**When is Higher Neuroticism Protective Against Premature Death?**

**Findings from UK Biobank**

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**Abstract**

We examined the association between Neuroticism and mortality in 321 456 people from UK Biobank and explored the influence of self-rated health on this relationship. After age- and sex-adjustment, a standard deviation increment in Neuroticism was associated with a 6% increase in all-cause mortality (hazard ratio = 1.06, 95% confidence interval = [1.03, 1.09]). After adjustment for other covariates, specifically self-rated health, higher Neuroticism was associated with an 8% reduction in all-cause mortality (hazard ratio = 0.92, 95% confidence interval = [0.89, 0.95]), and with reductions in mortality from cancer, cardiovascular disease and respiratory disease but not external causes. Further analyses revealed that higher Neuroticism was associated with lower mortality only in those with fair or poor self-rated health, and that higher scores on a Neuroticism facet related to worry and vulnerability were associated with lower mortality. Research into personality facet-mortality associations may elucidate mechanisms underlying Neuroticism’s covert protective association.

Keywords: Neuroticism, self-rated health, mortality, cohort study

**Introduction**

People with higher levels of the personality trait Neuroticism–-the tendency to experience negative emotions—are more likely to rate their health as poor (Goodwin & Engstrom, 2002; Jorm et al., 1993), and to report somatic complaints (Costa & McCrae, 1987; Neeleman, Bijl, & Ormel, 2004). They are also at increased risk of common mental disorders (Kotov, Gamez, Schmidt, & Watson, 2010; Lonnqvist et al., 2009; Malouff, Thorsteinsson, & Schutte, 2005). Given the evidence linking psychological distress with earlier death (Gale et al., 2012; Russ et al., 2012), one might expect that higher Neuroticism would be associated with increased mortality, but findings on this are inconsistent.

Whereas some studies found associations between higher Neuroticism and increased mortality (Shipley, Weiss, Der, Taylor, & Deary, 2007; Weiss, Gale, Batty, & Deary, 2009), others found no link (Almada et al., 1991; Costa, P. T., Jr, Weiss, Duberstein, Friedman, & Siegler, 2014; Iwasa et al., 2008; Jokela et al., 2013). A few studies have found that higher Neuroticism might protect against mortality (Korten et al., 1999; Ploubidis & Grundy, 2009; Weiss & Costa, 2005; Weiss, Gale, Batty, & Deary, 2013). One explanation for this protective effect might be that some variable moderates the relationship between Neuroticism and mortality. For example, there is some evidence that when high Neuroticism is accompanied by high conscientiousness it may have benefits for health, as indicated by lower levels of inflammatory biomarkers (Turiano, Mroczek, Moynihan, & Chapman, 2013), less smoking after the onset of disease (Weston & Jackson, 2015) and lower mortality—albeit in women only (Friedman, Kern, & Reynolds, 2010). The idea that higher Neuroticism might have health advantages in certain circumstances—the concept of “healthy Neuroticism”—was first put forward by Friedman who suggested that some people who are high in Neuroticism may be vigilant about their health and seek medical advice more readily (Friedman, 2000). Another plausible moderator of the Neuroticism/mortality relationship may be self-rated health. Self-rated health predicts mortality independently of objectively-measured health (Benyamini & Idler, 1999; Ganna & Ingelsson, 2015; Idler & Benyamini, 1997). People who are higher in Neuroticism are more likely to rate their health as poor (Chapman, Duberstein, & Lyness, 2007; Goodwin & Engstrom, 2002). Indications that self-rated health interacts with Neuroticism to affect mortality risk come from studies where higher Neuroticism was associated with lower mortality when effect estimates were adjusted for self-rated health (Korten et al., 1999; Weiss & Costa, 2005). Korten et al. report that this association was not apparent in univariate analysis (Korten et al., 1999), but they discuss the role of Neuroticism solely as a confounder of the relationship between self-rated health and mortality rather than considering why it should become protective after adjustment. In addition to its potential role as a moderator of the association between Neuroticism and mortality, self-rated health might act as a mediator. Longitudinal evidence shows that Neuroticism is associated with a faster decline in self-rated health which might contribute to mortality risk (Lockenhoff, Terracciano, Ferrucci, & Costa, 2012). A related possibility is highlighted by a study by Ploubidis and Grundy (2009) that showed that Neuroticism had an indirect and direct relationship with mortality risk. The former was mediated by, among other variables, self-rated health, and related to greater risk. The latter, in women, was not mediated by other variables, and related to reduced risk.

