Chapter 5:

Dimensions of Depression and Anxiety and the Metabolic Syndrome: Somatic Arousal is Associated with Somatic Symptoms of the Metabolic Syndrome

Abstract

Objective: To investigate the association between depression and anxiety symptoms and the metabolic syndrome (MetSyn), using a dimensional approach. The association between depression and anxiety, on the one hand, and the MetSyn as a cluster or its individual components, on the other hand, is equivocal. The categorical nature of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* might partly explain the inconsistent findings. *Methods:* In 2,433 Netherlands Study of Depression and Anxiety participants (mean age, 42.3 years; 33.1% male), three symptoms dimensions—lack of positive affect (PA, depression specific); negative affect (NA, aspecific); and somatic arousal (SA, anxiety specific)—were assessed by a shortened adaptation of the Mood and Anxiety Symptom Questionnaire. The association between symptom dimensions and MetSyn components (waist circumference, triglycerides, high-density lipoprotein cholesterol, glucose, and mean blood pressure) was analyzed, using linear regression analysis. *Results:* The occurrence rate of the MetSyn was 20.1% (*n*=490). SA, but not PA and NA, was strongly associated with four out of five MetSyn components, especially waist circumference, triglycerides, and blood pressure (β=0.046, *p*<.01; β=0.077, *p*<.001; and β=0.069, *p*<.001, respectively), and with the total number of MetSyn components (β=0.098, *p*<.001). *Conclusions:* Our results demonstrate a strong association of most of the MetSyn components with the SA dimension, but not with the NA and PA scales.

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Note: *Troughout the literature, different interchangeable names are used for the measured dimensions of the tripartite model. In this published chapter, the names that were used to describe the dimensions differ from the names that were used in the other chapters. In this chapter, the name negative affect (NA) is used in stead of general distress, the name positive affect (PA) is used in stead of anhedonic depression, and the name somatic arousal (SA) is used in stead of anxious arousal. This difference of terminology is purely circumstantial and does not reflect any difference in the used theoretical framework.*

5.1 Introcuction

Mood and anxiety disorders are related to an increased risk of cardiovascular morbidity and mortality (Penninx et al., 2001; Barth et al., 2004). The metabolic syndrome (MetSyn) is a cluster of cardiovascular risk factors (i.e., elevated waist circumference, triglycerides, blood pressure, and fasting glucose, and reduced high-density lipoprotein [HDL]) cholesterol) (Grundy et al., 2005) and is thought to mediate partly this relationship (Bjorntorp, 2001). The association between depression and anxiety and the MetSyn has been extensively investigated. Most studies (Heiskanen et al., 2007) focused on the association between depression and the cluster of the MetSyn and its individual components. Other studies (Skilton et al., 2007; Carroll et al., 2009), however less numerous, investigated the association between anxiety and both the MetSyn cluster and its individual components. In addition, in a recent publication (Reedt Dortland et al., 2010), we examined whether disorder status and symptom severity were associated with the MetSyn. No significant difference was found between subjects with and without psychopathology (both depression and/or anxiety). Only the subgroups of the most severely depressed or anxious subjects had increased occurrence rates of the MetSyn, an association predominantly driven by abdominal obesity and dyslipidemia. Despite these observations, the question remains whether a complete mood disorder diagnosis or rather only specific symptom dimensions are related to the MetSyn and whether the dichotomous MetSyn diagnosis or only some
of its components are related to psychopathology dimensions.

There are three major reasons that could explain why this question has so far remained unanswered. First, the studies have been conducted in widely differing samples, which limit the possibilities to formulate a broadly generalizable model. For instance, there have been differences in the settings (e.g., clinical population or the general population) (Ierodiakonou & Iacovides, 1987), age of the subjects (an elderly population or young adult patients) (Almeida et al., 2009; Franko et al., 2005), and the assessment of psychopathology (questionnaires versus clinical diagnoses) (Koponen et al., 2010; Goldbacher et al., 2009). Second, the categorical diagnostic approach (using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]) for depressive and anxiety disorders, lumping together disparate symptom clusters, may have limited the power to detect subtle associations (Goldberg, 1996). Patients with the

same diagnosis can be very different in terms of their symptom profiles, whereas other individuals with important mental health problems fail to meet the diagnostic criteria due to symptom heterogeneity. Third, like the DSM-IV diagnosis, the MetSyn concept is also heterogeneous, and is the subject of substantial debate (Kahn et al., 2005; Reaven, 2005). Because at least three of five components are needed to fulfil the criteria of the MetSyn, there are numerous combinations of components possible that all lead to the same MetSyn diagnosis. Studies (Tolker & Shirom, 2008) have shown that sometimes only specific components of the MetSyn are associated with depression, which cast doubt over the usability of the total MetSyn concept in psychopathology research. It is possible that, in the large variety of depression/anxiety symptoms, some are "specifically" associated with a distinct MetSyn component (e.g., energy loss, often leading to decreased physical activity, might lead to elevated waist circumference [WC]). Based on the criticized definition of the MetSyn and the possible specific associations between diagnostic and MetSyn symptoms, it would thus be informative to investigate the association between specific depression/anxiety symptoms, on the one hand, and the MetSyn, both defined as a cluster of symptoms and as individual components, on the other hand.

