Psychological distress, neuroticism, and cause-specific mortality: early prospective evidence from UK Biobank

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ABSTRACT

Background It is well established that psychological distress (depression and anxiety) is related to an increased risk of mortality. The personality trait of neuroticism, reflecting a relatively stable tendency towards negative emotions, has also been associated with elevated rates of death in some studies. Accordingly, we tested the possibility that it is the neuroticism trait itself, rather than the distress state, that is generating an increased risk of mortality.

Methods We used data from the UK Biobank study, a UK-wide prospective cohort study (2006–2010) in which distress was ascertained using the Patient Health Questionnaire and neuroticism using the Eysenck Personality Questionnaire-Revised Short Form.

Results A mean of 6.2 years of follow-up of 308,721 study members gave rise to 4,334 deaths. Higher neuroticism was weakly associated with total mortality (age-adjusted and sex-adjusted HR per SD increase; 95% CI 1.05; 1.02 to 1.09), and moderately strongly correlated with distress symptoms (r=0.55, p<0.0001). Distress symptoms were positively related to risk of total mortality (age-adjusted and sex-adjusted HR per SD increase in distress; 95% CI 1.23; 1.20 to 1.26). This gradient was, in fact, slightly strengthened after adding neuroticism to the multivariable model (1.30; 1.26 to 1.34) but markedly attenuated after taking into account other covariates which included health behaviours and somatic disease (1.16; 1.12 to 1.20). Similar results were apparent when cardiovascular disease, cancer and external cause of death were the end points of interest.

Conclusions While there was good a priori reasons to anticipate the neuroticism would at least partially explain the relation between distress symptoms and cause-specific mortality, we found no such evidence in the present study.

INTRODUCTION

Individual-participant and literature-based meta-analyses reveal dose-response relationships between higher levels of psychological distress (depression/anxiety) and the risk of premature mortality and selected chronic diseases.1–4 These observations have led to the speculation that treatment for distress could usefully occur in individuals at lower levels of distress than is currently recommended. The personality trait of neuroticism, reflecting a relatively stable tendency towards negative emotions, has also been associated with elevated rates of death and cardiovascular disease (CVD) in some studies.4 These inter-relationships raise the possibility that it is the neuroticism trait itself, rather than the distress state, that is generating an elevated risk of mortality. With no empirical examination of this hypothesis, we assessed the impact of controlling for neuroticism on the distress–mortality relation alongside a series of more traditional explanatory variables, including health behaviours.

METHODS

UK Biobank, a UK-wide, on-going, prospective cohort study, has been described in detail.3 In brief, between 2006 and 2010, 502,649 participants aged 37–73 years attended various geographically distributed research clinics. Members of the public visited an assessment centre completed a questionnaire, underwent an interview and took part in various physical assessments. Ethical approval was obtained from the National Health Service National Research Ethics Service and all participants providing written informed consent.

Assessment of psychological distress and neuroticism

Psychological distress was measured using the four-item version of the Patient Health Questionnaire (PHQ-4).6 Items are rated on a four-point Likert scale from 0 (not at all) to 3 (nearly every day) such that possible total scores range from 0 to 12 (higher scores denote greater distress). Scores on the PHQ-4 show good agreement with longer scales, and correlate with demographic risk factors for depression and anxiety.7 Neuroticism was measured with the 12-item Eysenck Personality Questionnaire-Revised Short Form.8 Other covariate data were collected using standard protocols, including: health behaviours (smoking status, alcohol intake, physical activity, dietary characteristics), physical attributes (body mass index, systolic blood pressure, forced expiratory volume in 1 min, grip strength), existing disease (physician diagnoses of vascular or heart problems, diabetes, cancer, asthma, chronic lung disease, deep vein thrombosis or pulmonary embolism at baseline) and socioeconomic status (highest attained educational qualification).

Study participants were linked to the National Health Service’s Central Registry at Southport, UK, which provided vital status data and, where applicable, cause of death. Having ascertained that the proportional hazards assumption had been met, we used Cox regression analyses with accompanying 95% CIs to summarise the association between psychological distress and mortality experience. In our
analyses, using the PHQ-4, psychological distress was categorised into three groups (score): 1 (0), 2 (1–2), 3 (≥3). The selection of these categories was data driven: we wanted sufficient numbers of deaths in each distress category to conduct robust statistical analyses.

RESULTS
In online supplementary table S1, we show the relation between categories of the distress score and study member characteristics at baseline. In general, people with a higher distress score had a less favourable risk factor profile as evidenced by poorer health behaviours, a higher prevalence of chronic disease and elevated neuroticism scores (r=0.55, p<0.0001). This was not a universal observation, however, in that levels of blood pressure and alcohol intake were somewhat lower in study members reporting a greater degree of distress.

