Sickness behavior in community dwelling elderly: associations with impaired cardiac function and inflammation

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Abstract

Sickness behavior is a cluster of symptoms such as anhedonia, fatigue and sleepiness that occurs as a response to an infection and alterations in the inflammatory response. Under normal circumstances sickness behavior is fully reversible once the pathogen has been cleared. Aging and chronic illness such as heart failure are associated with enhanced inflammatory activity that lasts for a long duration and no longer represents an adaptive response. The aim of this study was to describe sickness behavior in community dwelling elders and to test the hypothesis that inflammation mediates the relationship between impaired cardiac function and sickness behavior. Structural equation modelling (SEM) showed that the factor impaired cardiac function (i.e. NT-proBNP, left ventricular ejection fraction (LVEF) and the heart failure medications angiotensin converting enzyme inhibitor, angiotensin receptor blockade, beta-blocker and diuretics) was associated with both inflammation (i.e. C-reactive protein [CRP]) (β=.26) and sickness behavior (β=.31). Inflammation had a significant direct, but smaller, association with sickness behavior (β=.21). By this pathway inflammation also mediated an indirect association between impaired cardiac function and sickness behavior (β=.05). Including creatinine, blood glucose and ischemic heart disease, previous and current tumor, respiratory disease, age, and body mass index in the SEM model did not change these associations. In community dwelling elders, impaired cardiac function and inflammation were associated with a symptom cluster consisting of anhedonia, fatigue and sleepiness. Our results imply that some aspects of the symptom panorama in elderly with impaired cardiac function or heart failure could represent sickness behaviour.

Keywords: Heart failure, elderly, inflammation, sickness behavior

Background

Sickness behavior is a cluster of symptoms that occurs as a response to infection and alterations in the inflammatory response. Characteristics of sickness behaviors such as loss of energy or fatigue, somnolence, loss of interest in usual activities (anhedonia), poor appetite, weight changes and malaise serve as an adaptive response to conserve energy and resources in order to promote the resistance to pathogens and recovery from infection (Dantzer, 2006; Kelley, et al., 2003; Myers, 2008). Sickness behavior is, under normal circumstances, fully reversible once the pathogen has been cleared (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008).

Aging is associated with enhanced production of pro-inflammatory cytokines and can be said to be typified as a low grade inflammatory state (Hunt, Walsh, Voegeli, & Roberts, 2010a, 2010b). Studies have shown that aspects of sickness behavior such as depressive symptoms (Stordal, Mykletun, & Dahl, 2003) and sleep disturbances (Newman, Enright, Manolio, Haponik, & Wahl, 1997) are common among the elderly. These disturbances are also associated with increased cytokine concentrations (Penninx, et al., 2003; von Kanel, et al., 2006) and thus, aging itself may contribute to sickness behavior. Another condition associated with aging and inflammation is impairment of cardiac function and heart failure (Anker & von Haehling, 2004; Pasic, Levy, & Sullivan, 2003; Shih, Lee, Lee, & Boyle, 2011).

Impairment of cardiac function in heart failure can be defined as a reduced left ventricular ejection fraction (LVEF) below 50%. The measurement of LVEF is preferably performed with echocardiography and based on the end diastolic volume minus the end systolic volume divided by the end diastolic volume. Another commonly used measure of heart failure is N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) (McMurray, et al., 2012). This peptide provides information about myocardial wall-tension and is sensitive to subtle alterations in left ventricular filling

pressures (Alehagen, Lindstedt, Eriksson, & Dahlstrom, 2003). Treatment of heart failure and/or impaired cardiac function with angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockade (ARB), beta-blockers, and diuretics has proved to reduce symptoms such as oedema, and improve cardiac function (McMurray, et al., 2012). In heart failure, inflammation may be due to myocardial tissue injury and impairment of cardiac function with hemodynamic overload and/or under-perfusion of systemic tissues (Pasic, et al., 2003) as well as gut wall oedema (Sandek, et al., 2010). Impaired kidney function, diabetes, obesity, respiratory disease, previous or current tumor and ischemic heart disease are comorbid conditions associated with heart failure (McMurray, et al., 2012) as well as inflammation (Al-shair, et al., 2011; Bondia-Pons, Ryan, & Martinez, 2012; Bower, Ganz, Aziz, & Fahey, 2002; Ormstad, Aass, Amthor, Lund-Sorensen, & Sandvik, 2011; Rosner, Ronco, & Okusa, 2012) and therefore possible causes of sickness behaviour. Inflammation seems to speed the progression of impaired cardiac function as well as to be associated with a poorer prognosis (Anand, et al., 2005; Maeda, et al., 2000; Tsutamoto, et al., 1998).