So far, research on the association between depression and anxiety and the MetSyn has mainly focused on categorical and heterogeneous assessments of affective disorders symptomatology or anxiety and depression severity scales (Barefoot & Schroll, 1996; Frasure-Smith & Lesperance, 2005). In addition, diagnoses show overlapping criteria and comorbidity rates are high (Kessler et al., 2005; Brown et al., 2001). To overcome these problems, diagnoses should be more homogeneous and not dichotomous. A feasible alternative for categorical diagnoses is the use of a dimensional approach. Within a dimensional approach, a patient is described in terms of coexisting different symptom domains or dimensions, and not in terms of presence or absence of psychopathology. Each dimension provides specific information on the level of a specific symptom domain, running from absent or healthy to severe. Importantly, dimensions are continuous by principle. Along a continuous scale, changes from one level to another are subtle, whereas in a dichotomous scale, changes are rough and restricted (e.g., depressed versus non-depressed). This makes continuous variables more sensible for detection of (small) differentiating factors (Veen et al., 2011), thus increasing statistical power (MacCallum et al., 2002).

A well-known dimensional model is the tripartite model for depression and anxiety (Clark & Watson, 1991), which distinguishes three symptom dimensions. The broad "negative affect" (NA) dimension describes general symptoms of psychological distress (e.g., lack of concentration or pessimism) that are seen both in depression and anxiety and could account for their high comorbidity. The (lack of) "positive affect" (PA) dimension (also called anhedonic depression), covers anhedonic symptoms, which are mainly specific to depression. The "somatic arousal" (SA) dimension covers symptoms of hyperarousal (e.g., palpitations, shortness of breath, and dizziness), which are specific for anxiety, especially panic disorder. The dimensional model was not developed for

detection of DSM-IV diagnoses, but rather to provide a descriptive alternative for the presence or absence of psychopathological symptoms in a subject. The tripartite model was developed to circumvent the lack of diagnostic specificity due to the high levels of comorbidity observed in depression and anxiety, one of the major problems of the DSM-IV "golden standard." Typifying patients in terms of their NA, PA, and SA scores has two advantages: first, comorbidity is circumvented; and second, based on the profile of the scores, patients can be described in more specific terms of symptomatology. Several studies (de Beurs et al., 2007, Watson et al., 1995a) have shown these specific dimensions to be specifically increased in depression (PA) and anxiety (mainly panic disorder, SA) and that NA was more indicative for overall severity across patients.

The aim of the present study was to investigate the relationship between the symptom dimensions of depression and anxiety of the tripartite model, and the MetSyn and its individual components within the Netherlands Study of Depression and Anxiety (NESDA), as a dimensional approach makes it possible to look more specifically into these associations.

5.2 Methods and Materials

Subjects

Subjects selected for these analyses were baseline participants of NESDA, a cohort study among 2,981 individuals aged 18 years through 65 years. Respondents were recruited in the community, in primary care, and in specialized mental healthcare settings from September 2004 through February 2007, throughout The Netherlands. All subjects completed a medical examination, a face-to-face interview, and self-report questionnaires. A detailed description of NESDA is reported elsewhere (Penninx et al., 2008). The study protocol was approved by the Ethical Review Board of each participating centre and all subjects signed an informed consent.

In the same study sample, tricyclic antidepressant (TCA) users were found to have a significantly increased prevalence of the MetSyn (Reedt Dortland et al., 2010). This association was not found for users of other types of antidepressants, such as selective serotonin reuptake inhibitors (Reedt Dortland et al., 2010). Therefore, the relatively small group of TCA users (n = 80) was excluded from our analyses, so that the results would not be affected by the potential confounding influence of TCAs. Subjects with missing MetSyn or Mood and Anxiety Symptom Questionnaire (MASQ) values (n = 468) were excluded as well, resulting in a sample of 2,433 (81.6%) subjects. An important number of the included subjects comprised healthy controls or remitted patients (n=1449), whereas other subjects had a current diagnosis of pure depression (n=222), pure anxiety (n=226), or comorbid disorder (n=536). No inpatients were included. The included subjects did not differ from the excluded group in sex distribution, presence of cardiovascular disease (CVD), and physical activity. Included subjects were older (42.3 years versus 40.0 years, p<.001), were more educated (12.3 versus 11.3 years, p <.001), were less often smokers

(35.8% current smokers versus 50.9%, p<.001), and consumed more alcohol (16.4% consumed >2 glasses/day versus 15.3%, p<.001) compared with the excluded subjects.

