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Research report

Cognitive/affective and somatic/affective symptom dimensions of depression are associated with current and future inflammation in heart failure patients

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ABSTRACT

Background: Little is known about whether cognitive/affective depressive symptoms or somatic/affective depressive symptoms are associated with inflammation in heart failure (HF), or that the relation is confounded with disease severity.
Aim: To examine the association between depressive symptom dimensions in HF patients with inflammatory markers cross-sectionally and prospectively, while adjusting for appropriate confounders.
Results: Consecutive HF patients completed the Beck Depression Inventory at inclusion and at 12 month follow-up. Cytokines were assessed at both occasions. *Cross-sectional* — multivariate linear regression analysis ($n=110$) demonstrated that cognitive/affective depressive symptoms were independently associated with increased levels of sTNFR2 ($\beta=0.20$, $p<0.05$) and IL-1ra ($\beta=0.28$, $p<0.01$). Somatic/affective depressive symptoms were independently related to sTNFR2 ($\beta=0.21$, $p<0.05$). *Prospective* — ($n=125$) the level of cognitive/affective depressive symptoms at inclusion was prospectively associated with increased levels of sTNFR1 and sTNFR2 ($\beta=0.21$ and 0.25 resp. $p<0.05$), independent of covariates. Change in somatic/affective depressive symptoms over the 12 month period was associated with sTNFR2 ($\beta=0.30$, $p=0.008$). At symptom level, core depressive cognitions such as hopelessness and guilt drove the relation between the sTNF receptors and the cognitive/affective component, while having sleep problems was the most important associate of the somatic/affective dimension.
Conclusions: Baseline cognitive/affective depressive symptoms were prospectively associated with sTNFR1 and sTNFR2 in HF patients, while change in somatic/affective depressive symptoms was associated with sTNFR2, independent from clinical and demographic covariates. Further studies are warranted to replicate these findings and to examine the association between depression dimensions, inflammation and prognosis in HF.

1. Introduction

Depression is a major burden in patients with heart failure (HF), with the prevalence of significant symptoms of depression being at least twice as high as in the general elderly population (Lesman-Leegte et al., 2009; Rutledge et al., 2006). Although depression is related to a host of somatic parameters in heart failure (Angermann et al., 2011), depression also has prognostic value above and beyond these disease severity markers (Jiang et al., 2004; Junger et al., 2005; Rutledge, et al., 2006). Recently, it was shown that somatic/affective symptoms of depression were more strongly predictive of cardiovascular events and all-cause mortality than cognitive cognitive/affective symptoms of depression in HF patients (Hoen et al., 2010; Roest et al., 2011b; Schiffer et

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al., 2009). Mechanisms linking depression to HF progression or death, however, are as yet unclear. Inflammatory activity may be one potential mechanism, as excessive activation of the inflammatory response is a major factor in CHF (Torre-Amione, 2005). In fact, pro-inflammatory cytokines such as IL-1, IL-6, TNF-α and TNF-α's soluble receptors have been identified as prognostic markers in CHF (Deswal et al., 2001; Orús et al., 2000; Rauchhaus et al., 2000). Cytokines have also been linked to subjective behavioral parameters in patients with HF, with TNF-α and its soluble receptors being associated with symptoms of depression (Ferketich et al., 2005; Moorman et al., 2007; Parissis et al., 2004) and personality (Conraads et al., 2006; Denollet et al., 2009).

To date, it is unknown whether it is cognitive/affective depressive symptoms, somatic/affective symptoms of depression, or the confounding of depression with disease severity that explains the relation between depression and inflammatory activity in HF patients. Therefore, in the current study, we examined whether the depressive symptom dimensions in HF patients at the time of inclusion into the study and change in depression dimensions over time were differentially associated with cytokine levels at inclusion and at 12 month follow-up, while taking into account changes in disease severity during this period in the latter analyses.

Moreover, individual symptoms, especially sleep disturbance (Bryant et al., 2004; Lorton et al., 2006), have been reported to contribute disproportionately to the association between depression and inflammation (Raison et al., 2006), which calls for further clarification of factors most closely associated with immune activation. To further our understanding of the exact role of individual depressive symptoms in HF disease progression, we explored which symptoms within each dimension were most involved in the relation between depression and inflammatory activity, while controlling for covariates.

2. Methods

2.1. Patients and design

Consecutive patients attending the outpatient heart failure clinic of the TweeSteden hospital, a large general hospital in Tilburg and Waalwijk, The Netherlands, between October 17, 2003 and January 7, 2005 were included. Patients with diastolic heart failure (preserved pump function), age ≥ 80 - years, myocardial infarction in the month prior to inclusion, other life-threatening diseases (e.g. chemotherapy-treated cancer), serious psychiatric illness except mood disorders, or insufficient understanding of spoken and written Dutch language were excluded. With respect to the blood sampling, patients were excluded when there were signs of acute infection, patients presented with active episodes of gout or arthritis, or used of anti-inflammatory medication (total exclusion approximately 10% of the eligible sample).

Of 206 patients, 165 (80%) agreed to participate. Of those 165 patients, 5 patients were excluded because of a missing depression score at inclusion. Blood collection at baseline did not take place in 51 patients, as the blood collection sub-study only started in January 2004. We therefore had complete data at inclusion (blood and questionnaires) for 110 patients. With respect to the follow-up data, 6 patients were lost to follow-up due to death, while 3 were excluded due to medical or logistic (moving abroad) reasons. Thirteen additional patients refused participation at 12-month follow-up. Blood data at 12-month follow-up was missing for 15 patients. In total, we had complete 12-month blood samples accompanied by baseline and 12-month follow-up questionnaires for 125 patients. See Fig. 1 for a flow chart. The total study sample included 165 stable CHF patients (75.8% men; mean age ± SD = 65.7 ± 8.9 years; NYHA functional class III/IV = 53.9%) with a left ventricular ejection fraction (LVEF) of ≤40%.