To our knowledge no prior studies exploring the association between inflammation and the sickness behavior symptom cluster have been conducted in adults with heart failure. In patients with chronic heart failure, fatigue, anhedonia/depression and sleepiness are common (Brostrom & Johansson, 2005; Johansson, Dahlstrom, & Alehagen, 2007). Some studies have found that depressive symptoms are associated with inflammation (Johansson, et al., 2011; Wirtz, et al., 2008). But none of these prior studies analyzed the cluster of sickness behaviors as acontributor to the inflammatory response. Such a symptom cluster may stem from an inflammatory response initiated by impaired cardiac function and therefore may be evidence of sickness behavior in heart failure patients. On the other hand, sickness behavior could also be due to additive effects of age related changes, such as sleepiness, **anhedonia and fatigue**

(Hunt, et al., 2010a, 2010b). We therefore sought to investigate if inflammation mediates the relationship between impaired cardiac function and sickness behavior in a sample of community dwelling older adults.

Methods

Participants

The sample was derived from the epidemiological CoroKind study and has been described previously (Alehagen, Goetze, & Dahlstrom, 2007; Johansson, Alehagen, Svanborg, Dahlstrom, & Brostrom, 2009). The initial study took place between 1998 and 2000. All included subjects were aged 65-82 years and lived in a rural community with 10 300 inhabitants in the southeast of Sweden. All inhabitants in this age span were invited to clinical and echocardiographic examinations. Of 1130 individuals in the population, 876 agreed to participate (participation rate 78%). From January 2003 to June 2005 the cohort was again contacted and invited to repeat the clinical and echocardiographic examination. A total of 675 subjects agreed to participate. The reasons for not participating were: death (12 %), having moved to nursing homes or other parts of Sweden (3 %), declined (7 %) or not showing up to the appointment (1 %). The study protocol was approved by Regional Ethical review board of Linköping, Sweden.

Clinical examination

All participants were examined by a cardiologist, who took a patient history and performed a clinical examination. Diabetes mellitus was defined as ongoing treatment or fasting blood glucose $\geq$ 7 mmol/L. Hypertension was defined as a previous diagnosis of high blood pressure or a measured blood pressure of more than 140/90 mm Hg. Ischemic heart disease (IHD) was defined as history of angina pectoris and/or myocardial infarction. Respiratory disease was

established if the participant had a diagnosis or was undergoing treatment for chronic pulmonary disease or asthma. Previous or current tumor was defined by history. Cardiac function was assessed with Doppler echocardiography (Accuson XP-128c). Systolic function was divided semi-quantitatively by visual estimation into three classes: normal systolic function corresponded to a LVEF ≥ 50%; mildly impaired systolic function, LVEF 49-40%; and at least moderately impaired systolic function LVEF <40%. In the present study we also used N-terminal fragment of proBNP (NT-proBNP) as a measure of impaired cardiac function. **All clinical examinations were based on the European Society of Cardiology's guidelines for treatment of heart failure (McMurray, et al., 2012), which specify that echocardiography and NT-proBNP are important objective examinations to establish impairment of systolic function. High sensitivity C-reactive protein (CRP) was used as a routine marker of inflammation.**

Blood sampling

Blood samples were collected while the patients were at rest in a supine position using EDTA-vials. The vials were chilled on ice before centrifugation at 3000 *g*, 4ºC and then frozen at -70ºC. No sample was thawed more than twice. NT-proBNP was measured using an electrochemililuminesence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). Coefficient of variation was 4.8% at 26 pmol/L and 2.1% at 503 pmol/L (n = 70). CRP was analysed using latex-enhanced turbidimetric immunoassay (Roche Diagnostics GmbH, Vienna, Austria) with a lower detection limit of 0.03 mg/L and coefficient of variation of 1.7%.