Measurements

MASQ dimensions

The three dimensions of the tripartite model were measured with the 30-item adaptation (MASQ-D30) of the MASQ (Watson et al., 1995a; 1995b). The MASQ-D30 was previously validated and showed reliability and validity within the NESDA study (de Beurs et al., 2007; Chorpita & Daleiden, 2002; Wardenaar et al., 2010). The MASQ-D30 consists of three ten-item scales, representing NA, PA, and SA (Table 1). On each item, participants were asked to rate how much in the past week they have experienced "feelings, sensations, problems and experiences that people sometimes have" on a 5 point scale, 1 being "not at all" and 5 being "extremely." Higher scores indicate more severe symptom levels for that specific dimension.

MetSyn

The MetSyn and its components, when expressed as dichotomous variables (i.e., elevated WC, triglycerides, blood pressure, and fasting glucose, and reduced HDL cholesterol), were exactly defined according to the revised criteria of the National Cholesterol Education Program-Adult Treatment Panel III (Grundy et al., 2005). WC was measured with a measuring tape at the central point between the lowest rib and the highest point of the iliac crest, on light clothing. Triglycerides, HDL cholesterol, and glucose levels were determined by standardized routine laboratory assays, and diastolic and systolic blood pressures were measured during supine rest (OMRON M4 IntelliSense Digital Blood Pressure Monitor, HEM-752A, Omron Healthcare, Inc., Bannockburn, Illinois). Use of triglyceride or HDL cholesterol-influencing medication and use of antihypertensive or glucose reducing drug were registered. In addition, we used continuous variables for the MetSyn components (which is preferable when aiming for more statistical power) (MacCallum et al., 2002). In these analyses, we "adjusted" the values for those subjects, using a MetSyn component influencing medication. This was done following the methods described in several previous publications (Bays et al., 2003; Grundy et al., 2005). For the use of fibrates, 0.10 mmol/L (3.8 mg/dL) was subtracted from HDL cholesterol, and 0.67 mmol/L (60 mg/dL) was added to the triglycerides. For the use of nicotinic acid, 0.15 mmol/L (5.8 mg/dL) was subtracted from HDL cholesterol, and 0.19 mmol/L (17 mg/dL) was added to the triglycerides. For the use of antidiabetic medication and a glucose level of < 7 mmol/L (126 mg/dL), a value of 7 mmol/L (126 mg/dL) was given to glucose, as was done previously (33). Mean blood pressure (MBP) was expressed as the arithmetic mean of systolic and diastolic blood pressures, which were both measured twice during supine rest on the right arm (OMRON M4 IntelliSense Digital Blood Pressure Monitor, HEM-752A, Omron Healthcare, Inc.) and averaged over the two measurements. For persons using

antihypertensive medication, 10 mm Hg was added to systolic blood pressure, and 5 mm Hg was added to diastolic blood pressure, in line with earlier studies (Vogelzangs et al., 2007). These values represent the average decline in blood pressure in antihypertensive medication trials (SHEP, 1991; Tannen et al., 2006).

Table 5.1: This table lists all the symptoms incorporated in the three symptom dimensions of the MASQ-D30.

Negative Affect	Positive Affect	Somatic Arousal
Felt confused	Felt successful	Startled easily
Felt worthless	Felt really happy	Felt nauseous
Felt irritable	Felt optimistic	Felt dizzy or light-headed
Felt hopeless	Felt like I was having a lot of fun	Was trembling or shaking
Blamed myself for a lot of things	Felt like I accomplished a lot	Had pain in my chest
Felt dissatisfied with everything	Felt like I had a lot to look forward to	Had hot or cold spells
Felt pessimistic about the future	Felt really talkative	Was short of breath
Felt inferior to others	Felt really 'up' or lively	Muscles were tense or sore
Had trouble making decisions	Felt like I had a lot of energy	Heart was racing or pounding
Worried a lot about things	Felt really good about myself	Had trouble swallowing

