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Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from the Netherlands Study of Depression and Anxiety (NESDA)

Hester E. Duivis [a], Nicole Vogelzangs [b], Nina Kupper [a], Peter de Jonge [a,c,*], Brenda W.J.H. Penninx [b]

[a] *CoRPS-Center of Research on Psychology in Somatic Diseases, Tilburg University, Tilburg, The Netherlands*
[b] *Department of Psychiatry/EMGO+ Institute, VU University Medical Center, Amsterdam, The Netherlands*
[c] *Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

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Summary
Objective: Depression and anxiety have been suggested to be associated with systemic inflammation upregulation. However, results are not always consistent, which may be due to symptom heterogeneity of depression and anxiety. There are some indications that associations with inflammation are mainly driven by somatic symptoms of depression and anxiety. We therefore set out to evaluate the differential association of somatic and cognitive symptoms of depression and anxiety with inflammation, while adjusting for demographic, health related, and lifestyle related variables.
Methods: We evaluated baseline data from 2861 participants from the Netherlands Study of Depression and Anxiety (NESDA). The Inventory of Depressive Symptomatology and the Beck Anxiety Inventory were used to assess depressive symptoms and anxiety symptoms. For both scales somatic and cognitive symptoms scales were calculated. Baseline blood samples were collected to determine high sensitivity C-Reactive Protein (CRP), interleukin (IL)-6, and Tumor Necrosis Factor (TNF)-α. We used linear regression to analyze the associations adjusting for demographics and health indicators and markers for an unhealthy lifestyle.
Results: After adjustment for sociodemographic and health indicators, depressive symptoms were associated with higher levels of CRP, IL-6 and TNF-α. This association was mainly driven by somatic symptoms. For anxiety, somatic symptoms were associated with higher levels of CRP, IL-6

* Corresponding author at: University Medical Center Groningen, Interdisciplinary Center for Psychiatric Epidemiology, cc 72, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel.: +31 50 361 9005.
E-mail address: Peter.de.Jonge@umcg.nl (P. de Jonge).

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and TNF-α, whereas cognitive anxiety symptoms were associated with CRP (men only). Markers of an unhealthy lifestyle explained the significant associations.
Conclusions: Especially somatic symptoms of depression and anxiety are associated with inflammation. However, this association was mostly mediated through unhealthy lifestyles among depressed and anxious individuals.

1. Introduction

Depression and anxiety have been found to be prognostically associated with various somatic conditions, including cardiac disease (van Melle et al., 2004; Meijer et al., 2011), diabetes (Stuart and Baune, 2012) and obesity (Luppino et al., 2010). Low grade inflammation has been proposed as one of the physiological links between both depression and anxiety and adverse somatic outcomes (Howren et al., 2009; Stuart and Baune, 2012). In the last decade a substantial amount of research has been published on the depression–inflammation relationship, in healthy (Dowlati et al., 2010) and cardiac populations (Howren et al., 2009). Most of these studies concern cross-sectional research, although some prospective studies have been published (Gimeno et al., 2009; Stewart et al., 2009; Duivis et al., 2011; Shaffer et al., 2011).

Despite the substantial amount of research published on the depression–inflammation link, results are still conflicting (Howren et al., 2009), with some studies reporting positive associations (Bankier et al., 2009; Pizzi et al., 2010) and others reporting negative findings (Whooley et al., 2007; McGlory, 2009). Stewart et al. (2009) found that depressive symptoms predicted an upregulation of interleukin 6 (IL-6) after a 6-year follow-up in an otherwise healthy sample, but inflammation did not predict depressive symptoms after 6 years. Another study reported that recurrent depressive symptoms were associated with subsequent inflammation, although this association was largely explained by lifestyle behaviors (Duivis et al., 2011). In contrast, Gimeno et al. (2009) found that after 11 years of follow-up, C-Reactive Protein (CRP) and IL-6 were predictive of cognitive symptoms of depression, but not vice versa. It is obvious from the preceding that there is still considerable debate on whether or not depression and inflammation are associated and which factors contribute to this relationship. Meta-analyses (Howren et al., 2009; Dowlati et al., 2010) have also suggested that substantial heterogeneity exists between studies which could be attributed to the differences in the study samples studied or the questionnaires used to determine depressive symptoms.

Another possible explanation for inconsistencies in the depression and inflammation link could be that most studies report only on depression as a whole, whereas it might be more suitable to pay attention to individual depressive symptoms or dimension scores in relation to inflammation (Elovainio et al., 2009). Based on the sickness behavior theory (Dantzer et al., 2008), which argues that somatic depressive-like symptoms such as fatigue, sleeping problems, anorexia, and motor slowing can be the result of upregulated inflammation levels, one could expect that possible associations between depression and inflammation are being missed when taking depression as a whole into account. It could thus be hypothesized that somatic symptoms show a stronger association with inflammation than cognitive symptoms, and this should to be taken into account when investigating the depression–inflammation relationship.

In the case of anxiety, less research is conducted on the associations with inflammation. However, there is some evidence suggesting that anxiety is associated with inflammation (Bankier et al., 2008; Hoge et al., 2009; von Kanel et al., 2010) reporting small to large effect sizes. However, these studies included relatively small samples ($N < 120$), which could mask true effect sizes. As with depression, anxiety also consists of somatic and cognitive symptoms. Although no study has investigated the association of somatic and cognitive anxiety symptoms with inflammation, one study found that in women somatic symptoms of anxiety were associated with an increased CHD risk, whereas more psychological symptoms of anxiety were not (Nabi et al., 2010).