Instruments

For sickness behaviour a combination of three instruments were used.

The Hospital Anxiety Depression scale (HADS) measures the anhedonic aspects of depression (depressed sad mood and loss of interest or pleasure) and was therefore used as a measure of anhedonia (Zigmond & Snaith, 1983). The HADS has been used in numerous different types of settings (e.g., community care, primary care and hospital wards) and patient groups (Bjelland, Dahl, Haug, & Neckelmann, 2002) and found to be a reliable tool. Scores from the seven depression items range from 0-21, with higher scores indicating anhedonia (Zigmond & Snaith, 1983). **Reliability for the HADS has been found to be 0.82 (Bjelland, et al., 2002).**

Fatigue was measured using the vitality scale of the SF-36. The scores **range from** 0-100, with a higher score indicating higher levels of energy (Ware & Sherbourne, 1992). The vitality scale of the SF-36 has been used in studies examining the association between fatigue and inflammation in patients with breast cancer (Bower, et al., 2002; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006). **Reliability of the vitality (i.e. fatigue) scale of the SF-36 has been found to exceed 0.80 (Sullivan, Karlsson, & Ware, 1995).**

Sleepiness was measured with a single item **(i.e., How great are the problems do you have with sleepiness during the day?)** from the Uppsala Sleep Inventory (USI) (Liljenberg, Almqvist, Hetta, Roos, & Agren, 1988). The respondents rate their **problems on** a 5-point Likert scale ranging from no problems to very great problems. The whole USI has previously been used in surveys of both younger and elderly people, as well as patients with heart failure (Brostrom, Stromberg, Dahlstrom, & Fridlund, 2004; Mallon, Broman, & Hetta, 2002; Mallon & Hetta, 1997). **This single item measure of sleepiness has been used in previous studies (Johansson, et al., 2009).**

Analytic strategy and statistical analysis

Descriptive statistics and structural equation modelling (SEM) were used to analyse the data. **The SEM analysis** was inspired by Bowers model (Bower, 2007) which describes a potential association between cancer and cancer treatment, inflammation, and cancer-related fatigue. In that model, cancer and its treatment are assumed to activate the inflammatory network which in turn leads to symptoms of fatigue. In our model we included "impaired cardiac function", "inflammation" and "sickness behavior". According to the inflammation hypothesis of heart failure, the direction of the path in the SEM was drawn from impaired cardiac function towards inflammation (Pasic, et al., 2003). Paths were also drawn from "inflammation" to "sickness behavior", as well as between "impaired cardiac function" and "sickness behavior". The latent variable "impaired cardiac function" included three classes of LVEF, and the cardiac biomarker NT-proBNP. Cardiovascular medications used for patients with heart failure, namely **ACE-I, ARB, beta-blockers, and diuretics were also included since they can improve LVEF and decrease oedema and may thereby decrease inflammation.** The latent factor "inflammation" included plasma values of CRP. As sickness behavior can be seen as a symptom cluster (Myers, 2008), the variables anhedonia, fatigue and sleepiness were amalgamated to one latent factor labeled "sickness behavior". To explore a possible influence of **age and important comorbidities** on the relationship between impaired cardiac function, inflammation and sickness behavior, the impact of creatinine (i.e. marker of impaired kidney function), blood glucose (i.e. a marker of diabetes), obesity (i.e. body mass index) respiratory disease, previous or current tumor and ischemic heart disease (IHD) (all yes/no) were examined in the basic SEM model. These illnesses were chosen because of their known association to impairment of cardiac function and/or inflammation and/or sickness behavior.