We used data from UK Biobank to investigate the association between Neuroticism and mortality. Our aim was to investigate whether and how self-rated health influences the relationship between Neuroticism and risk of death from all-causes, cancer, cardiovascular disease, respiratory disease, and external causes.

**Methods**

**Participants**

The participants in this study took part in the baseline survey of UK Biobank (Sudlow et al., 2015) (<http://www.ukbiobank.ac.uk>), a resource established for identifying determinants of disease in middle aged and older people. Between 2006 and 2010, 502 655 community-dwelling people aged between 37 and 73 years and living in the United Kingdom were recruited to the study. UK Biobank received ethical approval from the Research Ethics Committee (REC reference 11/NW/0382).

**Measures**

*Neuroticism*

Participants completed the 12-item Neuroticism scale of the Eysenck Personality Questionnaire-Revised (EPQ-R) Short Form (Eysenck, Eysenck, & Barrett, 1985). Response options to the 12 items included “True”, “False”, “Do not know”, and “Prefer not to answer”, the latter two responses were coded as missing. We used the summed score for our main analyses. The EPQ-R Short Form has been concurrently validated in older people against the emotional stability scale of the International Personality Item Pool (*r* = -.84) and the Neuroticism domain of the NEO Five-Factor Inventory (*r* = .85) by Gow, Whiteman, Pattie, and Deary (2005).

*Self-rated health*

Participants were asked, “In general how would you rate your overall health?” Responses were coded as excellent, good, fair, or poor.

*Other covariates*

In addition to age and sex, we chose health behaviors, physical attributes, cognitive function, diagnosed disease and socioeconomic position as covariates on the grounds that they might mediate or confound the relationships between Neuroticism and mortality. All the covariates were assessed along with Neuroticism during the baseline survey. It was therefore not possible to be certain about the temporal ordering of all covariates.

Health behaviors included smoking status (never, ex-smoker, current smoker); frequency of alcohol intake (categorized into six groups: never, special occasions only, one to three times a month, once or twice a week, three or four times a week, daily or almost daily); number of types of physical activity performed in the last four weeks based on walking for pleasure, heavy do-it-yourself (e.g., weeding, lawn mowing, carpentry, digging), light do-it-yourself (e.g., pruning, watering the lawn), strenuous sports, and other exercise; and whether participants ate five or more portions of fruit and vegetables­­ per day (yes or no).

Physical attributes included body mass index (BMI), systolic blood pressure, forced expiratory volume in 1 second (FEV1), and grip strength, all of which were measured during a visit to a UK Biobank Assessment Centre. Body mass index (kg/m2)was calculated from height and weight. Systolic blood pressure was measured with an automated Omron device. FEV1 was measured using a Vitalograph Pneumotrac 6800. Grip strength of each hand was measured using a Jamar J00105 hydraulic hand dynamometer; the maximum value was used in analysis.

Reaction time was used as a measure of cognitive function. Reaction time and scores on other measures of processing speed are moderately highly correlated with intelligence such that people with higher intelligence tend to process information more quickly (Deary, Der, & Ford, 2001). Reaction time was measured using a Go/No-Go “Snap” game. Via a computer screen, participants were presented with two cards with symbols on them. If the cards were identical, participants were instructed to push the buttonbox as quickly as possible using their dominant hand. Twelve pairs of cards were shown. The first five pairs were used as a practice. Of the remaining seven pairs, four contained identical cards. Reaction time score was the mean time in milliseconds to press the button when one of these four pairs was presented. Internal consistency of the four test trials was high (Cronbach’s α = 0.85).

Participants provided information on whether they had been diagnosed by a physician with vascular or heart problems, diabetes, cancer, chronic bronchitis or emphysema, asthma, deep vein thrombosis or pulmonary embolism.

Socioeconomic position was assessed using highest educational qualification and Townsend deprivation score (Townsend, Phillimore, & Beattie, 1988)—based on census data on unemployment, car and house ownership, and overcrowding—of the participant’s postcode of residence.

*Mortality ascertainment*

Death certificate data from the National Health Service Central Registry on primary and secondary causes of death were available for deaths occurring up to June 12th 2015. For the current study, we examined mortality from all causes, cardiovascular disease (International Classification of Disease 10th revision codes I20-5, I50, I60-70, I73, I74), cancer (codes C00-C97), respiratory disease (codes J00-J99), and external causes (codes V01–Y99). Any mention of these causes on the death certificate was counted as death from that cause. The mean follow-up time was 6.25 years.