Individual cytokine values were set as missing if they constituted outliers (defined as >3 standard deviations (SD) of the mean for all cytokines; baseline: $n=2$ for TNF-α; $n=1$ for sTNFR1; $n=1$ for sTNFR2; $n=2$ for CRP; $n=2$ for IL-1ra; and $n=3$ for IL-6; 12 month follow-up: $n=1$ for TNF-α; $n=3$ for sTNFR1; $n=1$ for sTNFR2; $n=2$ for CRP; $n=2$ for IL-1ra; and $n=2$ for IL-6). A flow chart of patient inclusion is shown in Fig. 1.

Patients completed a questionnaire assessing depressive symptoms at the time of inclusion into the study and 12 months later. Blood samples were collected at both measurement occasions. The study protocol was approved by the local medical ethics committee in Tilburg, The Netherlands. The study was conducted conforming to the Helsinki Declaration, and every patient provided written informed consent.

2.2. Immunological techniques

All markers that were analyzed were chosen because of their relation with CHF pathology. We chose to analyze TNF-α and IL-1ra because TNF-α and IL-1 may induce dysfunction of the cardiac muscle (Mann and Young, 1994). As IL-1ra levels are easier to detect in blood serum than IL-1, we opted to analyze IL1-ra. Soluble TNF receptors are endogenous modulators of TNF-α, and may be responsible for prolonging the bioactivity of TNF-α (Aderka et al., 1992). We included both soluble receptors (sTNFR1 and sTNFR2) in our analysis. Finally, we analyzed IL-6 and CRP, both involved in the acute phase response and implicated in the development of ventricular hypertrophy (Aukrust et al., 1999). Blood was collected by venipuncture at the hospital during outpatient clinic hours (between 8 a.m. and 5 p.m.) preceding or following patients' clinic appointment. The blood was allowed to clot at room temperature and centrifuged. Serum samples were stored at −80 °C in anticipation of further processing. The inflammatory markers were measured using quantitative enzyme-linked immunosorbent assay (ELISA). ELISA-kits for TNF-α (sensitivity: 0.75 pg/ml), sTNFR1 (sensitivity: 0.079 ng/ml), sTNFR2 (sensitivity: 0.079 ng/ml), CRP (sensitivity: 0.38 pg/ml), IL-6 (sensitivity: 0.82 pg/ml) and IL1-ra (sensitivity: 0.079 ng/ml) were purchased from DiaMed Eurogen (Turnhout, Belgium). All tests were measured in accordance with the manufacturer's recommendations. Sensitivity of all tests was calculated by the mean of 6 zero-values + 3 standard deviations extrapolated on the standard curve. Values below sensitivity were raised to sensitivity value. The intra-assay variation was between 3.5 and 9.7% for all ELISAs, and the inter-assay variation between 6.1 and 10.5%.

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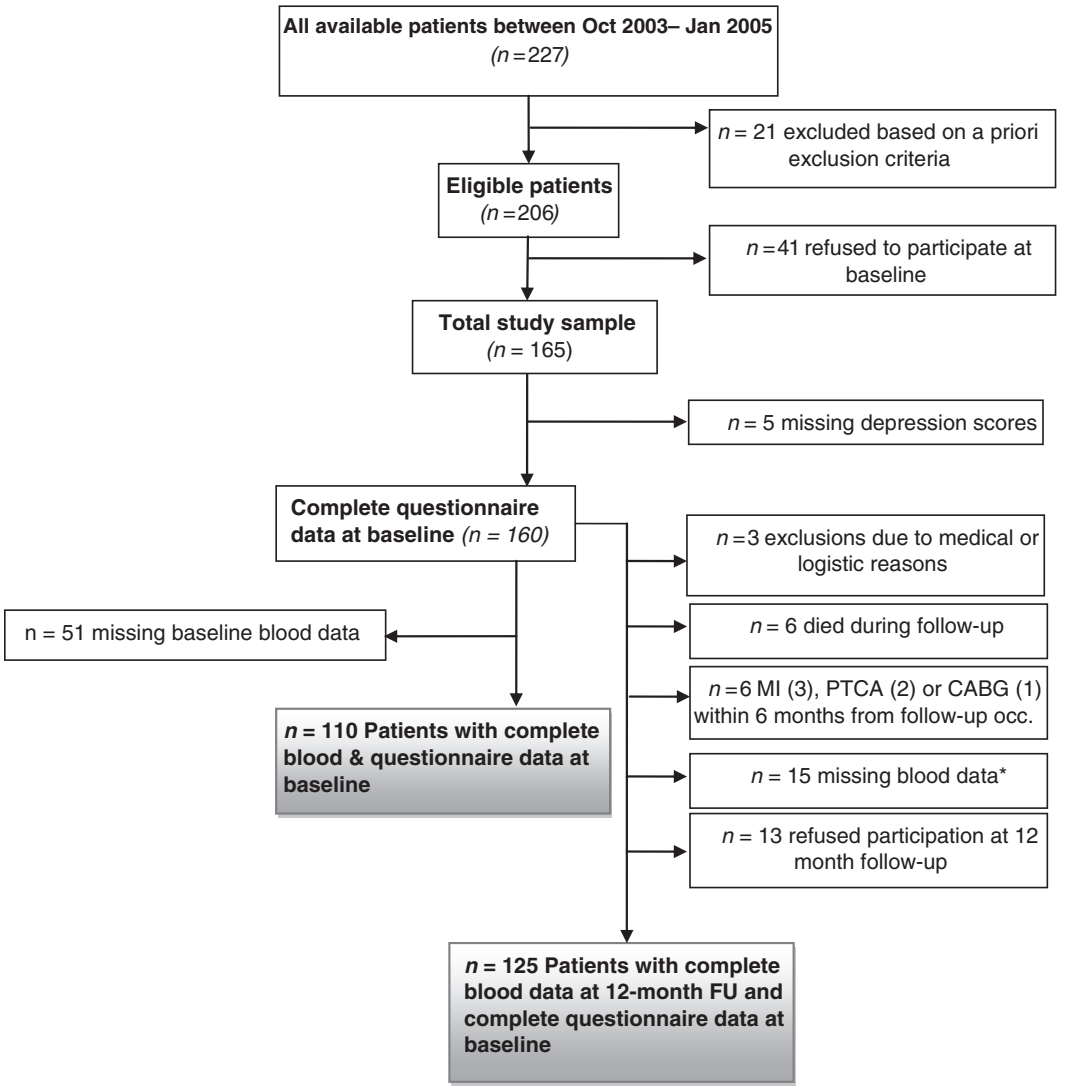