Categorical variables were tested with Chi-2 tests while continuous variables were analysed with Student's t-test or Mann-Whitney U-test, depending on distribution of normality. SEM was used to explore the relationships between impaired systolic function, inflammation and sickness behavior. In the SEM analysis, by the means of PRELIS analysis, polychoric correlations were used to derive estimates of covariance. Polychoric correlations estimate the correlations between latent estimates of the measured variables and assume a normal distribution of bivariate variables. To **obtain a normal distribution CRP, plasma-creatinine and NT-proBNP were logarithmically transformed.**

Associations in the SEM were derived using maximum likelihood methods and are described with their standardized coefficients. To assess Goodness of Fit the chi-square value, the Root Mean Square Error of Approximation (RMSEA) and **Comparative Fit Index (CFI)** were used to indicate how well the model fit in the population of community dwelling elderly. For the chi-square test, a high value and a significant test indicate a poor fit, but these parameters are influenced by sample size. An overall RMSEA below 0.06 and **a CFI $\geq$ 0.95 indicates a good fit** (Schreiber, 2008). Descriptive statistical analyses were performed with SPSS 18.0 (IBM, SPSS, Chicago, IL) and SEM analyses were performed with LISREL (Scientific Software International, Lincolnwood, IL). A $p<0.05$ in the SPSS analyses and a T-value of $\geq$ 1.96 in the LISREL analyses were considered significant.

Results

Out of the 675 participants investigated, 627 (93%) had follow-up data on cardiac function, inflammation, anhedonia, fatigue and sleepiness (i.e. sickness behaviour). Table 1 describe the characteristics of the studied sample. The mean age of the sample was 78 years and 47% were men. The vast majority had hypertension (78%) whereas 27%, 16%, 16% and 15% had a

history of ischemic heart disease, diabetes, tumour or respiratory disease. Approximately one third of the population was on ACE-I/ARB, β-blockers and/or diuretics. About one fifth (21%) of the population had at least mildly impaired LVEF. Median NT-proBNP was 258 ng/L and 25% had a plasma value >555 ng/L. Median CRP was 2.4 mg/ml with an upper quartile of 4.7.

Impaired cardiac function, inflammation and sickness behaviour

The covariance matrix used in the SEM analyses can be seen in Table 2. Figure 1 describes the basic SEM model of the association between impaired cardiac function, inflammation and sickness behaviour. The fit of the model was good (Chi Square=30.5, p=0.10: RMSEA=0.025, CFI=0.99), demonstrating that impaired cardiac function had significant direct associations with inflammation (β=.26) and sickness behavior (β=.31). Inflammation also had a significant direct, but compared to impaired cardiac function, smaller association with sickness behavior (β=.21). **A partial mediation was found between impaired cardiac function and sickness behavior mediated by inflammation (β=.05).** The total effect of impaired cardiac function on sickness behavior was β=.36.

To examine the influence of age, body mass index, plasma-creatinine, blood-glucose, respiratory disease, previous or current tumor and IHD on the associations between impaired cardiac function, inflammation and sickness behaviour, new SEM models were tested for each variable. Age (β=.39), blood glucose (β=.32), respiratory disease (β=.17), plasma-creatinine (β=.58) and IHD (β=.80) were all significantly associated with impaired cardiac function, whereas, body mass index and previous or current tumor were significantly associated with inflammation (β=.28 and β=.22). However, none of these new models revealed any major impact on the association between impaired cardiac function, inflammation and sickness behaviour. Both plasma-creatinine and IHD had strong associations with impaired cardiac

function. This is a logical finding since these can be seen as an aspect of the pathophysiology of heart failure. In a subsequent analysis we therefore added IHD and plasma-creatinine into the latent variable impaired cardiac function and explored if either variable had any impact on the associations between impaired cardiac function, inflammation and sickness behaviour. The fit of this model was also good (Chi Square=43.9, p=0.12: RMSEA=0.022, CFI=0.99). However, this model did not add any new information because all associations (β) were of the same magnitude as those found in the initial model (Figure 1). In this new model, the indirect effect between impaired cardiac function and sickness behavior (β=.05) mediated by inflammation also remained unchanged.

Discussion

In community dwelling older adults we found that inflammation was associated with a symptom cluster consisting of anhedonia, fatigue and sleepiness in those individuals with impaired cardiac function. This suggests that some of the symptoms experienced by elders with impaired cardiac function or heart failure represent sickness behaviour.

