Invited Commentary

Invited Commentary: Stress and Mortality

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Received for publication February 1, 2008; accepted for publication February 28, 2008.

In this issue of the Journal, Nielsen et al. (Am J Epidemiol 2008;168:481–91) use data from a large Danish study to provide evidence that self-reported stress is associated with increased all-cause mortality over the next 20 years. The finding is remarkable. In this commentary, the authors explore what is really meant by stress; they argue that it would be naïve to view stress as reported in this way, with some external exposure. It has to be seen through the lens of the participant’s personal experience, and this lens is likely to be clouded by personality, coping styles, and the common mental disorders—depression and anxiety. The authors discuss a wider literature concerning similar findings associating depression with mortality, suggesting three broad reasons for the association. First, the findings might be explained by the impact of stress or distress on well-established risk factors for cardiovascular disease and cancer. Second, there might be direct, underlying psychosomatic pathways by which stress or distress can affect immune or autonomic function. Third, there might be common causal pathways—shared genes or early adversities that predict both stress and mortality from other causes independently. The authors suggest that life course epidemiologic research is required to test these competing hypotheses.

cause of death; depressive disorder; mortality; prospective studies; stress, psychological

The finding by Nielsen et al. (1) that stress is associated with considerable increases in all-cause and some cause-specific mortality is remarkable. The investigators followed a large, random sample of the Danish population aged 20–93 years using baseline data collected in the early 1980s. The weak measure of stress (just two questions on duration and intensity) was associated with a significant increase in mortality over the next 20 years.

Is the finding valid? The authors (1) had a fair amount of additional baseline data on health and health-related risk behavior but only educational level and marital status as sociodemographic factors. Having accounted for these factors in multivariate models, estimates were reduced. As ever, residual confounding is a consideration. For example, socioeconomic circumstances are strong risk factors for mortality (2–4) but were incompletely controlled for in these analyses. A benefit of the study was that bias caused by sample attrition was minimized by very complete ascertainment of death using the Danish cohort. These findings are worthy of further exploration, particularly given that the answers to these questions on stress are likely to fluctuate within the same person over time, and some degree of misclassification error is likely to have attenuated the true underlying effect.

STRESS AND COMMON MENTAL DISORDERS

To interpret the findings, it is necessary to consider what the participants understood the stress measure to mean. Stress is a slippery concept with several meanings (5), the two main ones being 1) some form of objective pressure exerted on an individual, a meaning similar to epidemiologic exposures; and, alternatively, 2) a subjective internal experience, a sense of being unable to fulfill roles, of feeling anxious or depressed. Of course, the two may at times be different sides of the same coin, but they are not necessarily so. It is worth considering this possibility further because,
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According to the emphasis placed, the meaning of the questions used in this study may be quite different, which has implications if ever these findings were to be translated to a public health agenda.

As an external exposure—a set of experiences that happens to someone—reported stress would be expected to correlate closely with some kind of externally measured marker, but this does not seem to be the case (6). Stress, then, does not refer simply to how busy or overcommitted one is; an element of appraisal, influenced by personality and coping style, is always present. This might account for the gender differences reported because women, compared with men, may have interpreted the stress questions differently or taken into account their perceived level of support in a different way. The alternative meaning of stress is a mark of distress, a proxy for either emotional states such as anxiety and depression or emotional traits such as neuroticism. In clinical practice, the term “stress” is often used as a euphemism for negative emotions, which is acceptable to those who might otherwise be offended by psychiatric diagnostic labels, because it implies both a cause and effect: the person feels distressed because he or she is stressed, and the stress is something beyond his or her control. This meaning of stress is probably very close to lay understanding of anxiety and depression. It is certainly the case that subjectively reported stress is strongly associated with mental disorders in cross-sectional (7, 8) and longitudinal (9) studies.