An additional possible explanation for prior conflicting results of studies examining the link between anxiety/depression and inflammation could be the possible mediating effects of for instance lifestyle behaviors such as smoking, physical activity, alcohol consumption and overweight. These factors are not always included in multivariable analyses, even though there is considerable evidence that markers of an unhealthy lifestyle are associated with both depressive (Wiesbeck et al., 2008; Patten et al., 2009; Luppino et al., 2010) and anxiety symptoms (Mykletun et al., 2008; Strine et al., 2008) as well as inflammation (Eckel et al., 2005; Reichert et al., 2009; Dod et al., 2010). For instance, the meta-analysis by Howren et al. (2009) found that effect sizes were considerably smaller in studies that adjusted for body mass index (BMI). Furthermore, a meta-analysis on depression and overweight reported that obesity can be the result of depression, but also vice versa. Obesity has also been found to be associated with higher levels of inflammation (O'Connor et al., 2009). Finally, as the majority of studies has a rather small sample size ($N < 100$), reported effect sizes can be masked. In order to detect true significant associations and to be able to adjust for important confounders or mediators, large sample sizes are needed.

We previously found in a large sample of 2415 participants that depression diagnosis was associated with immune dysregulation in men with a late onset depression (Vogelzangs et al., 2012), but we did not distinguish in symptom dimensions of depression. We therefore set out to conduct secondary data-analysis in this same sample in which we will thoroughly investigate the relationship between symptoms profiles of depression and anxiety with inflammation. We hypothesize that (1) mainly the somatic symptoms of depression and anxiety are associated with inflammation, and (2) that the association between (somatic) depressive and anxiety symptoms and inflammation will be partly explained by markers of an unhealthy lifestyle such as smoking, alcohol intake, BMI and physical inactivity.

2. Methods

2.1. Design and participants

NESDA is an ongoing multi-center cohort study on the course of depressive and anxiety disorders in the adult (18–65 years) population. A total of 2981 participants were recruited from the community (n = 564:19%), primary care (n = 1610: 54%) and specialized mental health care (n = 807: 27%) including controls and persons with a current or past depressive and/or anxiety disorder for the baseline assessment from 2004 to 2007. Exclusion criteria were a primary clinical diagnosis of a psychiatric disorder like psychotic disorder, obsessive compulsive disorder, bipolar disorder or severe addiction disorder and not being fluent in Dutch. A detailed description of the NESDA study design and sampling procedures can be found elsewhere (Penninx et al., 2008). Participants who had missing data on either CRP, IL-6, or TNF-α were excluded from the analyses (n = 73). Additionally, participants who had not returned the questionnaire or had too many missing values on the Inventory of Depressive Symptomatology (IDS) (>6 missing items) or Beck Anxiety Inventory (BAI) (n = 47) (>8 missing items) were also excluded. This resulted in a total sample of 2861 participants. This final sample consisted of participant with a current or past depression and/or anxiety diagnosis (N = 2231) and controls (N = 630). Excluded participants were on average more often male (43% vs. 33%, p = .02), current smokers (50% vs. 38.1%, p = .01) and more often used tetracyclic antidepressants (4.2% vs. 1.7%, p = .05). On average excluded participants attained less years of education (mean = 11.5 vs. 12.2, p = .02). Their mean scores on the IDS somatic scale were on average slightly higher (9 vs. 7.9, p = .04). Total IDS scores, IDS cognitive scale scores, BAI total scores, BAI somatic, and BAI cognitive scores and inflammation levels were on average not different between excluded and included participants ($p > .05$). The study protocol was approved by the Ethical Review Board of each participating center, and all subjects provided a written informed consent.

2.2. Depressive and anxiety symptoms

2.2.1. Depressive symptoms

The 30-item IDS self-report version was administered (Rush et al., 1996). The IDS assesses the DSM-IV criterion symptom domains for major depressive disorder, and in addition commonly associated symptoms (e.g. anxiety, irritability) and symptoms relevant to melancholic and atypical features. The questionnaire consists of 30 items, each with four answer options (coded 0 through 3). The questionnaire uses a 7-day timeframe for assessing symptom severity. The psychometric properties of the IDS have shown to be acceptable; high correlations were found between the IDS scores on the Hamilton Depression Rating Scale and the Beck Depression Inventory-I (www.ids-qids.org).

Principal Component Analysis performed by Wardenaar et al. (2010) on the IDS revealed three dimensions, a mood cognition dimension, an anxiety arousal dimension and a sleep dimension. However, none of these subscales represent a pure somatic or cognitive symptoms scale as based on the symptoms from the DSM-IV (somatic: weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, and loss of energy of feeling tired; cognitive: anhedonia, feeling depressed, feelings of worthlessness, concentration problems, and recurrent thoughts of death). The anxiety arousal dimension encompasses somatic symptoms such as psychomotor agitation and psychomotor slowing. However, it also contains somatic complaints, gastrointestinal complaints and panic/phobic symptoms (Wardenaar et al., 2010), which are not a part of sickness behavior. We therefore created a pure somatic and a pure cognitive symptom scale based on DSM-IV criteria and previous research on somatic and cognitive depression symptoms (de Jonge et al., 2007; Hoen et al., 2010) (Table 1). Both the somatic and the cognitive subscale consisted of 10 items derived from the IDS (Table 1). Because the sleep symptoms were over represented (4 items; falling asleep, sleep during the night, waking up early, and sleeping too much), we created a variable combining the four sleep items by taking the mean score of all four items. This resulted in Cronbach's α = 0.69 for the somatic symptom dimension and Cronbach's α = 0.89 for the cognitive symptom dimension.

2.2.2. Anxiety symptoms

We used the 21-item BAI (Beck et al., 1988) to measure symptoms of generalized anxiety and panic symptoms. Respondents are asked to rate how much they have been bothered by each symptom over the past week on a 4-point scale, ranging from 0 (not at all) to 3 (severely, I could barely stand it). The BAI is scored by summing the ratings for all of the 21 symptoms to obtain a total score that can range from 0 to 63. The internal and test–retest reliability and validity of the BAI are well-established (Beck et al., 1988; Osman et al., 2002)

Previous research has shown that factorial validity analysis revealed that the BAI consists of two subscales accounting for 84% of the variance i.e. a somatic subscale and a subjective – or cognitive – subscale (Kabacoff et al., 1997). The somatic subscale consists of 14 items (Cronbach's alpha = .90) such as numbness or tingling, feeling hot, difficulty in breathing, and heart pounding and the cognitive subscale consists of 7 items (Cronbach's alpha = .88) such as fear of losing control, fear of dying, and being terrified or afraid (Table 1). These two subscales still discriminate adequately between patients with and without an anxiety disorder (Kabacoff et al., 1997).