A total of 308 721 people (142 983 women) had data on distress, neuroticism, other potential confounding variables and mortality. During a mean follow-up period of 6.2 years, 4334 people died. Table 1 shows the relation of distress scores with total and cause-specific mortality. Irrespective of the mortality outcome, there was a positive distress–death relationship such that an elevated mortality risk was apparent in people with higher distress scores. Higher neuroticism was weakly associated with total mortality (age-adjusted and sex-adjusted HR per SD (2.92) increase; 95% CI 1.05; 1.02 to 1.09), however, in none of our analyses did controlling for neuroticism have an attenuating impact on the distress–mortality end point associations. Indeed, positive confounding, whereby the distress–disease relationship was strengthened, was generally apparent. In contrast, separate adjustment for each cluster of covariates led to partial attenuation, with the greatest impact apparent for health behaviours, irrespective of the outcome interest. Controlling simultaneously for an additional 15 covariates led to more marked attenuation of risk although a dose–response association remained, as we illustrate for total mortality.
Inevitably, we have failed to capture all confounding factors, or assessed crudely some of those included here. Residual confounding is a perennial concern in observational epidemiology that should, in principle, be circumvented by using the randomised controlled trial design. While it would be unethical to precipitate prolonged bouts of distress and observe effects on mortality, an alternative approach is to reverse depression using a pharmacological and/or spoken therapy and evaluate the impact of mortality experience, anticipating a lower risk in the intervention arm. In one of the few such trials conducted, based on a population of cardiac patients, people successfully treated for depression did not experience a reduction in event-free survival relative to the usual care group. In a cluster randomised trial of older people recruited from primary care settings, however, improved survival was, however, apparent in the treatment arm.

Finally, the response proportion in UK Biobank, at 10%, is very low by comparison with other studies. While this has impact on accurately estimating disease prevalence and incidence—any calculations are likely to be underestimated—it has little implications for understating the aetiological role of risk factors for a given chronic disease for which UK Biobank was established. The original Whitehall study of London-based, non-industrialised civil servants (raised blood glucose as a risk factor for heart disease) and Framingham study based in a single, affluent Massachusetts town (elevated serum cholesterol as a risk factor for heart disease) have all yielded findings of major public health importance despite being obviously unrepresentative of the general population. If a study has a large enough sample and succeeds in capturing the range of values within the exposure of interest, the results should be transportable. This logic has recently been supported by comparing results from an occupationally based study of civil servants (the second Whitehall study) with those from the geographically diverse British Regional Heart Study where near identical HRs across an array of known risk factors for coronary heart disease were reported. Similarly, in another cohort study, the relation of risk factor data collected at study induction to future CVD mortality was the same as that in a smaller, select group resurveyed 8 years later.

Plausible mechanisms

That adjustment for an array of covariates, including neuroticism, did not eliminate the impact of distress on mortality risk inevitably raises speculation as to other mechanisms that may explain this relationship. Any such mechanisms are likely to be outcome-specific. Thus, bouts of acute anxiety may lead to acute coronary ischaemia that have been precipitated by coronary vasospasm and/or episodic elevations in blood pressure. Recurrent exposure to emotional disorder may also inhibit natural killer cell function which is implicated in immune system function, and therefore immunity-related cancers. The symptoms of fatigue, poor concentration and sleep disturbance, which characterise even moderately distressed individuals, may impact unfavourably on decision-making, risk perception, coordination and response time, so precipitating external causes of death such as accidents.

In conclusion, while there was good a priori reason to anticipate the neuroticism would at least partially explain the relation between distress symptoms and cause-specific mortality, we found no such evidence in the present study.
Meta-analyses of observational studies have shown that psychological distress (depression and anxiety) is related to an increased risk of total mortality and cardiovascular disease.

These gradients seem to be robust to control for various confounding factors, including health behaviours and socioeconomic status.

The personality trait of neuroticism, reflecting a relatively stable tendency towards negative emotions, has been associated with elevated rates of death and cardiovascular disease in some studies.

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Contributors CRG, AMM, GDB were involved in study concept and design; CRG, AMM and GDB were involved in statistical analysis; all authors were involved in interpretation of the data; CRG, AMM, GDB were involved in acquisition and preparation of the data set (including mortality linkage); CRG was involved in statistical analysis; all authors were involved in study concept and design; CRG, AMM, GDB were involved in study concept and design; CRG

Competing interests None declared.

Ethics approval Ethical approval was obtained from the National Health Service National Research Ethics Service.

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