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Somatic Depressive Symptoms, Vital Exhaustion, and Fatigue: Divergent Validity of Overlapping Constructs

The relative importance of “somatic” and “cognitive-affective” depressive symptoms as risk indicators for cardiovascular disease is an important current topic of scientific investigation. This issue of the journal includes four articles that evaluate the predictive value of somatic depressive symptoms, exhaustion, and/or fatigue as predictors of adverse cardiovascular disease outcomes and mortality. Although this is not a special issue, these articles were received in a relatively short time interval, indicating that this is an active research area. The studies extend current thinking regarding the predictive value of depression for adverse cardiovascular prognoses in clinical settings and the general population. This editorial reviews the results from these studies and addresses potential biobehavioral mechanisms, central nervous system pathways, and implications for interventions.

A critical evaluation of the literature in this area is important because of the overlap of the various phenotypes of interest, that is, depression, somatic depressive symptoms, vital exhaustion, and fatigue. Somatic depressive symptoms include fatigue, sleep problems, change in appetite, and psychomotor changes. Most of the somatic depressive symptoms overlap with characteristics of vital exhaustion, a condition characterized by lack of energy, increased irritability, and demoralization (referred to as “exhaustion” in the remainder of this text). The exhaustion construct was developed to identify individuals at risk for future acute coronary syndromes (1). Fatigue can be examined as a symptom by itself or as part of psychological constructs such as depression and exhaustion. Research has shown that fatigue is a multidimensional phenomenon including physical and mental components. Fatigue is one of the most common premonitory symptoms of myocardial infarction (MI) and sudden cardiac death. In some cases, fatigue can be considered as an angina equivalent reflecting underlying coronary artery disease, particularly when it is of recent onset and related to exertion. In female patients, fatigue is the most common symptom in the month before MI (2). However, fatigue, exhaustion, and somatic depressive symptoms are not attributable to underlying disease severity in most patients with cardiovascular disease because associations between these constructs and the number of diseased vessels, inducibility of myocardial ischemia, and cardiac pump function are minimal (3).

The substantial overlap in these constructs is partly explained by a) commonalities in the definition and actual item content of the respective assessment instruments and b) common etiologic precipitants (e.g., disease burden and prolonged psychological distress) and biobehavioral correlates (e.g., inflammation and physical inactivity). Differences between these constructs are mainly conceptual and individuals often meet criteria for one condition (e.g., depression) but not the other (e.g., exhaustion) (4,5). In addition, the typical presentation of depression in patients with cardiovascular disease often differs from what is observed in clinical psychology and psychiatry. Depressive cognitions (e.g., guilt, feelings of worthlessness, suicidal thoughts) are considerably more common in depressed psychiatric patients compared with depressed patients with cardiovascular disease (6). Somatic depressive symptoms may therefore have specific clinical implications for patients with cardiovascular diseases, and the articles in this issue of the journal add to the scientific basis of the importance of somatic depressive symptoms.

Vroege and colleagues (7) conducted a prospective study of 528 patients with MI to investigate whether somatic depressive symptoms overlap more strongly with exhaustion than cognitive-affective depressive symptoms and to evaluate the risk of these constructs for recurrent cardiovascular events (median follow-up, 2.2 years). Factor analysis revealed two components: somatic depressive and cognitive-affective depressive symptoms with 19 of 21 exhaustion items loading on the somatic depressive component. Exhaustion was associated with an increased risk of recurrent events (hazard ratio [HR] = 1.37, 95% confidence interval [CI] = 1.15–1.64 per standard deviation). The adjusted risk of the somatic depressive component (including the exhaustion items) was similar (HR = 1.39, 95% CI = 1.11–1.73 per standard deviation). The cognitive-affective component was not predictive of adverse outcomes (HR = 1.02, 95% CI = 0.82–1.27). Several items that loaded high on the somatic depressive component would be more plausibly grouped with the cognitive-affective component based on the actual item content (e.g., indecisiveness, irritability, difficulties concentrating). The authors included an interesting item analysis, showing that only 4 of the 21 items of the depression scale (Beck Depression Inventory) predicted depression (4). An investigation was that somatic depressive symptoms may reflect clinical HF severity, hence increasing depression scores and also accounting for the predictive value of depression for adverse HF outcomes. Somatic depressive symptoms (fatigue, sleep disturbance, and appetite change) and cognitive-affective depressive symptoms (the remaining six DSM-IV–based