Severity scales

Information on depression and anxiety severity was collected during the baseline measurement of the NESDA study (Penninx et al., 2008), using the Beck Anxiety Inventory (BAI) (Beck et al., 1988) and the Inventory of Depressive Symptoms self-report (IDS-SR;

www.ids-qids.org), in which the most severe groups were defined as “severe anxiety symptoms” with a score of ≥ 29 on the BAI and “very severe depressive symptoms” with a score of ≥ 49 on the IDS-SD. Previous NESDA research (Reedt Dortland et al., 2010) indicated that the prevalence rates of the MetSyn were increased in those with severe anxiety symptoms (*n*=185) in crude models and independently increased in those with very severe depressive symptoms (*n*=102) after fully adjusted models. Because information on the BAI and IDS-SR scores was available for our sample, we decided to investigate whether the previous found associations in the same cohort between the highest scores of the BAI and IDS severity scales and metabolic derangements would be driven by symptom dimensions.

Covariates

Covariates were grouped into two types of variables: sociodemographic and life-style variables. Sociodemographic variables included age, sex, and years of education. Life-style characteristics included smoking status (never/ former/current), alcohol use (<1/1–2/>2 drinks per day), both assessed by standardized questionnaires, and physical activity, which was assessed by the International Physical Activity Questionnaire (Booth, 2000) and expressed in 1000 Metabolic Equivalent-minutes in the past week. Metabolic Equivalent-minutes reflects the ratio of the associated metabolic rate for specific activities divided by the resting metabolic rate multiplied by the minutes performed activity. CVD was considered to be present when participants self-reported a diagnosis of coronary heart disease, cardiac arrhythmia, angina, heart failure, or myocardial infarction, confirmed with the use of cardiovascular medication. Medication use of any kind within the past month was registered by observation of drug containers brought in and coded according to the Anatomical Therapeutic Chemical Classification System (World Health organization, 2009).

Statistical Analyses

Sample characteristics were summarized, using means and standard deviations (SD) for quantitative variables and by percentages for categorical variables. Multivariate linear regression analyses were conducted to assess the association between each MASQ-D30 dimensions (i.e., PA, NA, and SA) and the individual continuous MetSyn components and the total number of MetSyn components. Analyses for each dimension were performed separately. To normalize residuals, non-normally distributed dependent variables were naturally log-transformed. After running crude models, we adjusted for basic covariates (i.e., age, sex, and years of education) in model 1, and for additional life-style-related covariates (i.e., smoking status, alcohol use, and physical activity) in model 2. Because sex differences in the association between anxiety, depression, and the MetSyn have previously been observed (Token et al., 2008; Kinder et al., 2004), appropriate interaction terms with sex were explored. To evaluate the influence of prevalent CVD, participants diagnosed with CVD were excluded in a sensitivity analysis.

To evaluate whether the earlier described association between severity of depressive and anxious symptoms and MetSyn abnormalities were driven by symptom dimensions, additional regression analyses were performed. We analyzed the association of BAI and IDS-SR severity categories with the individual MetSyn components and the total number of components by performing linear regression analyses, adjusting for models 1 and 2 covariates, and additionally adjusting for those symptom dimensions that demonstrated to be associated significantly with the MetSyn components in the main analyses.

Multivariate logistic regression analyses were performed to assess the association between the SDs of continuous scores of the three symptom dimensions and the MetSyn diagnosis. All assumptions for linearity were tested and fulfilled. All tests were two-tailed with $p < .05$ denoting statistical significance. Statistical analyses were done with SPSS 16.0 (SPSS Inc., Chicago, Illinois).

5.3 Results

General Characteristics

Sample characteristics are shown in Table 5.2. The mean age was 42.3 years (SD=13.1), 33.1% were men, and mean number of years of education was 12.3 years (SD=3.3). The criteria for the MetSyn were fulfilled by 20.1% (*n*=490). The reported means and SDs for each dimension are calculated from the continuous values of all subjects included (*n*=2433) for that dimension.

Symptom dimensions and MetSyn components

Outcomes of the linear regression analyses between MASQ-D30 dimensions and MetSyn components are shown in Table 5.3. PA showed a significant association with every MetSyn component in the crude model. Adjustments in model 1 led to a decrease of the β with >10% and to nonsignificant associations with WC, fasting glucose levels, and MBP. Analyses with the separate covariates of model 1 showed age to be the most important confounder. Associations of PA with triglycerides and HDL cholesterol became statistically nonsignificant after adjustment for life-style factors (model 2). No significant associations were found for NA with any of the MetSyn components, in the unadjusted and fully adjusted models.

