Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study

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Accepted 9 May 2003

Background Vital exhaustion, a psychological measure characterized by fatigue and depressive symptoms, has been suggested to be an independent risk factor for ischaemic heart disease (IHD) but the generality of the phenomenon remains in question. The aim of this study is to describe prevalence of these symptoms in a community sample and determine whether they prospectively predict increased risk of IHD and all-cause mortality in men and women.

Methods The study base was 4084 men and 5479 women aged 20–98 free of IHD examined in 1991–1993 in the Copenhagen City Heart Study. Events were ascertained through record linkage until 1998 for IHD and September 2000 for all-cause mortality. There were 483 first hospital admissions and deaths caused by IHD and 1559 deaths from all causes during follow-up.

Results The 17 items on the vital exhaustion questionnaire were frequently endorsed with prevalence ranging from 6 to 47 per cent, higher in women. All but 4 of the 17 items were significantly associated with IHD with significant relative risks (RR) ranging between 1.36 (95% CI: 1.08, 1.72) and 2.10 (95% CI: 1.63, 2.71). Associations with all-cause mortality were also observed, but were weaker. RR of both IHD and all-cause mortality increased with increasing item sum score and were similar in men and women. For IHD, RR reached a maximum of 2.57 (95% CI: 1.65, 4.00) for subjects endorsing ≥9 items. The similar RR for all-cause mortality was 2.50 (95% CI: 2.09, 2.99). Multivariate adjustment for biological, behavioural, and socioeconomic risk factors did not substantially affect the association for IHD but attenuated the association with all-cause mortality.

Conclusions Measures of fatigue and depression were common symptoms in this population sample and convey increased risk of IHD and of all-cause mortality. We propose this knowledge begin to be implemented in risk assessment in clinical practice.

Keywords Depression, fatigue, epidemiology, cardiovascular disease

Several prospective studies have shown associations between psychological measures and development of ischaemic heart disease (IHD).1 One such measure composed of items reflecting fatigue, hopelessness, and depression was labelled vital exhaustion2 and has been shown to prospectively predict IHD.3 Although it has been argued that the vital exhaustion construct is distinct

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from depression there is undoubtedly considerable overlap. In a factor analysis of the vital exhaustion construct, items reflecting fatigue were especially important for the prediction of myocardial infarction.

Previous studies of vital exhaustion and IHD have not been based on representative samples of the community. Furthermore, investigations of gender differences in the impact of symptoms of depression and fatigue on IHD have had mixed results. Therefore the generality of the phenomenon remains in question.

The aim of the present study was to describe the distribution of symptoms of fatigue and depression as defined in the vital exhaustion construct in a random sample of the general population, and to determine whether these symptoms prospectively predict IHD and all-cause mortality in both genders.

Methods

Population and design

We used data derived from the Copenhagen City Heart Study, a random, age-stratified sample of 19 698 individuals aged ≥20 years recruited in 1976 among 90 000 people living in a defined area in Copenhagen. A total of 14 223 subjects (response rate 72%) attended the first examination in 1976/78. At a follow-up in 1981, 83 500 new subjects age 20–25 were invited, and at the second follow-up conducted in 1991–1993 3000 new subjects were invited. The present analyses are based on the 10 135 subjects attending this third examination (response rate 61%). Subjects were followed until 31 December 1997 for fatal and non-fatal IHD (International Classification of Diseases, Eighth Revision [ICD-8] diagnosis codes 410–414 until 1 January 1994, ICD-10 diagnosis codes I21 to I25 from 1994 onwards) obtained from the National Board of Health and the National Hospital Discharge Register, respectively, and for all-cause mortality until 31 August 2000. Subjects with self-reported and verified IHD were included: Educational level, in three categories: ≤8 years of schooling (completed primary school); 8–11 years, and >11 years; as well as household income in seven categories. Cohabitation was registered dichotomously as living alone versus not living alone. Alcohol consumption was classified according to daily intake in: no daily consumption, ≤1 drink per day; 1–2; and >2 drinks per day, one drink containing 9–13 g alcohol. Physical activity in leisure time was classified into three categories as: sedentary; moderate activity <4 hours; and moderate activity >4 hours per week. Diabetes and family history of myocardial infarction were self-reported.