In the present study sickness behaviour was defined as including anhedonia, sleepiness and fatigue. These symptoms may be evidence of an inflammatory component representing sickness behaviour, although this symptom cluster has not been investigated in such a fashion. In patients with cancer, investigators have found inflammation to be associated with depression or fatigue (Bower, et al., 2002; Bower, et al., 2011; Orre, et al., 2009). Heart failure is another condition which has been found to be associated to an activated inflammatory network (Torre-Amione, et al., 1996), with depression (Lesman-Leegte, Jaarsma, Sanderman, Linssen, & van Veldhuisen, 2006), sleepiness (Brostrom, et al., 2004) and fatigue (Falk, Patel, Swedberg, & Ekman, 2009) commonly reported. Recent studies have

found inflammation to be associated with depression in patients with heart failure (Johansson, et al., 2011; Wirtz, et al., 2009). However, these studies have only evaluated depression or fatigue separately and not as a symptom cluster.

For nurses, knowledge about the underlying mechanisms of heart failure symptoms may be important for the development of treatment strategies. Our SEM models illustrate that impaired cardiac function had a direct association to sickness behaviour and inflammation. However, we also found inflammation to be directly associated with sickness behaviour, and importantly, inflammation mediated a partial indirect association between impaired cardiac function and sickness behaviour. Aging and comorbidity can increase inflammation and hence trigger sickness behaviour (Hunt, et al., 2010a). In our analysis, based on individuals mean aged 78 years, age and comorbid conditions were associated with impaired cardiac function and inflammation, but the presence of these variables did not change the associations found in the principal SEM model. These findings suggest that inflammation mediates the symptom response in elders with impaired cardiac function. From a clinical perspective, suffering from sickness behaviour may lead to less capability to perform daily activities. Patients may use this as a negative description of their self-image with wordings such as tiredness, loss of interest and laziness. To reduce this psychological burden, nurses can base their information on an explanation that this perception can originate from biological changes due to an impaired cardiac function.

From a biophysical perspective, several mechanisms due to impairment of cardiac function can lead to inflammation and thereby to sickness behaviour. Under-perfusion of systemic tissue, as well as changes in the cardiac endocrine function such as increased secretion of brain natriuretic peptides are some mechanisms (Clerico, Giannoni, Vittorini, & Passino, 2011; Pasic, et al., 2003). Another potential mechanism is increased permeability of the gut-wall due to oedema. This can induce translocation of gram-negative enterobacteria and

secretion of endotoxin (i.e. lipopolysaccharide, LPS), which is a potent stimulus of immune activation (Maes, Mihaylova, & Leunis, 2007). Oedematous patients with severe heart failure have been shown to have decreased intestinal absorption and higher plasma concentrations of LPS, TNF-a and TNF-receptors 1 and 2 compared non-oedematous heart failure patients and healthy controls (Sandek, et al., 2010). Gut-wall oedema can delay the absorption of medications and could hypothetically therefore be a sign of a more treatment resistant patient or just a patient with more severe heart failure and a worse prognosis. The impact of sickness behaviour has not been investigated in patients with heart failure. However, fatigue has been found to predict worsening heart failure (Ekman, et al., 2005). Depression (Johansson, et al., 2007; Lesman-Leegte, et al., 2009; Sherwood, et al., 2007) and fatigue (Smith, Kupper, de Jonge, & Denollet, 2010) have both been found to be associated with mortality. Nurses should be aware of these critical pathophysiological signs of sickness behaviour, and therefore observant of the above mentioned symptoms/conditions among elderly patients with heart failure.