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depression symptoms: depressed mood, anhedonia, psychomotor retardation or agitation, feelings of worthlessness or guilt, diminished concentration or ability to think, and suicidal ideation) were measured in 210 patients with HF using the Patient Health Questionnaire 9. The covariate-adjusted risk for the total Patient Health Questionnaire 9 was significant (HR = 1.07, 95% CI = 1.03–1.13 per unit). Risks for somatic (HR = 1.11, 95% CI = 1.02–1.21) and cognitive-affective (HR = 1.14, 95% CI = 1.06–1.22) depressive symptoms were similar in unadjusted models. However, cognitive-affective depressive symptoms were independently predictive of cardiac events (HR = 1.12, 95% CI = 1.03–1.22) after adjusting for health status (comorbidities and New York Heart Association functional class) and clinical and sociodemographic factors, whereas the risk of somatic depressive symptoms was attenuated (HR = 1.07, 95% CI = 0.97–1.19) in multivariable analysis. A direct comparison between cognitive-affective and somatic depressive symptoms was not reported. It is important to note that most events in this study (55/59) involved hospitalizations and not mortality and that multivariable models may have been overfitted because of including antidepressive medication use in the analyses. These aspects of the study may partly explain why the cognitive-affective depressive symptoms were better predictors than somatic depressive symptoms in multivariable models. The conclusion that the relationship of depressive symptoms with future cardiac events is not artificially inflated by the inclusion of somatic depressive symptoms in the assessment of depression is valid and consistent with the findings in other medical conditions.

The study by Smith and colleagues (9) examined whether fatigue contributed to the association between somatic depressive symptoms and increased risk of mortality in 380 patients with HF. Somatic symptoms of depression (using the Beck Depression Inventory I), self-reported exertion-related fatigue, and general fatigue were evaluated using questionnaires, and the primary end point was mortality (median follow-up, 2.3 years). Exertion-related fatigue (HR = 1.04, 95% CI = 1.01–1.06 per unit) but not general fatigue (HR = 1.02, 95% CI = 0.99–1.05 per unit) was associated with an increased mortality risk. The association between somatic depressive symptoms and mortality remained significant after adjusting for exertion-related fatigue (HR = 1.41, 95% CI = 1.05–1.88). Thus, the predictive value of somatic depressive symptoms for adverse HF outcomes is not merely the effect of fatigue but also involves other components of somatic depressive symptoms included in the factor score (e.g., loss of appetite, weight loss). The unadjusted risk of somatic depressive symptoms was not reported in this article. As in the study by Vroeqe et al. (7), several cognitive-affective items were included in the somatic depressive component (e.g., indecisiveness and dissatisfaction), and sleep problems unexpectedly did not load on the somatic depressive component. These findings indicate that factor analysis–based approaches may identify patterns of association across various seemingly unrelated symptoms, but such patterns tend to be sample dependent, are difficult to replicate, and result in the inclusion of cognitive-affective depressive items in the somatic depressive component, leading to problems with content validity (see also Carney and Freedland (10) for a similar concern related to factor analysis–based summary scores).

The study by Ekmann et al. (11) makes a unique contribution among this collection of articles in that a population-based sample was selected to investigate whether fatigue predicted nonfatal ischemic heart disease (IHD) and all-cause mortality among men born in 1953 (N = 5216). During 4 years of follow-up, 110 nonfatal MIs and 75 deaths were observed. Fatigue was associated with hospitalization for nonfatal IHD (HR = 1.98, 95% CI = 1.09–3.61) and all-cause mortality (HR = 3.99, 95% CI = 2.27–7.02). Depression (based on interview) was predictive of mortality (5/75 versus 91/4940, p < .001) but not IHD (3/110 versus 93/4940). However, the associations between fatigue and adverse outcomes became nonsignificant in multivariable models (HR = 1.57, 95% CI = 0.82–3.01 and HR = 1.90, 95% CI = 0.95–3.80, respectively) adjusting for socioeconomic position, life-style factors, depression, diabetes, hypertension, and antihypertensive medication use. Post hoc analyses suggested that associations were stronger for non-smoking men (fatigue–by–smoking status interaction, p = .04). This study relied on a two-item assessment of fatigue with only 6% of the sample classified as having elevated fatigue scores. This low prevalence of fatigue could explain that relatively large HRs (>1.5) were statistically nonsignificant. The findings show that fatigue is predictive of incident cardiovascular events but that this association may in part reflect confounding or effect modification by other biobehavioral factors. Fatigue may also not be optimally evaluated with a two-item scale.