2.3. Inflammatory markers

As described before (Vogelzangs et al., 2012) markers of inflammation were assessed at the baseline NESDA assessment and include high sensitivity C-Reactive Protein (CRP), interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF)-α which have been found to be associated with depressive symptoms and major depression in earlier studies (Howren et al., 2009; Dowlati et al., 2010; Vogelzangs et al., 2012). CRP is a non-specific acute phase protein synthesized in the liver in response to amongst others stimulation from IL-6 and IL-6 is a pro-inflammatory cytokine secreted by activated macrophages. TNF-α is the prototypic ligand of the TNF superfamily and plays a central role in inflammation. After an overnight fast, 50 ml blood was drawn which was immediately transferred to a local laboratory and kept frozen at −80 °C. High-sensitivity plasma levels of CRP were measured in duplicate

Table 1 Overview of the somatic and cognitive symptoms of depression (IDS) and anxiety (BAI) as measured with the items of the Inventory of Depressive Symptoms.

Somatic symptoms	Cognitive symptoms
(a) Depressive symptoms (IDS)	
Falling asleep[a]	Feeling sad
Sleep during the night[a]	Feeling irritable
Waking up to early[a]	The quality of mood
Sleeping too much[a]	Concentration/ decision making
Decreased or increased appetite	View of the self
Decreased or increased weight	Thoughts of death or suicide
Energy level	General interest
Feeling slowed down	Capacity for pleasure or enjoyment (excluding sex)
Feeling restless	Interest in sex
Leaden paralysis/physical energy	Interpersonal sensitivity
(b) Anxiety symptoms (BAI)	
Numbness or tingling	Unable to relax
Feeling hot	Fear of worst happening
Wobbliness in legs	Terrified or afraid
Dizzy or light-headed	Nervous
Heart pounding/racing	Fear of losing control
Unsteady	Fear of dying
Feeling of choking	Scared
Hands trembling	
Shaky/unsteady	
Difficulty in breathing	
Indigestion	
Faint/light-headed	
Face flushed	
Hot/cold sweats	

IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory.
[a] Merged to one variable reflecting sleeping problems.

by an in-house ELISA based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). The CRP assay was standardized against the CRM 470 reference agent. The lower detection limit of CRP is 0.1 mg/l and the sensitivity is 0.05 mg/l. Intra- and inter-assay coefficients of variation were 5% and 10%, respectively. Plasma IL-6 levels were measured in duplicate by a high sensitivity enzyme-linked immunosorbent assay (PeliKine Compact™ ELISA, Sanquin, Amsterdam). The IL-6 assay was standardized against a recombinant human IL-6 standard. The lower detection limit of IL-6 is 0.35 pg/ml and the sensitivity 0.10 pg/ml. Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. Plasma TNF-α levels were assayed in duplicate at Good Biomarker Science, Leiden, The Netherlands, using a high-sensitivity solid phase ELISA (Quantikine® HS Human TNF-α Immunoassay, R&D systems Inc, Minneapolis, MN, United States). The TNF-α assay was calibrated against a highly purified *Escherichia coli*-expressed recombinant human TNF-α. The lower detection limit of TNF-α is 0.10 pg/ml and the sensitivity 0.11 pg/ml. Intra- and inter-assay coefficients of variation were 10% and 15%, respectively. The distribution of CRP, IL-6, and TNF-α was tested for normality using skewness and kurtosis. These tests revealed that all three markers were not normally distributed. Values were therefore log transformed, which resulted in normal distributed variables.

Blood was collected between 0800 h and 0900 h in the morning of the baseline assessment. On average, blood was collected 5 days after the IDS and BAI were filled out (SD = 23 days).

2.4. Covariates

Sociodemographic factors included age, sex, and years of education. In addition, some health factors were assessed. In order to ascertain the presence of cardiovascular disease (CVD), self-reports and medication use were used (based on drug container inspection and World Health Organization Anatomic Therapeutic Chemical (ATC) coding; see Vogelzangs et al. (2010) for a detailed description). Presence of diabetes was based on fasting plasma glucose level $\geq$ 7.0 mmol/l or use of anti-diabetic medication (ATC code A10).

Participants were asked to bring the containers of the medication used during the month prior to the interview, so the research assistant could copy medicine names. We used the ATC classification (WHO, 2008) to classify frequently used (>50% of all days in past month) medication (Table 2). We included use of systemic anti-inflammatory medication (M01A, M01B, A07EB, and A07EC) and statin use (C10AA, C10B) as covariates. For antidepressant medication, selective serotonin reuptake inhibitors (SSRI; N06AB), serotonin–norepinephrine reuptake inhibitors (SNRI; SNRI; N06AX16 and N06AX21), tricyclic antidepressants (TCA; N06AA), and tetracyclic antidepressants (TeCA; N06AX03, N06AX05 and N06AX11) were included as covariates.

Markers of an unhealthy lifestyle were considered as covariates, because they have been linked to both psychopathology and inflammation. Smoking status was categorized as nonsmoker, former, and current smoker and alcohol intake was measured with the Alcohol Use Disorders Identification Test (Saunders et al., 1993; Boschloo et al., 2010) and defined as <1 glass per week, 1–14 glasses per week and >14 glasses per week. Body Mass Index (BMI) was determined as measured weight in kilograms divided by the square of the measured height in meters. Physical activity was assessed using the International Physical Activity Questionnaire (Craig et al., 2003). This 7-item instrument assesses the amount of time spent on vigorous, moderate, walking and sitting activities over the last 7 days. For instance, participants have to indicate on how many days during the last seven days they participated in heavy physical activities such as lifting, aerobics, or digging (during at least 10 min) and how many hours and/or minutes they spent on these activities on average. These scores are then used to calculate the total Metabolic Equivalent Total (MET)-minutes per week (ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity) (www.ipaq.ski.se).