Pharmacological treatment for heart failure, i.e. ACE-I/ARB, beta-blockers and diuretics, was in our model a part of the factor designated as impaired cardiac function. **Despite the potential anti-inflammatory secondary effects of these cardiovascular medications (i.e., improved LVEF and cardiac output, decreased oedema, and decreased immune activation),** inflammation mediated some of the association between impaired cardiac function and sickness behaviour. This suggests that other medications or non-pharmacological interventions with anti-inflammatory properties are needed to treat sickness behaviour. Clinical trials investigating treatment approaches of sickness behaviour are lacking. In the SADHART-CHF trial selective serotonin reuptake inhibitors (SSRI) was not superior to placebo to decrease depression in heart failure patients (O'Connor, et al., 2010). In a substudy of the same trial it was shown that those patients whose depression did not improve from

baseline levels, irrespective of SSRI or placebo, had more somatic/affective symptoms at baseline (Jiang, et al., 2011). Continuing depression suggests a symptom profile which could correspond with sickness behaviour. It is therefore possible that such aspects of sickness behaviour in heart failure may be less responsive to anti-depressant therapy. Statins have been shown to have anti-inflammatory effect in patients with coronary heart disease. Interestingly, in a retrospective analysis of the CORONA study, statins had favourable effects on cardiovascular deaths, all-cause mortality, and hospitalisations in a sub-group of patients with evidence of increased inflammatory activity (plasma value of CRP $\geq$ 2.0 mg/L) at baseline (McMurray, et al., 2009). Sickness behaviour was not included as an outcome in the CORONA trial, but these results imply that statins could be useful in heart failure patients with sickness behaviour.

Other approaches to decreasing inflammation include lifestyle changes focusing on anhedonia, fatigue and sleepiness. Studies suggest that exercise programs can decrease inflammation in non-heart failure populations (Pinto, et al., 2012) as well as in heart failure patients (Adamopoulos, et al., 2001). There is also evidence supporting the use of exercise programs for depressive disorders in patients without heart failure (Dirmaier, et al., 2012). Limited evidence also suggests that exercise programs can improve depressive symptoms in heart failure patients (Koukouvou, et al., 2004; Milani, Lavie, Mehra, & Ventura, 2011). Whether or not exercise can improve symptoms of sickness behaviour remains to be elucidated.

A limitation with the present study is that it was not specifically designed to examine an association between inflammation and sickness behaviour. We only had one marker of inflammation in our analysis. We also had a limited number of variables that could be used as indicators of sickness behaviour. Specifically, CRP was the only indicator of inflammation used. Although **CRP is commonly used as a routine marker of inflammation,** the

association between inflammation and sickness behaviour was small (β=.21) **and may be underestimated because we did not use more direct markers of chronic inflammation such as** interleukin-1, interleukin-6 or tumour necrosis alpha (TNF-a), the key cytokines triggering sickness behaviour (Dantzer, 2006). Another methodological reason for the low correlations found could be that data in this study were collected from community-dwelling older adults who may not have been sufficiently ill to demonstrate more robust associations. However, the association between different inflammatory markers and fatigue in cancer patients rarely exceeded r=.20; the highest correlation was r=.29 (Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007). A clinical reason for these low correlations could be that the symptoms included in the sickness behaviour cluster (anhedonia, fatigue, sleepiness) are not only caused by inflammation but may also occur as a response to other stressors such as low socio-economic status or bereavement (Cole & Dendukuri, 2003; Skobel, et al., 2005). Unfortunately, data on obstructive sleep apnea, cognitive impairment, **lethargy, loss of appetite, hyperalgesia** and physical capacity, also known to trigger inflammation, were not available for inclusion in the model. This may have underestimated the associations found between inflammation and sickness behaviour in the present study. Moreover, because of the cross-sectional study design the associations presented in the SEM models cannot be interpreted as strict causal relationships.

In summary, we have shown that inflammation and impaired systolic function both were associated with a symptom cluster of anhedonia, fatigue and sleepiness in community dwelling older adults. Our results imply that this symptom cluster could represent sickness behaviour in patients with heart failure. If these associations are supported in future research, innovative intervention approaches are needed for patients with heart failure and sickness behaviour.

Figure

Figure 1. Structural equation model of the associations (Beta weights) between impaired systolic function, inflammation and sickness behavior. The factor loadings are in italics. All effects and loadings shown are significant ($t<1.96$). Impaired cardiac function had a significant direct but also a significant indirect effect (.05) on sickness behavior mediated by inflammation.