The evidence from these four studies leads to several important insights. The overlap between somatic depressive symptoms and exhaustion is substantial (7), and these two constructs may not be readily disentangled based on statistical methods or epidemiologic study designs. Experimental designs and targeted treatment studies are probably needed to establish divergent validity. The inclusion of somatic depressive symptoms in the diagnosis of depression in patients with medical disorders that typically involve similar symptoms (e.g., fatigue and sleep problems in cardiovascular disease) is supported by the findings by Lee et al. (8). Furthermore, the predictive value of somatic depressive symptoms is not only based on fatigue because controlling for exertion-related fatigue did not eliminate the significant predictive value of somatic depressive symptoms for adverse HF outcomes (9). In general, it seems that the predictive value of somatic depressive symptoms, exhaustion, and fatigue is to some extent confounded—not eliminated—by disease-related factors such as symptom status and functional limitations in patients with cardiovascular disease. This confounding may play a lesser role in cognitive-affective symptoms, but the overall effect size of the cognitive-affective component of depression may be less than that of somatic depressive symptoms (10). The relative contribution of somatic versus cognitive-affective depressive symptoms varies across studies and may depend on whether the focus is on incident cardiovascular events in the general population or clinical outcomes in patients with cardiovascular disease, the nature of the clinical setting, and type of cardiovascular outcome (8,11).
Key differences between subtypes of depression, exhaustion, and fatigue are possibly better understood in their purported etiology and accompanying biobehavioral processes combined with potentially distinct central nervous system correlates and different responses to targeted treatments.

The etiology of depression is multifactorial and involves a combination of vulnerability factors and environmental precipitants; details are beyond the scope of this editorial. Exhaustion and fatigue are characteristically considered as “normal” responses to prolonged psychological or physical challenges. Because of the substantial overlap among somatic depressive symptoms, exhaustion, and fatigue, it is possible that these constructs share a common etiology. As shown in Figure 1, somatic depressive symptoms may reflect the adverse consequences of prolonged and uncontrollable psychological distress combined with the effects of physical limitations related to cardiovascular disease. Depression is by definition involved in somatic depressive symptoms as reflected by the adjective “depressive” (see the last paragraph for comment on this issue). Other important factors that may lead to somatic depressive symptoms are inflammation and/or impaired response to injury with subsequent sickness behavior (12), an unhealthy life-style (particularly physical inactivity, poor dietary habits, smoking, and alcohol overuse), comorbidities (e.g., diabetes mellitus and hypertension), and cognitive decline (resulting in increased mental effort required for routine daily activities). It is important to note that these associations are bidirectional, such that they may lead to somatic depressive symptoms, but also that somatic depressive symptoms may further promote the development and persistence of these biobehavioral factors (as indicated by the two-headed arrows in the figure). Factors that have a unidirectional influence in the etiology of somatic depressive symptoms are sleep disturbances, in rare cases substantially reduced cardiac pump function and unintended effects of medications. These etiologic factors may interact with central nervous system correlates of somatic depressive symptoms and can help determine optimal treatment targets. Conceptual models for the etiology of exhaustion or fatigue are very similar, and it is unlikely that the constructs of somatic depressive symptoms, exhaustion, and fatigue can be differentiated based on these biobehavioral factors.