Fig. 1. Study inclusion schedule. * Due to overlap in missingness/exclusion, numbers do not exactly subtract to final N.

2.3. Demographic and clinical variables

Socio-demographic information included gender, age, education, and marital status. Smoking status and anthropometric characteristics were assessed by means of self-report. Clinical variables comprised LVEF, New York Heart Association (NYHA) functional class, etiology of HF, time since HF diagnosis, performance on the 6-minute walk test (6MWT), risk factors (obesity, hypertension, diabetes mellitus, hyperlipidemia, and lack of physical activity), co morbidity (stroke, COPD, renal insufficiency, and peripheral arterial disease), cardiac history (MI, percutaneous coronary intervention (PCI), and coronary artery bypass graft surgery (CABG)), and medication (cardiac and psychotropic (antidepressants, anxiolytics, sedatives)). Information on clinical variables was obtained from the patients' medical records and from the treating cardiologist.

2.4. Symptoms of depression

Symptoms of depression were measured with the 21-item Beck Depression Inventory (BDI-I) (Beck and Steer, 1993). Each item is rated on a 0–3 scale. A total score is obtained by summing together all items. Analogous to the BDI-II, the BDI-I may also be divided into a cognitive/affective subscale (e.g., "I do not feel especially guilty" (score 0) to "I feel guilty all the time" (score 3)) by summing together items 1–13, and a somatic/affective subscale (e.g., "I am not tired sooner than otherwise" (score 0) to "I am too tired to do anything" (score 3)) by summing together items 14–21 (Beck and Steer, 1993). The BDI is a reliable and well-validated self-report measure of depressive symptomatology (Beck et al., 1988) that is widely used to assess depression in patients with cardiovascular disease. In the current study, we used both the total BDI score and its cognitive/affective and somatic/

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affective subscales, as the somatic/affective subscale may be confounded by indices of disease severity (Beck et al., 1996).

2.5. Statistical analyses

Prior to statistical analyses, the distributions of the cytokines were checked for normality, resulting in a correction by log transformation for CRP and IL-6. For the other cytokine skewness and kurtosis fell within the acceptable range. NYHA class (I–II vs. III; only a small proportion of patients were NYHA class I), etiology of HF, marital status, and education were recorded into dichotomous variables. Discrete variables were compared with the Chi-square test and continuous variables with Student's t-test for independent samples. Associations between depressive symptoms and characteristics at the time of inclusion into the study were assessed using Student's t-test for independent samples, whereas the associations between depressive symptoms and immunological parameters (both at baseline and at 12-month follow-up) were assessed using Pearson correlations. Paired sample t-tests were used to assess the degree of change in depressive symptom scores as well as in inflammatory markers over the 12-month period.

2.5.1. Baseline analysis

Two multivariate linear regression analyses were performed to examine the cross-sectional association between the two depression dimensions and the inflammatory markers while controlling for demographic and clinical variables and measures of disease progression (see Covariates section).

2.5.2. Prospective analysis

Multivariate linear regression analysis was used to examine the effects of depressive symptom dimensions as well as change in depressive symptoms on immunological parameters, while controlling for demographic and clinical variables and measures of disease progression (see Covariates section). All variables were entered in two steps, one including the depression dimension and change in that depression dimension, the second also including all covariates. A post-hoc analysis was performed by repeating above described analysis, now including both depressive symptom dimensions and their change in one single analysis.

The more in-depth analysis of the individual cognitive/affective and somatic/affective depressive symptoms in relation to the inflammatory markers that showed significant associations with the depression dimensions in above analyses, took place by calculating correlations and partial correlations including all covariates from the regression analysis. All tests were two-tailed, and $p<0.05$ was used to indicate statistical significance. SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used to analyze all data.

