Commentary: What should we make of associations between vital exhaustion and heart disease?

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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.

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What about reverse causation by occult disease? The authors repeated survival analyses excluding incident cases in the first 2 years of follow-up. They report that this did not change results (the actual estimates are not shown) and interpret this as arguing against reverse causation as an explanation. Presumably, this assertion is based on an assumption that individuals with undiagnosed CHD (sufficient to elevate feelings of exhaustion) would die within 2 years. This is a questionable assumption. Even advanced atherogenesis, which may be associated with feelings of exhaustion, as discussed above, can precede clinical CHD by several years. Heart failure is a relatively common (3% amongst those over 45 in a recent general population survey) condition characterized by symptoms of profound fatigue. It is most often precipitated by underlying CHD; however, in many cases this causal pathway has remained sub-clinical. Diagnosis of heart failure is difficult in the community and consequently the condition is often unrecognized. Undiagnosed heart failure is therefore another explanatory mechanism for an association between fatigue and CHD mortality. Since the overall 5-year survival associated with heart failure is between 50 and 75%, such reverse causality could generate an association between fatigue and CHD mortality apparent over several years of follow-up. Reverse causation by occult disease is particularly likely in general population studies (as opposed to workplace cohorts) such as this one since there is no buffering ‘healthy worker’ effect. For example in general population cohorts low cholesterol predicts non-CHD mortality due to its strong association with existing disease. In working cohorts this is less apparent.

Prescott and colleagues also dismiss the possibility of a substantial contribution of residual confounding to their estimates of effects of exhaustion. This conclusion is somewhat at odds with the data presented. For example consider their estimates of effects of vital exhaustion on all-cause mortality—arguably the ‘hardest’ outcome category. Age-adjusted estimates associated with increasing ‘dose’ of vital exhaustion were 1.23 (95% CI: 1.08, 1.40), 1.58 (95% CI: 1.35, 1.85) and 2.50 (95% CI: 2.09, 2.99) respectively (Table 5). Adjustment of these for established CHD risk factors (physiological and behavioural) along with adult income and educational attainment led to considerable attenuation towards the null-value (fully adjusted estimates were 1.09 (95% CI: 0.95, 1.25), 1.15 (95% CI: 0.96, 1.37) and 1.58 (95% CI: 1.28, 1.96) respectively). In other words, only the increased risk associated with the highest exposure category remained conventionally significant. In addition, the strength and magnitude of this estimate (along with that of those associated with ‘softer’ outcomes such as ‘first ischaemic heart disease’) was well within the bounds of artefact that can result from relatively modest imprecision in the measurement of even moderately correlated covariates. In addition, other factors that may be associated both with negative feelings in adulthood and, independently, with adult disease risk (such as early life environment) were not measured in this study. These considerations suggest that residual confounding is impossible to discount as an explanation for the findings presented.

Observational evidence is limited in its ability to resolve these issues and debate risks becoming more about the relative rhetorical skills of the protagonists rather than a question of science. Experimental evidence could help, and is also important in another context. Discovery of a novel cardiovascular risk factor seems of little public health utility if this factor is not amenable to modification and incorporation in an intervention strategy. Thus, the proof of the pudding in terms of both scientific and strategic relevance of exhaustion to cardiovascular disease may only come from randomized controlled trials assessing the effect of manipulating exhaustion on cardiovascular endpoints. Results of trials to date in this area are interesting. Prescott and colleagues acknowledge considerable overlap between their exhaustion construct, and that of depression. Others have gone further, and have taken these constructs to be essentially interchangeable. Several trials have now assessed the effect of manipulating depression on cardiovascular endpoints. Whilst they have succeeded in demonstrating reductions in depression (a worthwhile outcome in its own right) cardiovascular effects have not been shown. This suggests that depression does not cause increased risk of cardiovascular disease. Exhaustion may be similarly non-causally associated with cardiovascular risk.

Perhaps mindful of the disappointing results of treating depression as a cardiovascular intervention, Prescott and colleagues do not suggest treating exhaustion as a strategy to improve population cardiovascular health. However, irrespective of causality, exhaustion may, in some contexts, be a marker of increased cardiovascular risk. These authors thus argue that, ‘depressive symptoms and fatigue should begin to become part of risk assessment in clinical practice’.

This suggestion bears consideration from a clinical perspective. Most cardiovascular screening and risk assessment is undertaken in primary care and is designed to identify people whose absolute risk of heart disease is high enough for the probable benefits of intervention to outweigh the costs. The sensitivity and specificity of currently available assessment instruments is sub-optimal. Part of the problem relates to the fact that most instruments incorporate information from special tests (blood cholesterol for example) that is often unavailable. The addition of readily accessible risk marker information (for example on social position) may compensate for this missing information and improve the precision of risk assessment. Would incorporation of reports of depression or fatigue into risk assessment fulfil this role?

The short answer is that we do not know and it will be up to proponents of this strategy to demonstrate its usefulness. However there are reasons to be cautious. The first is that symptoms of depression and fatigue are extremely common in the community (for example around half of this study population reported that they ‘often feel tired’) and, the above discussions of sub-clinical pathology notwithstanding, are only likely to be attributable to heart disease in a small minority of cases. Incorporating measurement of depression and fatigue seems unlikely to improve the sensitivity of risk assessment in this situation. Further, if reports of these symptoms are substantially influenced by reporting tendency, as it appears they are, then their contribution to specificity may also be low.

Unhappiness is, unfortunately, widespread and primary care health workers are accustomed to being admonished for ‘failing’ to diagnose depression. However, currently, the rationale for increasing detection and treatment relates to improving quality of life rather than reducing CHD risk. Feelings of significant fatigue are also common and some health workers may feel reluctant to actively solicit even more of these from patients, without good evidence that this knowledge can lead to health improvement. In the case of CHD risk assessment, this evidence does not currently exist.
Consideration of 'psychosocial risk' remains popular within cardiovascular epidemiology and this area of research may yet yield important contributions to effective prevention and treatment.8,9 However, until it is clarified how such a contribution can be realized, cardiovascular risk assessment should continue to be based on established causal factors such as smoking, hypertension, diabetes, obesity, and dyslipidaemia, and risk reduction should be grounded in modification of these.32

References
25 Writing Committee for the ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. JAMA 2003;289:3106–16.