2.5. Statistical analyses

Characteristics of the participants were compared across men and women using independent *t*-tests for continuous

Table 2 Descriptives for the total sample, and for men and women separately.

	Total N = 2861		Men N = 950		Women N = 1911		
	N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	p*
Demographics + health							
Age	41.9	13.0	43.6	12.8	41.1	13.1	<.001
Education (years)	12.2	3.3	12.2	3.3	12.2	3.3	.685
Health							
Diabetes	138	5%	75	8%	63	3%	<.001
Cardiovasculair disease	163	6%	91	10%	72	4%	<.001
Medication use							
Anti-inflammatory drugs	129	5%	38	4%	91	5%	.355
Statins	191	7%	99	10%	92	5%	<.001
Antidepressants	697	24%	224	24%	473	25%	.491
SSRI	481	17%	150	16%	331	17%	.302
SNRI	110	4%	40	4%	70	4%	.473
TCA	77	3%	21	2%	56	3%	.263
TeCA	50	2%	24	3%	26	1%	.025
Markers of unhealthy lifestyle							
Smoking							
No	802	28%	229	24%	573	30%	.003
Former	970	34%	331	35%	639	33%	
Current	1089	38%	390	41%	699	37%	
Alcohol intake							
<1 glass per week	923	32%	207	22%	716	37%	<.001
1–14 glasses per week	1608	56%	635	67%	973	51%	
>14 glasses per week	330	12%	108	11%	222	12%	
BMI	25.6	4.9	26.2	4.5	25.3	5.2	<.001
Physical activity (in MET-minutes per week)	3678	3028	3728	3296	3652	2887	.544
Depression and anxiety							
IDS total score	21.4	14.1	20.8	14.7	21.8	13.8	.074
IDS somatic score	7.9	5.1	7.5	5.4	8.1	5.0	.004
IDS cognitive score	7.7	6.4	7.6	6.6	7.7	6.3	.725
BAI total score	12.0	10.6	11.2	10.6	12.5	10.6	.002
BAI somatic score	7.3	6.9	6.7	6.9	7.5	6.8	.004
BAI cognitive score	4.8	4.5	4.4	4.4	4.9	4.6	.005
Inflammatory markers							
C-Reactive Protein (mg/L)	0.25	1.24	0.11	1.21	0.32	1.25	<.001
Interleukin 6 (pg/L)	−0.28	0.98	−0.22	0.93	−0.31	1.00	.023
Tumor Necrosis Factor-alpha (pg/L)	−0.18	0.63	−0.17	0.55	−0.19	0.66	.382

BMI, body mass index; IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory.
* Calulated with *t*-tests, chi-square tests, ANOVA.

variables, chi-square statistics and ANOVA's for dichotomous and categorical variables, and Mann–Whitney *U* for the inflammatory markers.

The relationships of depressive symptoms and anxiety symptoms with inflammation were analyzed using linear regression analyses. Total depressive symptoms score, somatic symptoms of depression, cognitive symptoms of depression, total anxiety symptoms score, somatic symptoms of anxiety, and cognitive symptoms of anxiety were separately analyzed as predictors of CRP, IL-6, and TNF-α. In total, 24 models were analyzed. First unadjusted regression analyses were conducted. Next, a demographics and health model was evaluated, adjusting for age, sex, education level, presence of CVD and diabetes, anti-inflammatory medication and statin use. Secondly, when significant correlations between inflammatory markers and specific antidepressant medications were present, analyses were further adjusted for those specific medications. We chose to restrict analyses to these medications, because adjusting for all antidepressant medication possibly leads to overadjusting for those participants with the most severe depressive and anxiety symptoms. CRP was significantly negatively correlated with SSRI, and positively correlated with TCA, and TeCA use ($p < .05$). TNF-α was positively correlated with TCA ($p < .01$). There were no significant correlations between IL-6 and antidepressant medication use. Because of possible mediating effects of markers of an unhealthy lifestyle (O'Connor et al., 2009) smoking, alcohol intake, BMI, and physical activity were added in a final step to the previous models. To further investigate the mediating effects of

Table 3 Linear regression analyses for depressive symptoms (IDS) and inflammation.

	CRP		IL-6		TNF-α	
	β	p	β	p	β	p
IDS total score	Men		Total sample		Total sample	
Unadjusted	.162	**<.001**	.074	**<.001**	.061	**.001**
Demographics + health	.104	**.001**	.046	**.015**	.039	**.042**
Antidepressant medication	.092	**.005**	.046	**.015**	.035	.068
Lifestyle	.043	.159	.010	.586	.022	.273
IDS total score	Women					
Unadjusted	.057	**.012**				
Demographics + health	.015	.517				
Antidepressant medication	−.002	.929				
Lifestyle	−.038	.09				
IDS somatic	Total sample		Total sample		Total sample	
Unadjusted	.124	**<.001**	.088	**<.001**	.070	**<.001**
Demographics + health	.078	**<.001**	.054	**.005**	.045	**.018**
Antidepressant medication	.067	**<.001**	.054	**.005**	.042	**.028**
Lifestyle	.022	.231	.017	.366	.028	.155
IDS cognitive	Total sample		Total sample		Total sample	
Unadjusted	.054	**.004**	.046	**.015**	.050	**.008**
Demographics + health	.021	.268	.028	.128	.035	.067
Antidepressant medication	.004	.830	.028	.128	.031	.099
Lifestyle	−.028	.116	−.001	.954	.020	.303