The association between common mental disorders (anxiety and depression) and mortality has been observed over many years, in various populations, and it applies to many causes of mortality (10). Most early studies relied on standardized mortality ratios calculated for samples recruited from psychiatric services. Because many individuals with psychiatric disorder never receive care from specialist services, these studies are limited to participants who were at the most extreme end of a continuum of distress present in the population, and results were also potentially confounded by medication use and other iatrogenic impacts. These fairly unsophisticated studies generally could do little more than control for age and sex. Some more recent studies have been population based and have taken account of a range of risk behaviors, again finding associations between emotional state and mortality (11). The excess in all-cause mortality is not due to only suicide (12) and seems—in most, but not all, studies (13)—to apply to cardiovascular mortality (14, 15) and mortality from external causes (16, 17) more than to all, studies (13)—to apply to cardiovascular mortality (14, 15) and mortality from external causes (16, 17) more than to other types of cause-specific mortality.

Another piece of evidence is the apparently elevated mortality rates for depressed patients with established physical disease, so depression has been observed to increase mortality following myocardial infarction (18, 19), heart failure (20, 21), stroke (22, 23), human immunodeficiency virus/acquired immunodeficiency syndrome (24), renal disease (25), and cancer (26). These effect sizes have, for some studies, been impressive and apparently independent of disease severity variables.

**MECHANISMS**

What mechanisms might apply? The first and most obvious to rule out is the role of other well-established risk factors for mortality. People who are stressed, depressed, and anxious may have different risk factor profiles; in particular, they may exercise less (27), smoke more (28), and be more obese (29) than the rest of the population. In individuals with established disease, depression reduces compliance with medication and participation in rehabilitation programs (30). These variables are often considered confounders but might, more correctly, be pathway variables: if stress or depression has such an impact on risk behaviors, high-risk-population preventive strategies might attempt to lessen the impact of depression on mortality by targeting these behaviors in people with common mental disorders.

The second group of mechanisms comprises those hypothesized in the study by Nielsen et al. (1). Stress and depression are associated with a range of physiologic changes; for example, people with depression have greater platelet aggregation, increased markers of inflammation, reduced heart rate variability indicating a change in vagal tone, and relative overactivity of the hypothalamic-pituitary-adrenal system (reviewed by Musselman et al. (31)). The important question is whether interventions to reduce depression (or stress) would impact these intermediary variables and in so doing reduce the impact of depression on mortality. This psychosomatic approach is appealing, but is it likely to work? Randomized controlled trials of treatments for depression in high-risk groups have produced essentially negative findings (e.g., Glassman et al. (32), Berkman et al. (33), van Melle et al. (34)). Thus, in myocardial infarction patients, treating depression with antidepressants or psychotherapeutic interventions does not reduce mortality, even if it does reduce depressive symptoms.

The third group of explanations concerns common cause. It is possible that the same “upstream” variables increase susceptibility to both stress or depression and mortality. For example, the same genes might be associated with depression and mortality if they were involved in regulation of inflammatory or serotonergic pathways (35). Susceptibility to stress, and depression itself, is moderately heritable (36), as are many of the traditional risk factors related to mortality (37). So, it could be that we are witnessing a shared genetic liability, which might require multivariable twin analyses to disentangle. Alternatively, the Barker hypothesis would suggest that both cardiovascular mortality and depression are associated with fetal malnutrition (38). There is indeed some evidence that suicide, and anxiety and depression, are associated with low birth weight (39–41), as well as the more widely studied association between low birth weight and metabolic disorders. Finally, common cause might come from social adversity in childhood and early adult life; stressful events such as abuse and neglect may have a long-term impact on the hypothalamic-pituitary-adrenal system and manifest in later life as stress symptoms or depression (42). Investigating such common causes and identifying likely pathways require a life course approach (43). Studies are needed that characterize lifetime patterns or trajectories of mental and physical health (44) and health-related behaviors, and lifetime exposure to physical and social hazards, and they should be related to long-term mortality risk.
These common causes lend a degree of caution to any interpretation of the findings presented here (1). The authors optimistically suggest that interventions to reduce stress might improve longevity in the sample. We suggest that such interventions, if they could be applied to a large-enough population, might make people feel better but would probably have no impact on mortality. Stress and common mental disorders have a sufficiently damaging impact on quality of life to make any such interventions highly desirable. However, we suspect that they may disappoint if they aim to reduce mortality.

ACKNOWLEDGMENTS

Matthew Hotopf is funded by the South London and Maudsley NHS Trust NIHR Biomedical Research Centre. Conflict of interest: none declared.

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