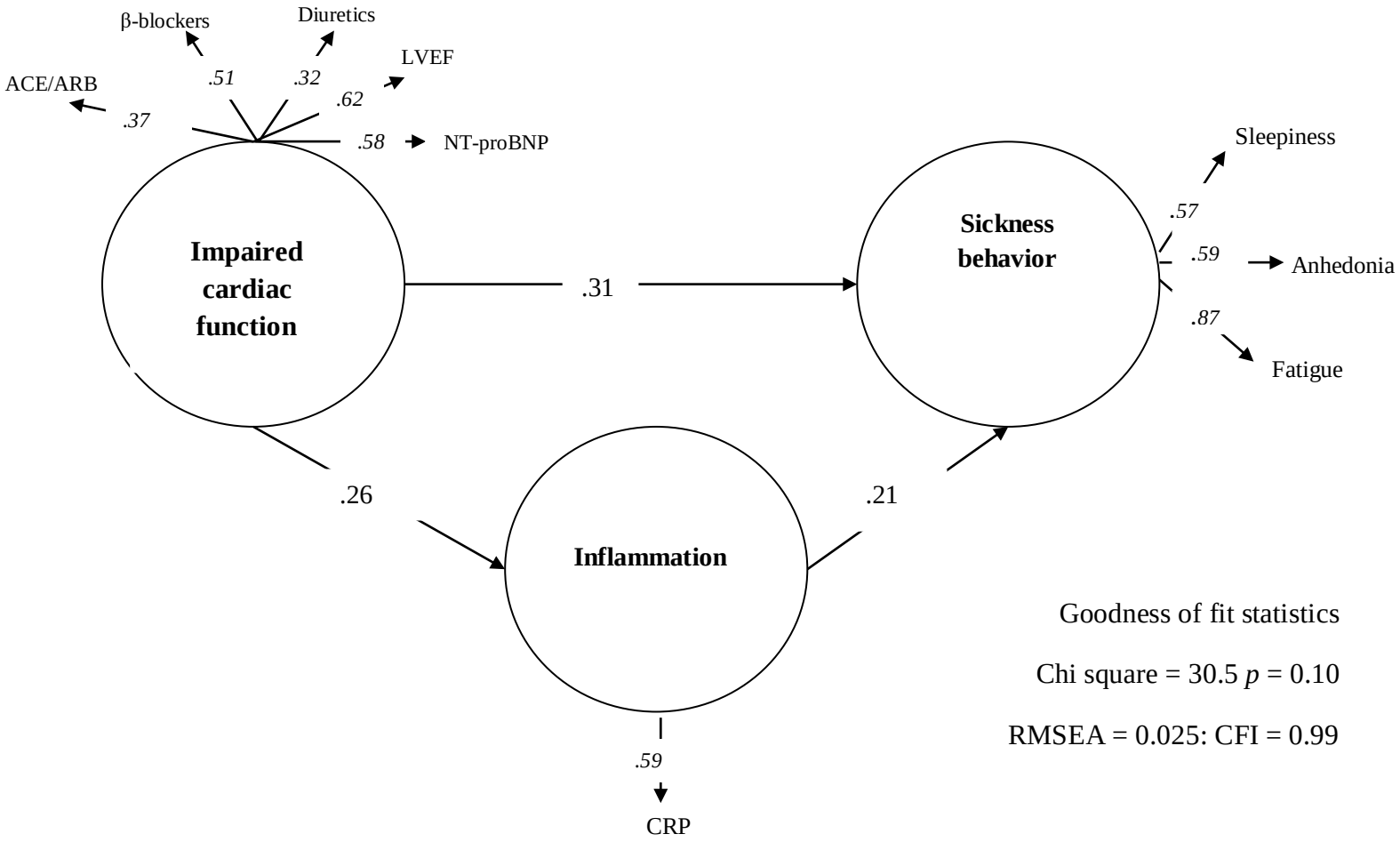
β-blockers
Diuretics
LVEF
ACE/ARB
.51
.32
.62
.37
.58
NT-proBNP
Impaired cardiac function
.31
Sickness behavior
Sleepiness
.57
.59
Anhedonia
.87
Fatigue
.26
.21
Inflammation
.59
CRP
Goodness of fit statistics
Chi square = 30.5 p = 0.10
RMSEA = 0.025: CFI = 0.99

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Table 1. Demographic and medical characteristics of the study sample (*N* = 627).