β reflects standardized coefficients.
Demographics + health: age, sex, years of education, presence of cardiovascular disease and diabetes, anti-inflammatory medication use, and statin use.
Antidepressant medication: Demographics + health + antidepressant medication; only adjusted for antidepressant medication use when significant correlation was present with inflammatory marker. CRP analyses were adjusted for selective serotonin reuptake inhibitor ($p = .04$), tricyclic antidepressants ($p < .01$), and tetracyclic antidepressants ($p < .01$). TNF-α analyses were adjusted for tricyclic antidepressants ($p < .01$). There were no significant correlations between IL-6 and antidepressant medication use, and therefore these analyses were not further adjusted.
Lifestyle: Demographics + health + antidepressant medication + smoking, alcohol intake, BMI, and physical activity.
IDS, Inventory of Depressive Symptomatology; CRP, C-Reactive Protein; IL-6, interleukin 6; TNF-α, Tumor Necrosis Factor-alpha.
Bold faced: $p \leq .05$.

markers of an unhealthy lifestyle, mediation analyses were conducted using the indirect method by Preacher and Hayes (Preacher and Hayes, 2008). This method estimates total, direct, and indirect unstandardized effects of the predictor (IDS or BAI [sub]scales) on the outcome (inflammatory biomarker) through the mediator variables smoking, alcohol intake, BMI, and physical activity, while controlling for covariates (Preacher and Hayes, 2008). Mediation analyses will only be conducted for significant associations found with linear regression analyses after adjustment for demographics, health, and medication use. Furthermore, mediation analyses will be adjusted for demographics, health, and medication use.

Since Vogelzangs et al. (2012) found sex differences in the association between depression and inflammation, we tested for the presence of interaction effects for sex and included the following interaction terms for sex (sex*IDS total, sex*IDS somatic, sex*IDS cognitive, sex*BAI total, sex*BAI somatic, sex*BAI cognitive) in respective models. When the interaction effect was found significant, regression analyses were repeated stratified for sex.

3. Results

3.1. Baseline characteristics

Table 2 shows the descriptive characteristics of the total study sample ($N = 2861$) of which 950 were male (33.2%). Men were significantly older than women (mean age 43.6 vs. 41.1, $p < .001$), were more often smoker (41% vs. 37%, $p = .003$), and had higher levels of BMI (mean BMI 26.2 vs. 25.3, $p < .001$). Women more often used <1 glass of alcohol per week (37% vs. 22%) and men more often used 1−14 glasses of alcohol per week (67% vs. 51%) ($p < .001$). Furthermore, cardiovascular disease ($p < .001$) and diabetes ($p < .001$) were more present in men and men used statins ($p < .001$) and TeCA ($p = .025$) more often than women. Men had higher IDS somatic symptoms scores than women ($p = .004$), whereas women had higher BAI total scores ($p = .002$), BAI somatic ($p = .004$), and BAI cognitive scores ($p = .005$). Finally, women had on average higher of CRP ($p < .001$) and lower levels of IL-6 ($p = .023$) (Table 2).

Table 4 Linear regression analyses for anxiety symptoms (BAI) and inflammation.

	CRP		IL-6		TNF-α	
	β	p	β	p	β	p
BAI total score	Men		Total sample		Total sample	
Unadjusted	.147	**<.001**	.059	**.002**	.057	**.002**
Demographics + health	.106	**.001**	.034	.070	.035	.067
Antidepressant medication	.094	**.003**	−.034	.070	.031	.107
Lifestyle	.038	.203	.001	.948	.021	.283
BAI total score	Women					
Unadjusted	.055	**.015**				
Demographics + health	.010	.682				
Antidepressant medication	−.004	.856				
Lifestyle	−.022	.327				
BAI somatic	Men		Total sample		Total sample	
Unadjusted	.165	**<.001**	.080	**<.001**	.064	**.001**
Demographics + health	.116	**<.001**	.050	**.008**	.038	**.046**
Antidepressant medication	.105	**.001**	.050	**.008**	.034	.080
Lifestyle	.045	.134	.015	.425	.023	.246
BAI somatic	Women					
Unadjusted	.073	**.002**				
Demographics + health	.026	.272				
Antidepressant medication	.012	.627				
Lifestyle	−.012	.601				
BAI cognitive	Men		Total sample		Total sample	
Unadjusted	.095	**.003**	.017	.356	.037	**.050**
Demographics + health	.073	**.018**	.005	.774	.024	.208
Antidepressant medication	.059	.060	.005	.774	.021	.266
Lifestyle	.020	.486	−.019	.305	.014	.454
BAI cognitive	Women					
Unadjusted	.020	.372				
Demographics + health	−.015	.503				
Antidepressant medication	−.026	.270				
Lifestyle	−.031	.150				

β reflects standardized coefficients.
Demographics + health: age, sex, years of education, presence of cardiovascular disease and diabetes, anti-inflammatory medication use, and statin use.
Antidepressant medication: Demographics + health + antidepressant medication; only adjusted for antidepressant medication use when significant correlation was present with inflammatory marker. CRP analyses were adjusted for selective serotonin reuptake inhibitor ($p = .04$), tricyclic antidepressants ($p < .01$), and tetracyclic antidepressants ($p < .01$). TNF-α analyses were adjusted for tricyclic antidepressants ($p < .01$). There were no significant correlations between IL-6 and antidepressant medication use, and therefore these analyses were not further adjusted.
Lifestyle: Demographics + health + antidepressant medication + smoking, alcohol intake, BMI, and physical activity.
BAI, Beck Anxiety Inventory; CRP, C-Reactive Protein; IL-6, interleukin 6; TNF-α, Tumor Necrosis Factor-alpha.
Bold faced: $p \leq .05$.

3.2. Symptoms of depression and inflammation

Table 3 shows results of the linear regression analyses associating depressive symptoms with inflammation. Significant sex interactions were found with depressive symptoms (IDS total score) predicting CRP (IDS: $\beta = .192$, $p = .003$; sex: $\beta = .156$, $p \leq .001$; IDS*sex $\beta = -.164$, $p = .02$), which lead us to stratify the concerning analyses for sex. Considering somatic symptoms and cognitive symptoms of depression, there were no significant interactions with sex for any of the markers (all p values for sex interactions $> .06$).