2.5.3. Covariates

While trying to preserve the delicate balance between overfitting the regression model and including the appropriate confounders (Babyak, 2004), we selected covariates for adjusted analyses based on their previously reported relation with our main predictors: the two dimensions of depression. Based on a power analysis using GPower 3.1 ($n=125$, $\alpha=0.05$, effect size $f^2=0.16$, this medium effect size was conservatively derived from previous findings in studies relating psychosocial factors to cytokine levels (e.g., Denollet, et al., 2009; Moorman, et al., 2007), we were able to include 14 predictors to reach a statistical power of 79% and 11 predictors to reach a power of 84%. Based on previous literature, we included obesity (BMI), disease severity (NYHA, LVEF, and 6MWT), change in disease severity (change in performance on 6MWT), change in depressive symptoms, and psychotropic medication use as confounders, as these relate to depression (Tousoulis et al., 2009). In addition, we added some variables as covariates that show an established relation with cytokine levels (for a review see O'Connor et al., 2009). Most favorable would be to control for age, gender, low education, psychotropic and anti-hypertensive medication, menopausal state of women and obesity, and to additionally control for statin use, aspirin use and current smoking in the analyses of CRP and IL-6 (O'Connor, et al., 2009). Psychotropic medication, lack of physical exercise, and obesity have been related to increased inflammation, but as they also may be confounders for depression these were already included. In the prospective analysis, we included psychotropic medication use at follow-up, because of the known influence on cytokines. In addition, inflammatory profiles may differ as a function of disease etiology. As all patients were optimally treated with anti-hypertensive drugs (ACE-inhibitors, ARBs and/or beta-blockers), and most women (all but 4 were aged >55, the upper boundary of the most common age range for menopause) were postmenopausal, we did not include these in the multivariable regression model. In conclusion, we included BMI, NYHA, LVEF, 6MWT, change in performance on 6MWT, change in depressive symptoms, psychotropic medication, HF etiology, age, and gender as covariates for all cytokines and smoking, statin use, aspirin use as additional covariates for CRP and IL-6.

3. Results

3.1. Patient characteristics

Patients who completed the study (assessments at inclusion and 12 month follow-up; $n=125$) did not differ significantly on demographic and clinical characteristics from patients who did not complete the study or were excluded (for reasons, see Methods section and Fig. 1; $n=38$; all p values >0.05). Demographic and clinical characteristics of the sample at inclusion and the sample at 12 month follow-up are shown in Table 1.

3.2. Disease and depression progression over the 12-month period

Over the 12-month period, 3 patients suffered an MI, 4 patients underwent a CABG procedure and 7 patients underwent PCI. Of these, 6 were excluded from the prospective analyses as the event or procedure took place within the last 6 months (see also Fig. 1). In total, 17 pacemakers were implanted (15 biventricular; 13.4%). Disease severity remained stable over the 12-month period, as 94% of patients remained classified in the same NYHA functional class. NYHA class worsened in two patients, with one patient progressing from class I to class II and one progressing from class II to

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Table 1
Demographic and clinical characteristics at baseline and at 12-month follow-up.

	Baseline sample ($n=110$[a])	Sample at 12-month FU ($n=125$[b])
Demographic		
Age, *mean* (*yrs*) ± *SD*	65.4 ± 8.7	66.5 ± 8.7
Male gender% (*n*)	73 (79)	76 (95)
Low educational level% (*n*)	62 (67)	61 (76)
Having a partner% (*n*)	77 (83)	77 (96)
Disease severity		
NYHA-class III% (*n*)	44 (49)	52 (69)
LVEF, *mean* (%) ± *SD*	30.2 ± 6.2	–
6MWT, *mean* (*m*) ± *SD*	279.0 ± 165.7	264.8 ± 16.7
Clinical		
Ischemic etiology% (*n*)	56 (60)	n/a
Years since HF diagnosis, *mean* (*yrs*) ± *SD*	4.1 ± 4.2	n/a
Cardiac history[c]% (*n*)	59 (58)	57 (71)
Co morbidity[d]% (*n*)	60 (59)	79 (92)
Devices[e]% (*n*)	12 (13)	25 (29)
Diabetes% (*n*)	24 (26)	26 (30)
Body mass index, *mean* ± *SD*	28 ± 4	28 ± 5
Physically active% (*n*)	51 (55)	53 (62)
Smoking% (*n*)	25 (27)	25 (32)
Medication		
ACE-inhibitors or AT II antagonists% (*n*)	81 (87)	81 (98)
Diuretics% (*n*)	74 (80)	78 (97)
Spironolactone% (*n*)	14 (15)	20 (24)
Digoxin% (*n*)	35 (38)	30 (36)
Beta-blockers% (*n*)	62 (67)	69 (83)
Calcium antagonists% (*n*)	8 (9)	12 (15)
Statins% (*n*)	46 (50)	41 (50)
Aspirin% (*n*)	44 (48)	42 (51)
Psychotropic medication[f]% (*n*)	10 (11)	21 (26)

[a] Number of patients at baseline comprises patients with both baseline depression scores and baseline blood samples.
[b] Number of patients at 12-month follow-up comprises patients with both baseline scores of depression and blood samples at 12-month follow-up.
[c] Previous myocardial infarction, coronary artery bypass surgery, or percutaneous coronary intervention.
[d] Stroke, chronic obstructive pulmonary disease, hypertension, peripheral arterial disease, renal insufficiency (based on glomerular filtration rate of creatinine).
[e] Implanted devices (ICD, PM, BVP).
[f] Selective serotonin reuptake inhibitor (SSRI), tri-cyclic anti-depressant (TCA), or benzodiazepines.

class III. Six patients improved: two from class II to class I, and four from class III to class II. Ejection fraction was only assessed at inclusion. The 6MWT gives a good indication of disease severity. Half of the patients (49.6%) performed worse on the 6MWT, with a decline of on average 133. 5 m (range 1–750) in walking distance at follow-up. Patients that improved on the 6MWT walked on average an additional 102.9 m (range 0–485). Finally, paired t-tests showed that the level of inflammation did not change significantly over the follow-up period (Table 2). Cytokine levels at inclusion correlated between 0.45 and 0.62 with cytokine levels at follow-up.