On the contrary, in the crude unadjusted model, SA showed a significant association with all MetSyn components except for fasting glucose. The associations for SA remained significant in both adjusted models with regard to WC (WC_{crude}: β=0.061, p=.003; $WC_{model\ 2}$: β=0.046, p=.01), triglycerides ($Trig_{crude}$: β=0.077, p<.001; $Trig_{model\ 2}$: β=0.046, p=.02) and MBP (MBP_{crude}: β=0.069, p<.001; $MBP_{model\ 2}$: β=0.068, p <.001).

Table 5.2. Sample characteristics (n=2433)

General characteristics	
Age	42.3 (13.1)
Sex (% men)	33.1
Years of education	12.3 (3.3)
Cardiovascular disease	5.8
Smoking	
Never	29.3
Former	34.9
Current	35.8
Alcohol consumption	
< 1 glasses/day	61.0
1-2 glasses/day	22.4
> 2 glasses/day	16.4
Physical activity (1000 MET minutes)	3.7 (3.06)
Metabolic syndrome components	
Waist circumference total (cm)	88.7 (13.8)
HDL- cholesterol (mmol/l)	1.6 (0.4)
Triglycerides (mmol/l)	1.3 (0.8)
Glucose (mmol/l)	5.2 (0.9)
Systolic blood pressure (mmHg)	136.2 (19.7)
Diastolic blood pressure (mmHg)	81.5 (11.1)
Mean blood pressure (mmHg)	108.9 (14.7)
Number MetSyn components	1.45 (1.3)
Metabolic syndrome (%)	20.1
Symptom dimensions (mean scores)	
MASQ Positive affect	33.4 (9.7)
MASQ Negative affect	20.0 (8.6)
MASQ Somatic arousal	15.7 (6.1)

Means and standard deviations (SD) are given for age, years of education, physical activity, number of metabolic syndrome components and the three symptom dimensions. Percentages are given for sex, smoking status, alcohol consumption, and presence of metabolic syndrome.
HDL: High Density Lipoprotein; MET: Metabolic Equivalent.

Table 5.3: Linear regression for association between MASQ dimensions and metabolic syndrome components in 2433 subjects.

	Waist Circumference		Triglycerides		HDL Cholesterol		Glucose		Blood Pressure		Number of MetSyn Components	
	B	p-value	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Negative Affect												
Crude	.070	.001	.097	< .001	- .063	.002	.079	< .001	.076	< .001	.107	< .001
Model 1	- .001	.94	.044	.02	- .039	.04	.027	.15	.008	.64	.036	.05
Model 2	- .009	.60	.021	.29	- .012	.52	.026	.17	.009	.63	.019	.29
Postive Affect												
Crude	- .002	.93	.031	.12	- .036	.08	.008	.68	- .028	.17	.018	.37
Model 1	.016	.34	.042	.03	- .017	.36	.036	.05	- .001	.94	.033	.07
Model 2	.011	.51	.022	.25	.001	.08	.037	.05	- .002	.90	.020	.27
Somatic Arousal												
Crude	.061	.003	.077	< .001	- .056	.01	.025	.22	.069	< .001	.098	< .001
Model 1	.050	.01	.064	.001	- .045	.02	.023	.21	.062	< .001	.074	< .001
Model 2	.046	.01	.046	.02	- .018	.32	.023	.22	.068	< .001	.062	.001

β, standardised β by linear regression analyses.

Abbreviations: HDL, high density lipoprotein.

Model 1: adjusted for age, sex and years of education (sociodemographic factors)

Model 2: additionally adjusted for smoking status, alcohol use and physical activity (life style factors).

The significant crude association of SA with HDL cholesterol weakened after adjustment in model 1, and further in model 2 to a nonsignificant level. Also, the association of SA with the number of metabolic syndrome components (Nr.) remained highly statistically significant throughout all models ($Nr._{crude}$: β=0.098, *p*<.001; $Nr._{model\ 2}$: β=0.062, *p*<.001). The graded, positive association between SA and the number of MetSyn components, and SA and quartiles of the individual fully adjusted MetSyn components are shown in Figure 5.1. In sensitivity analyses in which 141 subjects with CVD were excluded excluded, results did not change (data not shown). None of the interaction terms between dimensions with sex were statistically significant, which suggests that associations were largely similar for men and women.