Unique central nervous system or other biologic markers for the diagnosis of depression, exhaustion, or fatigue have not been identified. Some evidence indicates, however, that different brain circuits and neurotransmitter pathways play a role in somatic versus cognitive-affective symptoms of depression (13–15). Areas involved in somatic depressive symptoms seem to include reduced activity in the prefrontal cortex (several areas, particularly dorsolateral and ventromedial regions), basal forebrain (mainly involved in sleep disturbances), hypothalamus (related to appetite and other “drives” and apathy), nucleus accumbens, striatum, cerebellum, and spinal cord (related to physical fatigue). In addition, the nonmotor functional aspects of the basal ganglia may contribute to fatigue by feedback to the striatum and thalamus, that is, a dysregulated cortical-subcortical circuitry. Dysregulated functional activity within or between areas such as the anterior cingulate (possibly as a compensatory mechanism), the parietal cortex, and possibly the amygdala may also coincide with fatigue (16). Pertinent neurotransmitter alterations include changes in dopaminergic and noradrenergic pathways for symptoms of fatigue and energy depletion, serotonergic pathways for appetite, and all three pathways for sleep and psychomotor changes. In contrast, the brain areas of direct importance to the cognitive-affective depressive symptoms seem to be more focal, primarily involving the ventromedial prefrontal cortex, orbitofrontal cortex, and the amygdala. Other areas related to cognitive-affective depressive symptoms, particularly anhedonia, include the nucleus accumbens and the rostral anterior cingulated cortex (17). The neurotransmitters involved in cognitive-affective symptoms primarily include serotonergic but also dopaminergic and noradrenergic pathways. In other words, it can be hypothesized that the cerebral structures involved in somatic depressive symptoms are more widespread throughout the brain compared with cognitive-affective symptoms. Furthermore, it could be that noradrenergic and dopaminergic pathways play a relatively important role in somatic depressive symptoms compared with cognitive-affective depressive symptoms.

Interventions can be improved by differentially targeting somatic versus cognitive-affective depressive symptoms. It is critical to determine whether somatic depressive symptoms reflect a marker of underlying cardiovascular disease (in which case, they are primarily of diagnostic value) or whether these symptoms are indeed independent risk factors. Evidence indicates that the latter is the case in most patients and that it may therefore be possible to reduce cardiovascular risk by improving somatic depressive symptoms. Little is known about effective interventions specifically designed to reduce somatic depressive symptoms. One study targeted exhaustion in patients after angioplasty and revealed no consistent positive effects on 2-year cardiovascular prognosis (18). Factors outlined in Figure 1 may provide a framework to identify individually tailored intervention targets that can be used to interfere with vicious cycles of mutually reinforcing factors that result in the sustained presence of somatic depressive symptoms. It is also possible that patients’ motivation to seek

![Figure 1. Multifactorial aspects of somatic depressive symptoms. Bidirectional associations are depicted by two-headed arrows.](image-url)
treatment for depression is less if somatic aspects are more prominent than cognitive-affective aspects; screening and referral strategies may need to take this into account as well. Differences in depressive symptom profiles and related treatment seeking behavior may also be important in understanding differences in efficacies of interventions between men and women, various sociodemographic groups, and patients with general medical conditions versus patients in psychiatry and clinical psychology. Given the findings reported in this issue of the journal and the review by Carney and Freedland (10), it will be important to further develop interventions that differentially target the somatic components of depression (e.g., behavioral activation, stress reduction) and cognitive-affective components (e.g., cognitive behavioral therapy) of depression. Similarly, pharmacotherapies may be selected based on depression symptom profiles, taking into account that intervening on dopaminergic and noradrenergic pathways may be contraindicated in patients with cardiovascular disease.

The four articles in this issue of *Psychosomatic Medicine* provide an important extension to a previous special issue published in this journal under the editorship of Dr. David S. Sheps focusing on depression in cardiovascular disease (19,20). The introductory article stated that “Research on the relationship between depression and heart disease has important implications for clinical practice, not only for specialists in psychosomatic medicine but for other physicians as well.” This still holds true, also for the components of depression such as somatic depressive symptoms. However, one of the problems with the term “somatic depressive symptoms” is that it implies that fatigue, sleep problems, and other symptoms in this category reflect underlying depression, which may or may not be the case. It could therefore be argued that a better term would be “somatic symptoms,” which in turn is problematic because this implies the incorrect notion that symptoms mainly have physical and not psychological determinants. It may therefore be preferable to identify signs and symptoms per se and only generate clusters and syndromes if they have etiologic, mechanistic, or therapeutic implications. New research needs to move beyond statistical procedures and epidemiologic designs to identify pertinent symptoms relevant to cardiovascular disease. In addition to the somatic and cognitive-affective depressive symptoms reviewed here, other symptoms that often accompany depression and cardiovascular disease need to be investigated, particularly anxiety, irritability, hopelessness, and social withdrawal. These symptoms are in their essence self-reported phenomena that cannot be equated or substituted with biologic or central nervous system measures. Clinical, experimental and intervention studies are needed to determine the potential different biobehavioral pathways by which somatic depressive symptoms, exhaustion, and fatigue affect cardiovascular and other disease outcomes and how targeted treatments can be further developed.

**REFERENCES**