Statistical analyses

The Cox proportional hazards model was used to assess the independent contribution of each item of the vital exhaustion construct and a summed item score of vital exhaustion to the occurrence of IHD and all-cause mortality. Age was used as underlying time scale and age at baseline was used as entry time, thus ensuring optimal adjustment for age. Analyses were initially performed separately by gender. Since these indicated similar

### Table 1 The 17 items in the vital exhaustion construct in order of increasing prevalence

<table>
<thead>
<tr>
<th>'Do you …?'</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>Think you have come to a dead end</td>
<td>6.5%</td>
</tr>
<tr>
<td>Feel that you want to give up</td>
<td>7.9%</td>
</tr>
<tr>
<td>Sometimes wish you were dead</td>
<td>8.4%</td>
</tr>
<tr>
<td>Feel altogether weak</td>
<td>8.9%</td>
</tr>
<tr>
<td>Feel deserted</td>
<td>13.5%</td>
</tr>
<tr>
<td>Feel fine (no)</td>
<td>14.7%</td>
</tr>
<tr>
<td>At the moment feel that you do not have what it takes</td>
<td>18.8%</td>
</tr>
<tr>
<td>Have feelings of hopelessness recently</td>
<td>22.1%</td>
</tr>
<tr>
<td>Sometimes feel your body is like a battery running out</td>
<td>21.4%</td>
</tr>
<tr>
<td>Ever wake up with a feeling of exhaustion</td>
<td>23.7%</td>
</tr>
<tr>
<td>Lately have difficulties concentrating</td>
<td>21.4%</td>
</tr>
<tr>
<td>Lately feel listless</td>
<td>25.4%</td>
</tr>
<tr>
<td>Do little things irritate you more than they used to</td>
<td>23.4%</td>
</tr>
<tr>
<td>Sometimes just feel like crying</td>
<td>33.3%</td>
</tr>
<tr>
<td>Feel you have not accomplished much recently</td>
<td>27.0%</td>
</tr>
<tr>
<td>Sometimes have difficulty coping</td>
<td>36.9%</td>
</tr>
<tr>
<td>Often feel tired</td>
<td>47.3%</td>
</tr>
</tbody>
</table>
effects in men and women further analyses were performed on pooled data after formally testing for interaction with gender. All covariates were treated as categorical variables as described above and tests for interaction were done using the likelihood ratio test. The assumption of proportional hazards was assessed by graphical inspection of the estimated log-survival curves and formally tested as described by Grambsch and Therneau.15

Results
The individual vital exhaustion items were quite frequently endorsed, especially by women (Table 1). Figure 1 gives age-adjusted relative risk (RR) of IHD for each of the 17 items listed by increasing prevalence of symptoms. These results were similar in men and women and are given for the pooled data. The Figure illustrates that there was no association between the prevalence of a symptom and its associated risk. Items such as ‘often feel tired’ and ‘have difficulty coping’, which had high prevalence, could be perceived as less specific than more rare symptoms such as ‘want to give up’ and ‘sometimes wish you were dead’, but RR were similar. Associations for all-cause mortality were significant, but weaker, than for IHD (Figure 2).

Mean vital exhaustion item score was 3.57 (SD 3.90) in women and 2.59 (SD 3.43) in men. Tables 2 and 3 present background characteristics and potential confounders by level of vital exhaustion item score in men and women. There were no substantial gender differences. The most marked associations with the vital exhaustion item score were seen for diabetes, behavioural risk factors (smoking, physical inactivity, alcohol consumption), and for socioeconomic factors.

There were 455 IHD events among the 9202 subjects with full information on vital exhaustion item score. Table 4 presents the age-adjusted RR of IHD for men and women. Elevated scores on vital exhaustion were associated with higher levels of risk with increasing risks for higher scores. Although the risk for men was significantly increased for item scores of ≥1 and women only had elevated risk for higher scores, there was no difference between men and women in the overall magnitude of the association. In addition, the risks were similar in younger and older subjects (not shown). The result of the multivariate model for the complete sample reveals a clear dose–response effect as shown in Table 5. These associations were almost unaffected by adjustment for biological, behavioural, and socioeconomic risk factors. Repeated analysis including only the 110 deaths caused by IHD yielded hazard ratios of 1.48 (95% CI: 0.90, 2.43), 2.58 (95% CI: 1.49, 4.48), and 2.80 (95% CI: 1.44, 5.45) for 1–4, 5–9, and ≥9 item scores, respectively.