To evaluate whether another measure for somatic symptoms would give comparable results, we repeated the linear regression model analyses with the validated BAI somatic subscale (36). These analyses confirmed an association for the somatic BAI subscale and a much less consistent association for the nonsomatic BAI subscale. The associations with the BAI somatic scale score remained significant in the fully adjusted models for the number of MetSyn components (Nr. MetSyn: β =0.072, *p*<.001), and all MetSyn components, except for HDL cholesterol, which showed a trend toward significance with a β=-0.033, *p*=.08 (WC: β=0.056, *p*<.001; Trig: β=0.083, *p*<.001; Gluc: β=0.038, p=.04; MBP: β=0.046, *p*=.01). There was a strong Intercorrelation between the somatic symptom dimension of the MASQ (SA) and the subscale of the BAI (r_{sBAI}=0.73, *p*<.001). We did not analyze associations with subscales of the IDS-SR because earlier work by Wardenaar et al. (2010) did identify three subscales but none of these was a clear somatic subscale (in factor analyses, the rather restricted somatic items were attributed to all three subscales). So, no valid somatic IDS subscale exists. Therefore, it is not appropriate to use a subscale in a comparative analysis. To explore whether results would also be consistent for the nonsomatic symptom subscale, we also conducted linear regression analyses with the nonsomatic BAI subscale (BAI subjective scale score). We expected that associations for the subjective BAI subscale would be similar to those for the PA and NA dimensions of the MASQ-30, which was confirmed. None of the associations with the BAI subjective scale score were statistically significant in the fully adjusted models, with exception of the number of MetSyn components (β=0.041, *p* =.02).
Regression analyses performed to investigate whether previously found positive associations between MetSyn abnormalities and symptom severity were driven by symptom dimensions, in particular, the SA dimension, showed the following: Initial significant outcomes (in which the number of MetSyn components was the dependent variable and BAI and IDS-SR severity categories were the independent variables) lost statistical significance after adjustment with the SA dimension. This means that the earlier described associations between the high severe groups according to the BAI and IDS-SR with the MetSyn were largely attributable to a high SA score.

Table 5.4: Logistic regression for the association between standard deviations (SDs) of continuous scores on MASQ dimensions and the odds of metabolic syndrome in 2433 subjects

	OR of MetSyn per SD increase of MASQ-D30 dimension	95% CI	*P*-value
Positive Affect			
Crude	1.16	1.05-1.28	.004
Model 1	1.02	0.92-1.14	.67
Model 2	0.99	0.88-1.10	.99
Negative Affect			
Crude	1.01	0.92-1.12	.78
Model 1	1.01	0.99-1.02	.28
Model 2	1.04	0.93-1.16	.51
Somatic Arousal			
Crude	1.19	1.08-1.31	< .001
Model 1	1.18	1.06-1.30	.002
Model 2	1.15	1.04-1.28	.008

Abbreviations: OR, odds ratio per SD increase, by logistic regression analysis; CI, confidence interval
Model 1: adjusted for age, sex, years of education.
Model 2: additionally adjusted for lifestyle factors: smoking status, alcohol use and physical activity.

Symptom dimensions and cluster of the MetSyn

Logistic regression analyses of the symptom dimension with the MetSyn showed a small but significant crude relationship between PA and the MetSyn. NA was not significantly associated with the MetSyn. The initial significant crude relationship between SA and the MetSyn remained statistically significant throughout multivariable adjustment (odds ratio per SD increase, 1.15; 95% confidence interval, 1.04–1.28; *p*=.008) (Table 5.4). Analyses, in which the associations of BAI or IDS severity categories with the MetSyn were adjusted for SA, showed that the severity category indicator lost statistical significance after adjustment.

5.4 Discussion

The main finding of this study is that only SA symptom dimension is strongly and independently associated with most of the MetSyn components (especially WC,

triglycerides, and MBP) and shows a graded association with the number of MetSyn components. Using a dimensional approach, SA was thus associated with an increased metabolic risk. No independent associations between MetSyn with NA and PA were observed. These results are supported by our finding that the somatic scale of the BAI is associated with the MetSyn components, whereas the non-somatic scales are not. Approaching depression and anxiety dimensionally, the aspecific NA dimension and the depression specific PA dimension did not show any association with the MetSyn. We only found a strong and consistent relationship between the somatic arousal dimension and multiple MetSyn components. This is in line with previous research on symptom dimensions of especially depression in relation to somatic outcomes, in which the somatic/affective sub-dimension, rather than other important dimensions (e.g., cognitive/affective and appetitive), was most strongly associated with cardiovascular risk and outcome (De Jonge et al., 2006; Bosch et al., 2009). It seems we are looking at a specific sub-dimension: the “somatic depression/anxiety” sub-dimension. On the one hand, this subtype could be reflective of underlying dysregulated homeostasis mechanisms due to anxious or depressed mood states, such as inflammation (Howren et al., 2009), impaired hypothalamus-pituitary-adrenal axis function (Brown et al., 2004; Vreeburg et al., 2009a), or a higher sympathetic and lower parasympathetic autonomic tone (Licht et al., 2010).