3.2.1. IDS total score

In line with our previous findings (Vogelzangs et al., 2012), unadjusted analyses showed a positive significant association between IDS total score and CRP (men: $\beta = .192$, $p = .003$; women $\beta = .057$, $p = .012$), IL-6 ($\beta = .074$, $p < .001$), and TNF-α ($\beta = .061$, $p = .001$). Demographic and health adjusted regression analyses revealed a positive significant association between IDS total score and CRP for (men only: $\beta = .104$, $p < .001$), IL-6 ($\beta = .046$, $p = .015$) and TNF-α ($\beta = .039$, $p = .042$). Additional adjustment for antidepressant use that showed an association with inflammatory markers, only had an effect on the association between IDS total score

Table 5 Summary of Preacher and Hayes mediator model analyses (1000 bootstraps) between IDS/BAI (IV), and inflammation (DV).[a]

Independent variables (IV)	Mediating v ariables (M)	Dependent variable (DV)	Effect of IV on M (a)	Effect of M on DV (b)	Direct effect (c′)		Total effect (c)	
					Effect	*p*	Effect	*p*
IDS total score (men only)		CRP			.005	.061	.008	.005
	BMI	CRP	.015	.091**				
	Physical activity	CRP	−17.77*	.000				
	Smoking	CRP	.004*	.260**				
	Alcohol use	CRP	−.004**	−.040				
IDS total score		IL-6			.002	.260	.003	.015
	BMI	IL-6	.025**	.038**				
	Physical activity	IL-6	−19.73**	.000				
	Smoking	IL-6	.005**	.088**				
	Alcohol use	IL-6	−.004**	−.042				
IDS somatic score		CRP			.005	.262	.015	.002
	BMI	CRP	.080**	.103**				
	Physical activity	CRP	−25.90*	.000				
	Smoking	CRP	.010**	.108**				
	Alcohol use	CRP	−.007**	−.031				
IDS somatic score		IL-6			.005	.150	.010	.004
	BMI	IL-6	.088**	.039**				
	Physical activity	IL-6	−34.081**	.000				
	Smoking	IL-6	.012**	.088**				
	Alcohol use	IL-6	−.009**	−.042				
IDS somatic score		TNF-α			.004	.082	.005	.027
	BMI	TNF-α	.086**	.010**				
	Physical activity	TNF-α	−32.37**	.000				
	Smoking	TNF-α	.012**	−.017				
	Alcohol use	TNF-α	−.009**	−.048				
BAI total score (men only)		CRP			.006	.089	.011	.003
	BMI	CRP	.036**	.090**				
	Physical activity	CRP	−24.90*	.000				
	Smoking	CRP	.004	.263**				
	Alcohol use	CRP	−.003	−.046				
BAI somatic score (men only)		CRP			.010	.047	.018	.001
	BMI	CRP	.061**	.090**				
	Physical activity	CRP	−24.40	.000				
	Smoking	CRP	.007	.262**				
	Alcohol use	CRP	−.004	−.045				
BAI somatic score		IL-6			.004	.177	.007	.009
	BMI	IL-6	.045**	.038**				
	Physical activity	IL-6	−25.50**	.000				
	Smoking	IL-6	.014**	.087**				
	Alcohol use	IL-6	−.006**	−.043				

IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory.

[a] Adjusted for age, gender, years of education, presence of cardiovascular disease and diabetes, anti-inflammatory medication use, statin use, and anti-depressant medication use.

* $p < .05$.

** $p < .001$.

and TNF-α (adjusted for TCA; $\beta = .035$, $p = .068$). Final additional adjustment for lifestyle made the remaining associations non-significant for all three markers ($p > .15$).

Mediation analyses were conducted for IDS total score and CRP (men only) and IL-6 which both had a significant total effect (c path) (Table 5). The direct effect was not significant for IDS total score and CRP and IL-6 (c′ path) (Table 5) which suggests a mediation effect of the mediator variables. Significant associations were found for IDS total score and higher BMI, smoking, physical activity, and alcohol use (a path)

(Table 5). Both a higher BMI and smoking were significantly associated with CRP and IL-6 (path b) (Table 5). In sum, these analyses suggest an overall effect of IDS on CRP and IL-6, with BMI and smoking largely mediating this effect.

3.2.2. IDS somatic symptoms

Somatic symptoms of depression were significantly associated with all three markers in an unadjusted model (CRP: $\beta = .124$ $p < .001$; IL-6 $\beta = .088$, $p < .001$, TNF-α: $\beta = .070$, $p < .001$). All associations remained significant after adjustment for demographics and health (CRP: $\beta = .078$, $p < .001$; IL-6: $\beta = .054$, $p \leq .001$, and TNF-α: $\beta = .045$, $p = .018$). Final adjustment for lifestyle made the association non-significant for CRP, IL-6, and TNF-α.

Mediation analyses showed a direct association between somatic symptoms of depression and BMI, physical activity, smoking, and alcohol use (a path) and a direct association between BMI and smoking status and CRP and IL-6 (b path) (Table 5). Furthermore, a direct association was found for BMI and TNF-α (b path) (Table 5). Although total effects were found for somatic symptoms of depression and all three markers (c path), no significant direct effects were found for somatic symptoms of depression and any of the markers (c′ path) (Table 5). Taken together, these results imply an overall effect of IDS somatic symptoms on CRP, IL-6, and TNF-α with BMI and smoking mediating this effect.

3.2.3. IDS cognitive symptoms

Cognitive symptoms of depression were significantly associated with CRP ($\beta = .054$, $p = .004$) IL-6 ($\beta = .046$, $p = .015$), and TNF-α ($\beta = .050$, $p = .008$). After adjustment for demographics and health, all associations diminished to non-significance.