The total BDI score and the cognitive/affective symptoms dimension at inclusion and at follow-up correlated highly with each other ($r=0.70$ and 0.73 respectively), while the assessments of the somatic/affective symptom dimension over the 12-month period were more modestly correlated ($r=0.58$). Paired samples t-tests showed that the differences in scores were smaller than a quarter of a point on the BDI scale, and were non-significant (see Table 2). Only a small number of patients received treatment for their psychological problems. While 11 patients were prescribed antidepressants (SSRI or TCA) or a sedative (benzodiazepine) at inclusion, at 12 month follow-up 26 patients were prescribed these medications. Non-pharmacological psychosocial treatment was given to 4 patients at inclusion and 3 patients at follow-up. Over time, 5 patients that were in treatment at inclusion were not at 12 month follow-up, while 14 patients were in treatment at follow-up while they were not at inclusion. There was no effect of treatment status at inclusion on the change in depression score over time ($F=0.20$, $p=0.66$).

3.3. Cross-sectional relations between depressive symptoms and cytokines

Table 2 shows descriptive information on the cytokine levels. Table 3 displays the cross-sectional unadjusted correlations between depressive symptoms (total score, somatic/affective symptoms and cognitive/affective symptoms) and cytokine levels at inclusion and follow-up.

Multiple linear regression analysis on the cross-sectional inclusion data demonstrated that in the presence of HF etiology, usage of psychotropic medication, NYHA class, LVEF, 6MWT, and BMI as covariates, cognitive/affective symptoms of depression were associated with increased levels of sTNFR2 ($\beta=0.20$, $p=0.046$) and IL-1ra ($\beta=0.28$, $p=0.005$) and with CRP at trend level ($\beta=0.19$, $p=0.06$). Similar multivariable regression models for somatic/affective symptoms of depression showed that sTNFR2 ($\beta=0.21$, $p=0.04$) was significantly and positively related to somatic/affective symptoms of depression. Both IL-1ra ($\beta=0.18$, $p=0.09$) and CRP ($\beta=0.19$, $p=0.06$) tended ($p<0.10$) to be higher with increasing levels of somatic/affective symptoms of depression. Significant covariates were BMI (CRP: $\beta=0.19$) and exercise capacity (CRP: $\beta=-0.26$; TNF-α: $\beta=-0.22$).

3.4. Prospective associations between depression at inclusion and cytokine levels at follow-up

Table 2 shows the means (SD) for the cytokine levels at 12 month follow-up, while Table 4 presents the results from the linear regression analysis.

In step one, only the depression variables (either cognitive/affective or somatic/affective symptoms of depression and the change in these symptoms over time) were entered. Results showed that the level of cognitive/affective depression at inclusion was positively associated with hsCRP, sTNFR1 and sTNFR2 at 12-month follow-up, while somatic/affective depression at inclusion was positively associated with sTNFR1 and sTNFR2.

Moreover, change in somatic/affective depressive symptoms over the 12-month follow-up period was significantly associated with both sTNFR1 and sTNFR2, while change in cognitive/affective depressive symptoms was not associated with any of the inflammatory biomarkers.

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Table 2
Mean depression scores and levels of inflammatory markers at baseline and at 12-month follow-up.

	Baseline	12-mo FU	Difference (95% CI)	test statistic	p value
Depression					
BDI total	8.4 (5.4)	8.3 (6.0)	0.13 (−0.63–0.9)	0.338	0.74
BDI cognitive/affective	3.1 (3.5)	3.1 (4.0)	0.07 (−0.40–0.54)	0.303	0.76
BDI somatic	5.1 (3.0)	4.9 (3.1)	0.22 (−0.25–0.69)	0.940	0.35
Inflammatory markers					
CRP (log pg/ml)	1.58 (1.07)	1.44 (1.21)	0.10 (−0.14–0.35)	0.843	0.40
TNF-α (pg/ml)	6.55 (4.04)	6.60 (4.26)	−0.15 (−0.98–0.69)	−0.345	0.73
sTNFR1 (ng/ml)	4.08 (1.65)	4.20 (1.84)	0.06 (−0.32–0.44)	0.322	0.75
sTNFR2 (ng/ml)	2.67 (1.58)	2.68 (1.65)	−0.08 (−0.38–0.22)	−0.545	0.59
IL-6 (log pg/ml)	0.43 (0.68)	0.49 (0.74)	−0.07 (−0.21–0.07)	−0.980	0.33
IL1-ra (ng/ml)	0.31 (0.28)	0.27 (0.20)	0.01 (−0.03–0.06)	0.575	0.58

The paired t-tests for the inflammatory markers have been performed for a smaller sample ($n=85$) since not all patients provided blood at both measurement occasions.

Fully adjusted linear regression models showed that the cognitive/affective depression dimension remained a significant associate of sTNFR1 and sTNFR2, while trend associations were observed for hsCRP and IL1-ra. The association between the somatic/affective depression dimension and the soluble TNF receptors was for a large part explained away by covarying levels of physical exercise capacity, NYHA class and age.

Change in somatic/affective depressive symptoms remained a significant associate of sTNFR2 in the presence of all a priori selected covariates.

When entering both cognitive/affective and somatic/affective symptom dimensions of depression and their change over time in one regression model (leaving out LVEF due to statistical power considerations), cognitive/affective depression levels at inclusion remained a significant predictor of sTNFR2 ($\beta=0.21$, $t=2.01$, $p=0.047$), but not the somatic/affective symptom dimension ($\beta=-0.01$, $t=-0.38$, $p=0.97$), again controlled for all other included confounders mentioned above. Change on cognitive/affective depression and change in somatic/affective depression were not significantly associated with cytokine levels at 12-month follow-up in this combined analysis ($\beta=0.09$, $p>0.36$ for both).