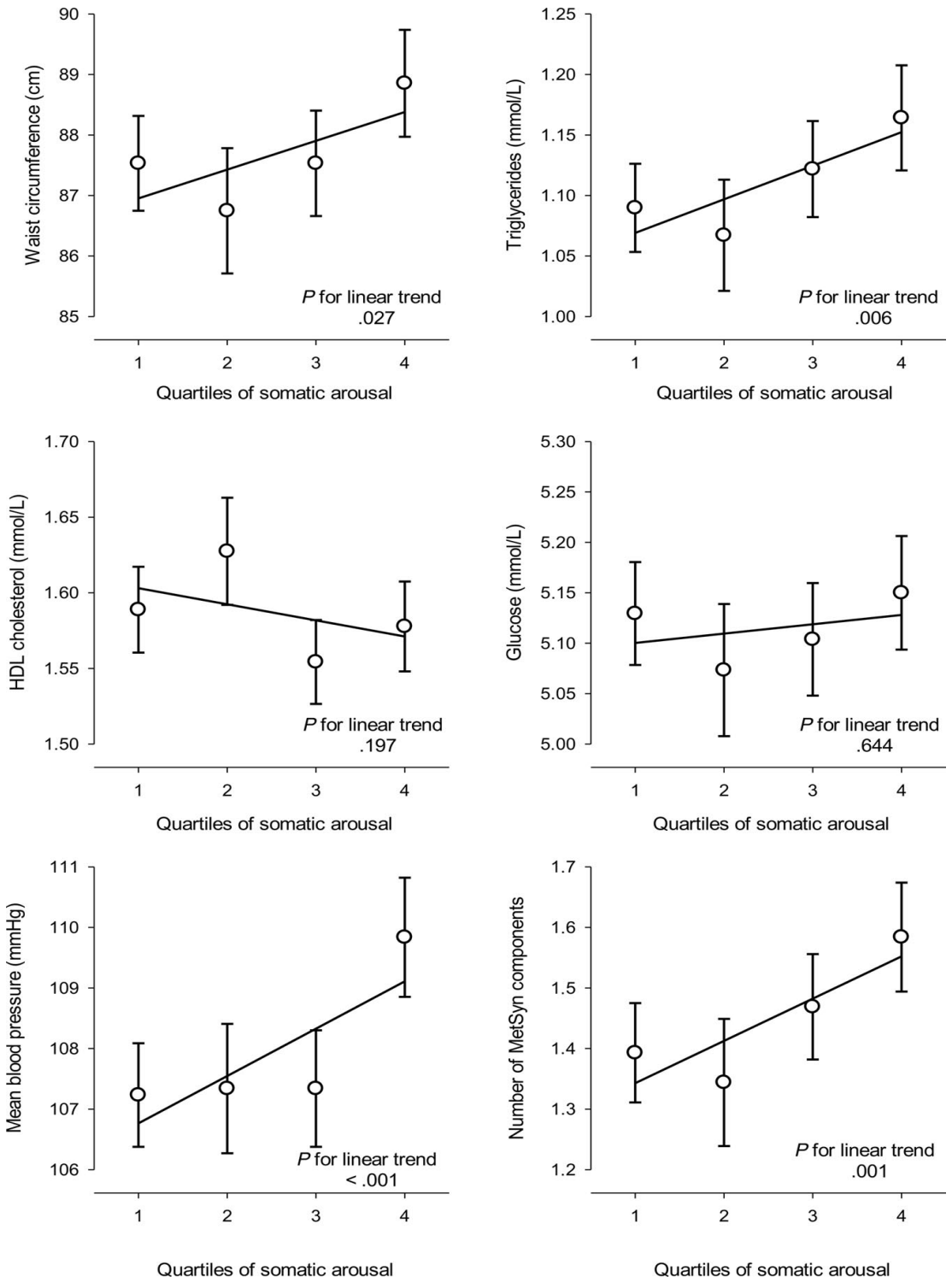

Figure 5.1: Adjusted (geometric) means across quartiles of somatic arousal on the MASQ-D30, for the individual MetSyn components and the total number of MetSyn components. Data are adjusted for age, sex, educational level, alcohol consumption, smoking status and physical activity. Error bars indicate 95% confidence intervals of the mean, and regression lines are shown. $N_{quartile\ 1}$ =744; $N_{quartile\ 2}$ =436; $N_{quartile\ 3}$ =652; $N_{quartile\ 4}$ =601.

