64] which controls for false significance at $\alpha = .05$ when hypotheses are dependent, gives an adjusted *P*-value of .01. With this threshold, most results, particularly the cross-sectional findings, remain statistically significant and so the primary conclusions of the study are not substantially altered.

A substantial strength of the current study is the prospective design with measurement of predictors, outcomes, and confounders at three waves. The design of NESDA also oversampled participants with depression and anxiety disorders, which is a strength over general community-based cohorts in that there is a broader range of depression and anxiety symptoms than the typically positively skewed distribution.

CONCLUSIONS

Metabolic dysregulation is associated with depressive symptoms, anxiety symptoms, and antidepressant use. Furthermore, psychological and pathophysiological perturbations in depression and anxiety and the pharmacological effects of antidepressants may have short-term enduring effects on metabolic health. Although in the long-term one does not appear to exacerbate the other, the consistent cross-sectional associations and negative consequences of psychopathology on short-term metabolic health are nonetheless concerning since depression and anxiety are chronic conditions and antidepressants are widely prescribed. The results of the current study highlight the ongoing need to assess metabolic health in people with psychopathology, particularly those on antidepressant medication.

Acknowledgments. The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of The Netherlands Organisation for Health Research and Development (ZonMW, grant no. 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, IQ Healthcare, Netherlands Institute for Health Services Research, and Netherlands Institute of Mental Health and Addiction [Trimbos]). Dr. Hiles received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement no. 658897. Dr. Lamers received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no. PCIG12-GA-2012-334065. The work of Professor Penninx and Révész was supported through a NWO-VICI grant (no. 91811602).

Conflict of interest. Professor Penninx has received research funding from Jansen Research.

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