There were 1430 deaths from all causes among the 9202 subjects. As for IHD, associations were similar in men and women showing higher risk with increasing item scores (Table 4). However, in contrast to IHD hazard ratios were attenuated after adjusting for biological risk factors and further attenuated after adjustment for behavioural and socioeconomic risk factors. In the multivariate-adjusted model only the highest scores on vital exhaustion conveyed a significantly increased risk of all-cause mortality, although the trend remained clearly significant (Table 5).

All survival analyses were repeated with exclusion of the first 2 years of follow-up to evaluate the effect of symptoms caused by pre-clinical cardiovascular disease. This reduced the number of IHD cases from 455 to 300 and number of deaths from 1430 to 1165 but did not change the results (not shown). This lessens the likelihood that we have observed a spurious association due to the elevation of exhaustion scores in severely ill respondents.

Discussion
This is the second prospective investigation to observe an association between a measure of vital exhaustion and the incidence


**Figure 1** Age-adjusted risk of first ischaemic heart disease (IHD) by questionnaire item in 5479 women and 4048 men in the Copenhagen City Heart Study. Results from Cox regression analyses shown as hazard ratio (HR). Items shown in order of increasing prevalence
of IHD. We found strong graded relationships in both sexes irrespective of age even after extensive control for traditional risk factors. Symptoms were common with more than half the population reporting some degree of fatigue. The fact that the majority of the items on the questionnaire are predictive of health outcomes when considered individually attests to the strength of this phenomenon.

There is considerable overlap in the symptoms of vital exhaustion and depression but in the absence of a standard measure of depression we cannot address the potential distinction.
empirically. However, the similarities suggest that the findings of this study are also relevant to the burgeoning literature on depressive symptoms and coronary disease.

The adjusted risk of IHD was approximately doubled in those reporting vital exhaustion and fatigue. Similar hazard ratios were found in the previous prospective study of 3877 males. With the exception of a case-control study with very high RR associated with vital exhaustion, most other studies of vital exhaustion, fatigue, or depression have reported risks in the range reported here.

The ability of vital exhaustion to predict IHD events was evident in the data of both women and men as well as in all age groups. Although the effects of vital exhaustion in women have been investigated in a case-control study, this is the first demonstration of their importance in a sample of healthy women followed prospectively. To the extent that the symptoms of vital exhaustion overlap with those of depression, the findings of this study are relevant to the question of gender difference in the health impact of depressive symptoms. Furthermore, the prevalence of vital exhaustion as measured by individual items was higher in women than in men. Therefore the potential impact of these symptoms should be of special concern for women. The similarity of the associations with disease in men and women suggests that the higher prevalence in women cannot be put down to gender-related cultural differences in expression of emotions.

IHD can lead to depression and fatigue, and the possibility of reverse causality caused by sub-clinical disease at study entry was considered. Precautions were taken to reduce this risk: the study was prospective and subjects with pre-existing IHD based
Recent studies have failed to confirm any associations between vital exhaustion and clinical events such as myocardial infarction or total mortality. However, the data from the Kuopio Ischaemic Heart Disease Risk Factor Study suggest that vital exhaustion is associated with an increased risk of end-points, including IHD deaths and total mortality. This finding is consistent with earlier observations that they convey a substantially increased risk of IHD and some mortality risk. The biological mechanisms relating fatigue and depressive symptomatology to HPA-axis rather than causal factors. Further studies are needed to verify associations between fatigue and depression and thrombolytic and thrombogenic factors.

The role of burden of infections has not yet been solved and it is possible that fatigue is a marker of frequent sub-clinical infections and of arterial inflammation. In one study vital exhaustion was positively associated with serological markers of inflammation: antibody titres against chlamydia pneumonia, cytomegalovirus, and interleukines (IL) 1, and IL6.