Elevated levels of inflammatory markers could induce a depressive episode (48); altered lipid patterns caused by high levels of cortisol (Bjorntorp, 2001; Chrousos, 2000) could lead to other lipid-related symptoms (overweight, abdominal obesity, and hypertriglyceridemia) (Veen et al 2011; Vogelzangs et al., 2009); and activation of sympathetic nervous system leads to increased blood pressure (Shibao et al., 2007) and, thus, to hypertension (Bjorntorp, 2001; Lambert et al., 2010). This network of pathways can, thus, result in an increased metabolic or cardiovascular risk and cardiovascular disease. On the other hand, the reverse mechanism could be active. Ongoing metabolic dysregulations could be causing (especially SA) symptoms of depression and anxiety (Mast et al., 2008l Alexopoulos et al., 1997; Steffens et al., 2002; Ajilore et al., 2007; Huber, 2008). Regardless of the underlying mechanisms and the direction of causality, the dose-response gradient between the number of MetSyn components and levels of SA indicates that, when more SA symptoms are present, more MetSyn abnormalities are present. Apart from biological mechanisms, other processes may be involved during a depressive episode as a consequence of anhedonia, such as altered life-style patterns (poor diet and decreased physical activity) (LaMonte et al., 2005; Hu & Willett, 2002), which might induce metabolic changes and cardiovascular risk factors.

Previous research based on NESDA data (8) showed that the prevalence rates of the MetSyn were increased in those with the highest levels of depressive symptoms based on the BAI and the IDS-SR. After adjustment for the MASQ SA dimension, the earlier described associations lost statistical significance. These results indicate that the earlier described association between MetSyn and the most severe depression and anxiety symptom scales can be explained by the fact that these persons had high scores on the SA dimension.

In terms of metabolic risk evaluation and detection, a dimensional approach has more differentiating capacities compared with the widely used diagnostic DSM-IV categories. The somatic symptom dimension could, therefore, be the key feature in the association between depression/anxiety and somatic outcomes.

Using a dimensional approach, the level of a symptom dimension varies differentially between diagnostic groups (e.g., singular depression, singular anxiety, or comorbid state). At the same time, all symptom dimensions can be present at a significant level within every diagnostic group. This means that the clinical presentation of a subject is dependent on the symptom dimension(s) with the highest scores. Our results demonstrate that the SA dimension is associated with several MetSyn components. The fact that SA levels are not equally high for every depressed and/or anxious subject might explain the inconsistent findings in literature on the association with the MetSyn.

Our study has several strengths. This is, to our knowledge, the first study describing the relationship between depression and anxiety dimensions in relation to the MetSyn. We not only approached the MetSyn and its components as continua, in line with the idea that MetSyn components have a natural continuous distribution (Ingram, 2009), but also depression and anxiety symptom dimensions (Ingram, 2009). Because we

chose this approach, we were able to show a dose-response gradient with SA levels. Furthermore, the results are based on a large sample, making results reliable. Finally, in the analyses, we adjusted for a substantial number of covariates, minimizing the chance that the findings can be explained by confounding.

This study presents some limitations. First, the tripartite model is a rather simple dimensional model. Probably, there are more relevant subdimensions present (Hollander-Gijsman et al., 2010). Second, the sample includes both healthy controls and subjects with (remitted) psychopathology, who were recruited from the community as well as mental healthcare settings. As inpatients were excluded, our results cannot be generalized to this group. Third, the concept of the MetSyn has been criticized (Kahn et al., 2005; Reaven, 2005), and our findings support the idea that it may be worthwhile to study (the number of) individual metabolic components in addition to a dichotomous MetSyn variable. Finally, due to the cross-sectional design, our results cannot be used to make any causal inferences. Prospective studies, especially across more heterogeneous populations, would help to understand the direction of the potential causal relationship.

In this sample, in which previously the association between a categorical diagnosis, on the one hand, and the MetSyn components, on the other hand, was found only for the most severe depressive symptoms (Reedt Dortland et al., 2010), we demonstrate a strong association between the SA symptom dimension and the metabolic syndrome and its individual components, especially WC, triglycerides, and blood pressure, and the number of MetSyn components. Not every depressed subject is at increased metabolic risk. But our findings suggest that those with an elevated SA level are. Those with elevated non-somatic dimensions scores (i.e., PA and NA) did not show an increased metabolic risk. This indicates the additional value of a dimensional approach in terms of metabolic risk evaluation. In addition, we found that the association between depression severity (BAI severity categories) and the MetSyn is, in part, driven by the SA dimension. Although our results need to be replicated, the discriminating ability of a dimensional approach could facilitate the identification of those with a higher metabolic risk within a clinical population with apparently the same diagnoses.