Table 3
Bivariate correlations between depressive symptoms (total BDI, cognitive/affective and somatic/affective symptoms) and inflammatory markers.

Total BDI	Baseline ($n=107$)	12 months ($n=125$)
CRP	0.26**	0.22*
TNF-α	0.07	−0.03
sTNFR1	0.03	0.27**
sTNFR2	0.24*	0.25**
IL-6	0.01	0.09
IL1-ra	0.21*	−0.03
Cognitive/affective		
CRP	0.24*	0.23*
TNF-α	0.06	0.01
sTNFR1	0.03	0.30**
sTNFR2	0.21*	0.29**
IL-6	−0.04	0.10
IL1-ra	0.24	−0.04
Somatic/affective		
CRP	0.24*	0.14
TNF-α	0.05	−0.08
sTNFR1	0.02	0.12
sTNFR2	0.22*	0.11
IL-6	0.07	0.05
IL1-ra	0.12	−0.01

* $p<0.05$.
** $p<0.01$.

3.5. Which cognitive/affective and somatic/affective symptoms explain the relationship with 12-month cytokine levels?

More in-depth analysis of the individual cognitive/affective and somatic/affective depressive symptoms in relation to sTNFR1 and sTNFR2 concentrations showed that the relation between the cognitive/affective depressive symptoms score and the soluble TNF receptor levels was driven by core depressive cognitions such as hopelessness, blame, suicidal ideation and guilt (see Table 5 for cognitive/affective and somatic/affective symptom prevalences and correlations), while controlling for the covariates used in the multiple regression models. With respect to the somatic/affective depression dimension, only loss of sleep was significantly and inversely associated with both soluble TNF receptors in partial correlations.

4. Discussion

The results of the current study showed that the cognitive/affective depressive symptom dimension was prospectively associated with higher levels of both soluble TNF receptors, while change in somatic/affective depressive symptoms was associated with increased levels of sTNFR2, independent of etiology, indices of disease severity, exercise capacity and change in depression over time. When analyzing both subcomponents and their change over time in a single analysis, only baseline cognitive/affective depression remained a covariate-independent associate of sTNFR2. This is in concurrence with two previous studies in HF patients (Ferketich, et al., 2005; Redwine et al., 2009), although it should be emphasized that these studies were cross-sectional, had small sample sizes ($n\leq56$), and did not

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Table 4
Multivariable associates of inflammatory markers at 12 month follow-up.

Variable	CRP		IL-6		TNF-α		sTNFR1		sTNFR2		IL-1ra	
	β	p	β	p	β	p	β	p	β	p	β	p
Model 1a: *cognitive/affective depressive symptoms*												
BDI: Cognitive/affective	**0.20**	**0.03**	0.07	0.48	0.03	0.74	**0.29**	**0.001**	**0.32**	**0.000**	−0.06	0.52
Change in cognitive symptoms	0.05	0.59	−0.09	0.34	0.07	0.44	0.10	0.25	0.08	0.38	−0.09	0.32
Model 1b: *cognitive/affective depressive symptoms adjusted for covariates*												
BDI: Cognitive/affective	*0.18*	*0.08*	−0.03	0.76	−0.01	0.93	**0.21**	**0.03**	**0.25**	**0.01**	*−0.16*	*0.09*
Change in cognitive symptoms	0.04	0.97	−0.14	0.18	0.05	0.62	0.12	0.22	0.09	0.36	*−0.16*	*0.09*
Age	0.13	0.20	−0.07	0.52	0.09	0.42	*0.18*	*0.07*	*0.19*	*0.06*	0.02	0.83
Gender	−0.13	0.19	−0.10	0.34	−0.03	0.81	0.06	0.54	0.06	0.53	−0.07	0.50
Etiology	0.13	0.17	0.14	0.22	0.04	0.74	0.04	0.67	−0.02	0.83	**0.23**	**0.02**
NYHA class	−0.04	0.93	0.14	0.16	−0.01	0.93	**0.24**	**0.01**	0.08	0.41	**0.21**	**0.03**
LVEF	0.07	0.51	0.08	0.45	−0.04	0.69	−0.01	0.92	−0.06	0.54	0.05	0.58
Body mass index at 12 mo	**0.25**	**0.02**	−0.05	0.66	0.12	0.25	0.12	0.21	0.05	0.61	**0.26**	**0.01**
Psychotropic medication at 12 mo	−0.09	0.40	−0.13	0.20	0.13	0.23	0.07	0.48	0.003	0.97	0.14	0.15
Physical exercise capacity (6MWT)	*−0.24*	*0.08*	**−0.43**	**0.002**	−0.10	0.47	−0.11	0.37	−0.21	0.10	*−0.21*	*0.08*
Change in physical exercise capacity	−0.10	0.43	**−0.33**	**0.01**	−0.11	0.41	0.01	94	−0.14	0.22	*−0.20*	*0.08*
Smoking at 12 mo	0.08	0.41	−0.06	0.55	–	–	–	–	–	–	–	–
Statin use at 12 mo	−0.17	0.12	0.08	0.48	–	–	–	–	–	–	–	–
Aspirin use at 12 mo	0.07	0.52	0.15	0.16	–	–	–	–	–	–	–	–
% variance explained by model (R^2)	21		17		5		26		21		24	
Model 2a: *somatic/affective depressive symptoms*												
BDI: Somatic/affective	0.15	0.15	0.11	0.31	0.003	0.97	**0.25**	**0.02**	**0.30**	**0.002**	0.06	0.56
Change in somatic/affective symptoms	0.07	0.48	0.13	0.22	0.12	0.26	**0.24**	**0.02**	**0.36**	**0.000**	0.12	0.26
Model 2b: *somatic/affective depressive symptoms adjusted for covariates*												
BDI: somatic/affective	0.06	0.64	−0.08	0.54	−0.12	0.34	0.10	0.43	0.15	0.21	−0.10	0.42
Change in somatic/affective symptoms	0.10	0.42	0.04	0.72	0.07	0.56	0.16	0.15	**0.30**	**0.008**	0.02	0.87
Age	0.14	0.19	−0.06	0.59	0.09	0.40	*0.17*	*0.08*	*0.18*	*0.06*	0.03	0.79
Gender	−0.12	0.27	−0.08	0.45	−0.04	0.71	−0.01	0.92	−0.04	0.73	−0.03	0.80
Etiology	0.16	0.16	0.10	0.41	0.02	0.91	0.08	0.41	0.02	0.87	*0.18*	*0.08*
NYHA class	−0.03	0.76	0.14	0.18	−0.02	0.89	**0.25**	**0.01**	0.08	0.41	*0.19*	*0.06*
LVEF	0.08	0.44	0.05	0.65	−0.03	0.74	0.01	0.95	−0.05	0.59	0.03	0.79
Body mass index at 12 mo	**0.23**	**0.03**	−0.02	0.85	0.13	0.21	0.10	0.29	0.03	0.75	**0.28**	**0.005**
Psychotropic medication at 12 mo	−0.07	0.52	−0.13	0.24	0.15	0.15	0.09	0.37	0.03	0.80	0.13	0.19
Physical exercise capacity (6MWT)	*−0.27*	*0.06*	**−0.44**	**0.003**	−0.16	0.27	−0.15	0.28	*−0.23*	*0.08*	−0.21	0.12
Change in physical exercise capacity	−0.11	0.39	**−0.32**	**0.02**	−0.15	0.24	−0.01	0.91	−0.15	0.21	−0.18	0.14
Smoking at 12 mo	0.08	0.44	−0.02	0.87	–		–		–		–	
Statin use at 12 mo	−0.17	*0.12*	−0.03	0.80	–		–		–		–	
Aspirin use at 12 mo	0.06	0.58	0.18	0.10	–		–		–		–	
% variance explained by model (R^2)	19		16		8		21		22		20	