We found a clear socioeconomic gradient in vital exhaustion. Psychosocial factors such as social isolation, lack of control at work, and hostility are more prominent in low social class groups, as are smoking, insulin resistance, and other risk factors. It has been proposed that psychosocial pathways may mediate the inverse association between socioeconomic status and IHD, perhaps involving the hypothalamic-pituitary-adrenal (HPA)-axis, a principal pathway activated as part of the physiological stress response, which has been linked to psychosocial factors. This would raise the possibility that depressive symptoms and fatigue might be markers of chronic stress and affected HPA-axis rather than causal factors.

Although still present, associations between depression and fatigue and all-cause mortality were weaker. This may indicate specificity of disease but also calls for analyses of other disease entities, in particular cancers. At present this study does not allow analyses of specific disease entities due to insufficient number of end-points.

In conclusion, these data show that symptoms of fatigue and depression are common in the general population, and confirm earlier observations that they convey a substantially increased risk of IHD and some mortality risk. Although the biological mechanisms relating fatigue and depressive symptomatology to IHD are not yet fully understood, we feel that depressive symptoms and fatigue should begin to become part of risk assessment in clinical practice.

Acknowledgements
The Danish Heart Foundation, The Danish Ministry of Health, and the Heart, Lung and Blood Institute of the United States National Institutes of Health (grant R01 HL54780).
References


Interest in premonitory symptoms of heart disease, principally pain but also less specific symptoms such as malaise and fatigue, is longstanding within cardiology. Descriptions of these premonitory symptoms have generally involved an explicit assumption that they relate to established pathology and represent ‘early warnings’ of the presence of disease, rather than having any causal relation to disease itself. However, around 20 years ago, Appels described a prodromal constellation of symptoms including physical exhaustion and feelings of hopelessness preceding major coronary heart disease (CHD) events. He suggested this syndrome of ‘vital exhaustion’ was causally related to these subsequent events, a relation arising perhaps through the neuroendocrine mechanisms typically invoked in relation to a proposed psychosocial aetiology of heart disease. Subsequently, several prospective associations between exhaustion (measured in various ways) and coronary events have been reported. The paper by Prescott and colleagues in this issue of the International Journal of Epidemiology adds to this evidence. What are its implications for the treatment and prevention of cardiovascular disease?

The fundamental difficulty encountered when trying to answer this question is in making the judgement as to whether associations between heart disease and a, now vast, array of negative ‘psychosocial factors’ are likely to be causal—such that they suggest novel intervention strategies. The alternative is that these associations may reflect pitfalls inherent in the interpretation of observational data and that ultimately they are likely to lead to interventional dead ends.

The arguments on both sides are well rehearsed. An artefactual, i.e. non-causal, association between vital exhaustion and heart disease could arise through three principle mechanisms. The first is reporting bias—individuals who report they are more exhausted may also report more disease symptoms in the absence of more objective pathology. The converse may also occur; both tendencies will tend to generate a spurious association between exhaustion and disease.

Second, as discussed above, reverse causation must be considered. Heart disease that has not yet been formally diagnosed may itself lead to symptoms of exhaustion. A growing literature illustrates how the inflammatory processes implicated in atherogenesis may contribute to feelings of depression and fatigue. Reported experience of these feelings may precede recognition of their full pathological significance by some time. This may lead to their mistaken characterization as a cause, rather than a consequence, of CHD.

Third, feelings of exhaustion may be part of life, lived in difficult, materially disadvantaged social circumstances that increase risk of heart disease through a number of mechanisms. These material factors, acting across the life trajectory, may be the fundamental cause of the increased disease risk associated with increased exhaustion. Exhaustion itself may have no additional causal contribution. Concentrating on exhaustion, rather than the material disadvantage experienced across the life course that underlies it, may be missing the point in terms of effective prevention.

The paper by Prescott and colleagues recognizes and attempts to address some of these issues. Indeed, it partly exemplifies the psychosocialists’ refutation of artefactual explanations of their findings. For example, the association between exhaustion and all-cause mortality reported is almost as strong as that between exhaustion and first CHD event. The latter outcome was dominated by non-fatal events, so conceivably may have been influenced by reporting bias. However, the authors reasonably argue that all-cause mortality is an un-biased outcome. Analysis of CHD deaths alone showed similar patterns of association, again appearing to make reporting bias a less plausible explanation of the findings described in this paper.