3.3. Symptoms of anxiety and inflammation

Table 4 shows the results of the linear regression analyses associating anxiety symptoms with inflammation. Significant interactions were found for sex and BAI total score when analyzing CRP (BAI total score: $\beta = .192$, $p = .004$; sex: $\beta = .140$, $p < .001$; BAI*sex: $\beta = -.166$, $p = .020$), sex and somatic symptoms of anxiety (BAI somatic $\beta = 203$, $p = .003$: sex: $\beta = .135$, $p < .001$; BAI somatic* sex: $\beta = -.162$, $p = .021$), and sex and cognitive symptoms of anxiety (BAI cognitive: $\beta = .145$, $p = .036$; sex: $\beta = .132$, $p < .001$; BAI cognitive*sex: $\beta = -.141$, $p = .051$). These results will therefore be presented stratified for sex. No sex-interactions were found for IL-6 or TNF-α (all $p > .05$).

3.3.1. BAI total score

BAI total score was significantly associated with CRP (men: $\beta = .147$, $p < .001$; women: $\beta = .055$, $p = .015$), IL-6 ($\beta = .059$, $p = .002$), and TNF-α ($\beta = .057$, $p = .002$). Adjusting for demographics and health only yielded significant association between BAI somatic symptoms and CRP in men ($\beta = .106$, $p < .001$). Final adjustment for lifestyle diminished the association to non-significance ($\beta = .038$, $p = .203$).

Additional mediation analyses showed a direct effect of BAI total score on BMI and physical activity (a path) and a direct effect of BMI and smoking status on CRP (b path) (Table 5). Significant total effects were found for BAI total score and CRP (c path) (Table 5). No significant direct effects were found for BAI total score and CRP (c′ path) (Table 5), which suggests an overall effect of BAI total score on CRP levels with BMI mediating this effect.

3.3.2. BAI somatic symptoms

Unadjusted regression analyses showed that somatic symptoms of anxiety were significantly associated with CRP (men: $\beta = .165$, $p < .001$; women: $\beta = .073$, $p = .002$), IL-6 ($\beta = .080$, $p < .001$), and TNF-α ($\beta = .064$, $p = .001$). The associations remained significant after adjustment for demographics and health (CRP men only: $\beta = .116$, $p < .001$; IL-6: $\beta = .050$, $p = .008$; TNF-α: $\beta = .038$, $p = .046$). Additional adjustments for antidepressant use diminished the association between somatic symptoms and TNF-α (adjusted for TCA; $\beta = .034$, $p = .080$). Finally, adjusting for lifestyle resulted in diminished, non-significant associations for somatic ($\beta = .045$, $p = .134$) symptoms of anxiety and CRP and for somatic anxiety symptoms and IL-6 ($\beta = .015$, $p = .425$).

Mediation analyses showed a direct effect of somatic symptoms of anxiety on BMI, smoking status, physical activity and alcohol use (a path) (Table 5). BMI and smoking status showed a direct effect on CRP and IL-6 (b path) (Table 5). Significant total effects were found for somatic symptoms of anxiety and CRP and IL-6 (c path) (Table 5). Significant direct effects were only found for somatic symptoms of anxiety and CRP (c′ path) (Table 5). This suggests an overall effect of somatic symptoms of anxiety on CRP and IL-6 levels with BMI and smoking largely mediating this effect, although for CRP some non-mediated association remained.

3.3.3. BAI cognitive symptoms

Unadjusted regression analyses revealed significant association between CRP (men only $\beta = .095$, $p = .003$) and TNF-α ($\beta = .037$, $p = .050$). After adjusting for demographics and health cognitive symptoms of anxiety remained associated with CRP (men) only ($\beta = .073$, $p = .018$). No associations were found between cognitive anxiety symptoms and IL-6 or TNF-α. Further adjustment for antidepressant use diminished the association between cognitive symptoms and CRP (adjusted for SSRI, TCA, and TeCA; $\beta = .059$, $p = .060$).

4. Discussion

This study shows that higher depressive symptoms were associated with higher inflammatory levels of CRP, IL-6, and TNF-α, but this was mainly driven by the somatic — and not the cognitive — symptoms of depression. This supports the hypothesis that somatic symptoms and cognitive symptoms of depression are differently associated with inflammation. Regarding symptoms of anxiety, total, somatic and cognitive symptoms were all similarly associated with higher CRP (men only). IL-6 and TNF-α levels were only associated with somatic symptoms of anxiety. For all significant associations, lifestyle played an important role, with BMI explaining most of the relationship.

The results from this study support the hypothesis that somatic and cognitive symptoms are differently associated with inflammation suggesting that the association between depression and inflammation is mainly driven by somatic symptoms. This is in concordance with some previous

findings. Elovainio et al. (2009) found that somatic symptoms were more strongly associated with CRP in men than in women, even after full adjustment for covariates. In contrast to our findings, Elovainio and colleagues found significant associations between cognitive symptoms and CRP. However, these were unadjusted or for every covariate separately adjusted analyses. Contradictory findings have also been reported. Kupper et al. (2012) found that both somatic and cognitive symptoms were cross-sectionally associated with inflammation in a sample of heart failure patients. Furthermore, cognitive symptoms of depression were associated with subsequent inflammation, whereas change in somatic symptoms over a 12 month period were associated with inflammation (Kupper et al., 2012). One possible explanation for the differences in the cross-sectional results between these studies could be that our study and Elovainio and colleagues' study consisted of somatic healthy participants, whereas Kupper and colleagues used a sample of heart failure patients, whom probably have higher levels of inflammation to begin with due to their disease status. Furthermore, the heart failure sample is on average older, possibly affecting cognitive functions comparable to cognitive symptoms of depression (i.e. concentration).

Interestingly, in a recent review on somatic symptoms of depression as a predictor of cardiac disease, Carney and Freedland (2012) describe that somatic symptoms are more often residual symptoms of a depression in remission and are also risk factors for chronic or recurrent depression. Previous research has shown that especially recurrent depressive symptoms are associated with future inflammation in stable coronary heart disease patients (Duivis et al., 2011, 2012). It could be that somatic symptoms reported on in this study are a reflection of residual symptoms of depression and a risk factor for future depressive symptoms or depression, with a possible role for inflammation.