Note: mo = months. This table shows standardized beta coefficients. Boldfaced: significant at a $p<.05$ level (see p values for exact value); Italic: significant at trend level (p value between .05 and .10).

evaluate the link between depressive symptoms and soluble TNF receptors, nor the association with somatic/affective symptoms of depression.

Most previous studies on depression and inflammation in HF were small (Andrei et al., 2007; Ferketich, et al., 2005; Parissis, et al., 2004; Redwine et al., 2007), except one study ($n=129$) (Moorman, et al., 2007), such that adjustment for confounders was often not feasible. Our finding show that, unadjusted, both the baseline level as well as the change in somatic/affective depression over time was significantly associated with higher levels of 12-month sTNFR1 and sTNFR2. However, the covariates NYHA class and (change in) exercise capacity explained the majority of the shared variance, suggesting that the confounding of depression with disease severity may in part explain this relation.

Our results also add to the ongoing debate as to the nature of depression in heart disease (de Jonge et al., 2006, 2007; Doyle et al., 2006), as cognitive/affective symptoms of depression in HF seem to be more pronounced than might have been expected from observations in post-MI patients (Martens et al., 2006). The identification of depression subtypes might enhance diagnosis and treatment of depression in heart failure patients (Ormel and de Jonge, 2011). This is supported by reports on the differential effects of cognitive/affective and somatic/affective symptom dimensions on mortality (Bekke-Hansen et al., 2011; de Jonge, et al., 2006; Roest et al., 2011a; Schiffer, et al., 2009) and the differential mechanisms (de Jonge et al., 2007; Shaffer et al., 2011) potentially underlying the association between depression dimensions and disease progression and mortality in HF.

In patients with HF, the evidence for the association between depression and cardiovascular mortality is mixed (Pelle et al., 2010; Schiffer, et al., 2009; Sherwood et al., 2011; Testa et al., 2011). The one study that discriminated

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Table 5
(Partial) correlations of the individual cognitive/affective depressive symptoms with soluble TNF receptor levels.