Characteristic	Value
Age, mean (SD)	78 (4)
Sex, male % *(n)*	47 (296)
Body mass index, mean (SD)	27.1 (4.2)
Systolic blood pressure, mean (SD)	149 (23)
Diastolic blood pressure, mean (SD)	75 (11)
Diabetes, % *(n)*	16 (102)
Hypertension, % *(n)*	78 (486)
Ischemic heart disease, % *(n)*	27 (170)
Previous or present tumor, % *(n)*	16 (103)
Respiratory disease, % *(n)*	15 (96)
Left ventricular ejection fraction, % *(n)*	
≥ 50%	79 (495)
49–40%	13 (81)
< 40%	8 (51)
NT-proBNP ng/L, median (25^{th}–75^{th} quart)	258 (140–555)
CRP mg/L, median (25^{th}–75^{th} quart)	2.4 (1.1–4.7)
Creatinine µmol/L , median (25^{th}–75^{th} quart)	74 (63–90)
Blood glucose mmol/L, mean *(SD)*	5.8 (2.2)
ACE/ARB, % *(n)*	26 (162)
β-blockers, % *(n)*	36 (230)
Diuretics, % *(n)*	35 (221)
Anhedonia (HADS), mean *(SD)*	3.8 (2.6)
Fatigue (vitality scale SF-36), mean *(SD)*	61.5 (22)
Sleepiness, mean *(SD)*	2.2 (0.9)

Note. ACE/ARB = Angiotensin converting enzyme inhibitor/angiotensin receptor blockade; CRP = C-reactive protein; HADS = Hospital Anxiety Depression Scale; NT-proBNP = N-terminal of probrain natriuretic peptide.

Table 2. Estimates of covariance of the variables used in the semi-structural equation analyses. The correlations were derived by means of PRELIS analysis.

	NT-proBNP	CRP	Anhedo-nia	Sleepiness	Fatigue	BMI	Creatinine	B-glucose	Resp Dis.	Tumour	ACE/ ARB	B-blocker	Diuretics	Age	IHD	LVEF
NT-proBNP	1.0															
CRP	0.140	1.0														
Anhedonia	0.082	0.088	1.0													
Sleepiness	0.116	0.116	0.355	1.0												
Fatigue	0.220	0.153	0.515	0.489	1.0											
BMI	-0.06	0.182	-0.025	0.027	0.038	1.0										
Creatinine	0.209	0.158	0.069	0.104	0.116	0.064	1.0									
B-glucose	0.032	0.099	-0.016	0.034	0.105	0.172	0.114	1.0								
Resp-Dis.	0.088	0.127	0.026	0.103	0.141	0.070	0.042	0.020	1.0							

Tumour	0.045	0.137	-0.065	0.111	0.068	0.133	0.018	-0.017	0.026	1.0						
ACE/ARB	0.154	0.048	0.101	0.149	0.186	0.200	0.185	0.258	0.157	0.071	1.0					
B-blocker	0.299	0.049	0.034	0.100	0.127	0.122	0.053	0.074	0.020	0.126	0.219	1.0				
Diuretics	0.202	0.157	0.042	0.101	0.163	0.235	0.131	0.101	0.199	0.242	0.458	0.332	1.0			
Age	0.364	0.049	-0.010	0.099	0.196	-0.092	0.137	0.082	0.028	0.083	0.032	0.029	0.041	1.0		
IHD	0.246	0.052	0.054	0.159	0.160	0.027	0.160	0.128	0.100	0.054	0.223	0.516	0.123	0.257	1.0	
LVEF	0.369	0.074	0.109	0.091	0.181	-0.007	0.251	0.107	0.003	0.012	0.236	0.319	0.163	0.284	0.475	1.0

Note: ACE/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blockade; B-glucose = beta glucose; BMI = body mass index; CRP = C-reactive protein; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal of probrain natriuretic peptide; Tumor = previous or present tumor; Resp Dis = respiratory disease.