Comparable to the results from Elovainio et al. (2009) and Bremmer et al. (2008), we also found sex differences in the associations between depressive symptoms and anxiety symptoms with inflammation. It has been suggested that differences between men and women in the association between depression/anxiety and inflammation are the results of hormonal differences (Jilma et al., 1997; Cushman et al., 1999). However, in our previous study on depression diagnosis and inflammation, hormonal status did not affect the association between depression and inflammation. Another potential explanation could come from non-biological pathways. For example, it has been suggested that women have a greater risk for depression than man as a result of insufficient support and stressful life events (Maciejewski et al., 2001; Kendler et al., 2005). Gender differences were only present for CRP, which is a more general marker for inflammation than IL-6 and TNF-α are. Possibly, these psychosocial factors only have less impact on other, more specific markers of inflammation.

As was found in previous research (Hamer et al., 2009; Stewart et al., 2009; Duivis et al., 2011), this study shows that lifestyle, and mainly BMI, explained a significant part of the association between depressive symptoms and inflammation. Obesity has been found to be associated with depression (de Wit et al., 2010; Luppino et al., 2010). A meta-analysis on the prospective association between overweight and depression showed that the relationship is bi-directional, in other words, depression predicts obesity and obesity is a risk factor for depression (Luppino et al., 2010). Obesity has also been found to be associated with higher levels of inflammation (Miller et al., 2003; O'Connor et al., 2009). Research suggests that adipose tissue produces IL-6 and TNF-α (Miller et al., 2003; O'Connor et al., 2009) and this is therefore a plausible link between depressive symptoms and inflammation (Miller et al., 2003). Furthermore, Dod et al. (2010) found that intervening in markers of an unhealthy lifestyle, by changing food intake and enhancing moderate exercise, had significant effects on lowering inflammation levels after 12 weeks. As higher levels of inflammation are found to be associated with adverse health outcomes such as cardiac risk factors (Toprak et al., 2011) and diabetes (Stuart and Baune, 2012), promoting weight loss in people with depressive symptoms could have beneficial effects on levels of inflammation and possibly future health status.

Regarding anxiety and inflammation, we found a significant association between total anxiety symptoms and CRP (men only) whereas somatic symptoms were associated with CRP (men only), IL-6, and TNF-α. These associations also diminished after lifestyle differences were considered. In line with our findings on total symptoms of anxiety, previous studies also reported on a positive association between anxiety and inflammation (Pitsavos et al., 2006; Liukkonen et al., 2011). Liukkonen et al. (2011) found that men reporting anxiety symptoms had elevated levels of CRP levels compared to those who did not report symptoms of anxiety. However, their findings were not affected by adjustment for a range of covariates including BMI, whereas our results became non-significant after adjusting for markers of an unhealthy lifestyle behaviors (smoking, alcohol intake, BMI, and physical inactivity), with BMI having the strongest effect on the association. Furthermore, similar to our findings, they did not find support for this association in women. In contrast, Pitsavos et al. (2006) found significant associations for anxiety and inflammation in women. Interestingly, the results published by Liukkonen and colleagues and Pitsavos and colleagues did not diminish after adjustment for markers of an unhealthy lifestyle behaviors as our results did. Previous research has shown a positive relationship between BMI and inflammation on one hand (Ferrante, 2007; Samaan, 2011) and BMI and anxiety on the other hand (Roberts et al., 2007). One possible explanation could be that our sample partly consists of psychiatric patients, in contrast to the healthy samples used by Pitsavos et al. and Liukkonen et al. Around 27% of the participants are recruited in specialized mental health care. It could be that this group of participants has more adverse markers of an unhealthy lifestyle behaviors contributing to inflammation and/or anxiety compared to healthy participants. Furthermore, our results suggest that also the anxiety-inflammation relationship is mainly driven by somatic symptoms. Somatic symptoms of anxiety consist of hot flushes, respiration, heart pounding, shaking hands and difficulty breathing. This sheds a new light on anxiety and inflammation. In contrast to somatic symptoms of depression, somatic symptoms of *anxiety* are not similar to symptoms of sickness behavior, but may be seen as a reflection of autonomic control, suggesting a role for the autonomic nervous system (ANS). The ANS is also associated with higher levels of inflammation (Haensel et al., 2008; Miller et al., 2009; Haarala et al., 2011) and could possibly be

involved in the anxiety-inflammation link. However, studies examining anxiety and the ANS show conflicting results (Friedman, 2007; Licht et al., 2009, 2010) as to whether the ANS and anxiety are associated. Possibly, the ANS is only involved in the somatic symptoms of anxiety and affects immune function simultaneously.

This study is conducted on cross-sectional data, implying that no inferences can be made on the direction of the relationship of depression and anxiety with inflammation. There is some evidence that suggests that depressive symptoms are associated with subsequent inflammation (Hamer et al., 2009; Stewart et al., 2009; Duivis et al., 2011; Copeland et al., 2012), but the opposite has been reported as well (Gimeno et al., 2009). Regarding anxiety there is little evidence on the direction of the association, though it has been suggested that pro-inflammatory cytokines rise in the presence of anxiety, due to chronic stress (O'Donovan et al., 2010). Up to date there is no longitudinal research conducted which could provide insight into the direction of the anxiety-inflammation relationship and into a more thorough understanding of mechanisms involved in this relationship.

Another limitation is that this is a secondary data-analysis using inflammatory markers. Finally, we assessed circulating levels of inflammatory markers, which show a high degree of intra-individual variation. This could explain why we found the rather modest associations between symptoms of depression and anxiety with inflammatory marker levels in our study.

Some strengths can be attributed to our study, such as a large sample size with a wide range on psychopathology thereby increasing the power of our analyses, which made it possible to adequately adjust for potential confounders. In addition, multiple inflammatory markers were assessed.

In conclusion, our results suggest an association between depressive and anxiety symptoms with inflammation, in which associations were mainly driven by the somatic symptom components. Nevertheless, adjustment for markers of an unhealthy lifestyle factors diminished all associations to non-significance indicating that it is the poorer lifestyle of depressed and anxious patients that puts them at risk for inflammation.

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Conflict of interest

None of the authors report competing interest.

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