	Prevalence of the item (%)*		sTNFR1 at 12 months				sTNFR2 at 12 months			
			r	p	Partial *r***	p	*r*	p	Partial *r***	p
Cognitive/affective symptoms										
Sadness	20	13	**0.23**	**0.01**	0.14	0.16	**0.20**	**0.03**	*0.18*†	*0.07*
Hopelessness	18	15	**0.18**	**0.049**	0.14	0.14	**0.28**	**0.002**	**0.25**	**0.01**
Failure	8	9	−0.03	0.72	−0.09	0.39	0.03	0.78	0.02	0.78
No pleasure	62	56	**0.18**	**0.047**	0.10	0.30	**0.20**	**0.03**	0.13	0.18
Guilt	9	9	0.14	0.13	0.14	0.16	**0.23**	**0.009**	**0.27**	**0.005**
Feel punished	7	7	0.14	0.12	0.14	0.16	**0.20**	**0.02**	**0.20**	**0.04**
Disgust with self	7	10	0.06	0.50	0.01	0.91	0.11	0.23	0.06	0.58
Blame	13	9	**0.18**	**0.050**	0.14	0.16	**0.22**	**0.02**	**0.21**	**0.03**
Suicidal ideation	6	4	**0.25**	**0.005**	**0.22**	**0.03**	*0.16*†	*0.08*	0.13	0.19
Crying	23	21	0.11	0.24	0.12	0.22	−0.02	0.83	−0.02	0.83
Irritation	42	38	0.13	0.15	0.14	0.16	0.10	0.28	0.10	0.31
No interest in others	22	17	0.07	0.41	0.03	0.77	−0.01	0.90	−0.05	0.60
Indecisiveness	34	38	0.05	0.60	0.01	0.89	**0.20**	**0.03**	0.13	0.16
Somatic/affective/affective symptoms										
Attractiveness	12	9	−0.06	0.54	−0.07	0.51	0.03	0.73	0.02	0.87
Lack of energy	74	75	0.08	0.36	−0.02	0.84	0.06	0.47	−0.03	0.76
Loss of sleep	52	45	**−0.22**	**0.02**	**−0.22**	**0.02**	**−0.25**	**0.005**	**−0.26**	**0.007**
Fatigue	88	90	0.09	0.34	0.02	0.85	*0.16*†	*0.07*	0.12	0.21
Loss of appetite	32	30	0.14	0.11	0.08	0.45	0.11	0.22	0.02	0.84
Weight loss	20	15	0.002	0.98	−0.04	0.66	0.06	0.54	−0.02	0.87
Somatic/affective preoccupation	30	25	0.06	0.48	0.07	0.51	0.04	0.62	0.05	0.61
Loss of sexual interest	60	60	0.14	0.11	0.06	0.55	0.05	0.60	−0.08	0.42

Note: Results only shown for significant findings in multiple regression analysis. Bold-faced: $p<0.05$. † and italic: $p<.10$
* Percentage of patients that indicated the presence of this symptom (scores of ≥1 on the individual BDI item) at baseline || at 12 months.
** Controlled for covariates: age, gender, etiology, NYHA class, LVEF, body mass index at 12 months, psychotropic medication at 12 months, physical exercise capacity (6MWT), and change in physical exercise capacity over the follow-up period.

between cognitive/affective and somatic/affective symptom dimensions only examined all-cause mortality (Schiffer, et al., 2009), while it would be more informative to study the differential effects of depression dimensions on cardiovascular mortality. Mostly however, mortality research has taken place in post-MI patients and one could question whether persistent cognitive/affective depressive symptoms in the end-stage of the disease, where they are also more prevalent, would have a different effect on mortality and might exert this effect differently, as was recently suggested (Ormel and de Jonge, 2011).

These findings also link to the vascular depression hypothesis, which suggests that long-term immune activation plays a role in the etiology of late-life depression, and potentially the generation of cognitive/affective depressive symptoms by inducing cerebrovascular lesions, thereby impairing neuronal plasticity and inducing neurochemical imbalances (Hayley et al., 2005). This view is supported by studies showing that cytokines may induce depression by acting on brain function (Dantzer et al., 2008; Raison, et al., 2006). The current results show that several cognitive/affective symptoms were associated with inflammatory activity, important ones being suicidal ideation and hopelessness. These symptoms may indicate a certain degree of adaptational difficulties and learned helplessness, which could affect self-management strategies, and ultimately disease progression.

With respect to the individual somatic/affective symptoms, it is known that hypersomnia is associated with inflammation and sickness behavior (Lorton, et al., 2006), as well as fatigue, reduced sexual activity and anhedonia (Raison, et al., 2006), which was partly replicated in the current study, as lack of sleep was inversely associated with higher sTNFR2. Taken together, it appeals for psychological treatment of depressive symptoms in HF patients, which may also lead to a reduction in inflammation.

Our findings support the notion that immune activation may comprise one of the pathways that link psychological factors to the progression of CAD and HF (Rozanski et al., 2005), and that a psychoneuroimmunological approach may enhance our understanding of these conditions (Kop, 2003). Although our knowledge of the biology of stress has increased in the past decade, and more importantly our ability to modify such inflammatory processes by means of behavioral interventions (Carlson et al., 2003; van Dixhoorn and White, 2005), we are still far from understanding the complex interplay between psychological factors and cytokines and their respective link to cardiovascular prognosis.

This study has some limitations. Since cytokines interact with and regulate other cytokines in complex ways, the current results may represent an oversimplification of complex network of immunological pathways associating with depressive symptoms in the pathogenesis of HF. Because of the dependence of the individual cytokines in the analyses, as well as the fact that heart disease in a multifactorial disease with many factors of small effect, we opted not to correct for multiple comparisons as this would inevitably lead to a substantial increase in (costly) false negatives. Further, the patient sample comprised stable outpatients and not newly diagnosed patients. However, time since diagnosis was not a significant correlate of depressive symptoms. Importantly though, it is difficult to determine the specific time point for the onset of HF, as HF is a gradual process

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that may be diagnosed a while after the actual onset. Because of this, the current prospective analyses were not adjusted for "baseline" cytokine levels. Strengths of the current study include its relatively large sample size, the multiple assessments of depression and cytokines, the extensive covariate adjustment and the division of depressive symptoms into its core subcomponents.

In conclusion, baseline cognitive/affective depressive symptoms were prospectively associated with sTNFR1 and sTNFR2 in HF patients, while change in somatic/affective depressive symptoms was associated with sTNFR2, in the presence of clinical and demographic covariates. Further studies are warranted to replicate these findings and to examine the association between depression dimensions, inflammation and prognosis in HF.

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Conflict of interest

All other authors declare that they have no conflicts of interest.

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