**Statistical analysis**

Having checked that the proportional hazards assumption was met, we used Cox proportional hazards regressions to examine all-cause and cause-specific mortality according to a standard deviation (SD) increment in Neuroticism. Survival time in days was calculated from date of attendance at the Assessment Centre to date of death or June 12th 2015, whichever occurred first. We first examined associations between Neuroticism and all-cause and cause-specific mortality with adjustments initially for age and sex, then with further adjustment for health behaviors, physical attributes, markers of socioeconomic position, reaction time and existing illness, and finally with adjustment for self-rated health. We estimated the impact on the hazard ratio (HR) of adjusting for individual covariates using the following formula described by Batty, Der, Macintyre, and Deary (2006):

(1) ([HRage & sex adjusted – 1] – [HR age, sex, & covariate adjusted – 1] / [HRage & sex adjusted – 1]) × 100.

We then examined whether relationships between Neuroticism and all-cause and cause-specific mortality were moderated by levels of self-rated health by including interaction terms in age- and sex-adjusted models and testing whether the interaction was statistically significant. We also examined the relation of Neuroticism and all-cause and cause-specific mortality, stratifying by level of self-rated health, with adjustment for the other covariates as previously.

Neuroticism, like other personality factors (Costa & McCrae, 1995), has a hierarchical structure with items defining lower-order facets, which, in turn, define the factor. Therefore, we examined whether any Neuroticism facet or facets uniquely predicted mortality risk, or whether the association between Neuroticism and mortality risk was attributable to the common variance. To do so we first used an exploratory structural equation model with an oblique bi-factor Geomin rotation (Jennrich & Bentler, 2011, 2012) in Mplus version 7.4 (Muthén & Muthén, 1998-2015) to extract a general Neuroticism factor and two facets that were orthogonal to the general factor but correlated with each other. Next, we entered the general Neuroticism factor score and the facet scores, simultaneously, in further Cox models that were like those described above.

We carried out multiple tests of statistical significance. To reduce the likelihood of false positive results, we adjusted the *p*-values for the false discover rate (FDR) using an approach described by Benjamini and Hochberg (Benjamini, Drai, Elmer, Kafkafi, & Golani, 2001). We report results with and without this correction. In view of the very large sample size, only *p-*values < 0.001 were considered statistically significant.

Our analytical sample is based on 321 456 participants (64% of the 502 655 people recruited to UK Biobank) who had complete data on Neuroticism, self-rated health, and other covariates at baseline and mortality during follow-up.

**Results**

Table 1 shows the baseline characteristics of the study participants according to whether they died during the follow-up period. In this very large sample with 4497 deaths, most covariates were significantly associated with survival at *p* < 0.0001, such that death in the follow-up period was associated with older age, being male, smoking, daily or almost daily alcohol drinking, taking less exercise, eating fewer than five portions of fruit and vegetables per day, higher BMI, higher systolic blood pressure, lower FEV1, slower reaction time, having a diagnosis of various physical diseases, not having a degree, living in an area of greater social deprivation, and poorer self-rated health.

Mean Neuroticism scores were lower among participants who died during the follow-up period. This difference arose because men tend to score lower in Neuroticism and have higher mortality: when men and women were analyzed separately, there was no difference in mean Neuroticism between participants who survived and participants who died: mean scores were 3.54 (*SD* = 3.17) and 3.54 (*SD* = 3.15), respectively, in men (*p* = 0.987), and 4.50 (*SD* = 3.23) vs. 4.43 (*SD* = 3.28) in women (*p* = 0.330).

People who were higher in Neuroticism rated their health as poorer; the rank-order correlation between Neuroticism and self-rated health (based on 4 categories), *r*S = 0.23, *p* < 0.0001. Neuroticism scores tended to be lower with increasing age, *r* = -0.10, p<0.0001.

**Table 1**

***Baseline characteristics of the study participants according to survival over the follow-up period (n=321 456)***

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Died during follow-up**  |  |
|  | **Yes** **(n=4 497)** | **No****(n=** **316 959)** | ***p*-value** |
| Age (yrs), mean (SD) | 61.0 (6.76) | 56.1 (8.06) | <0.0001 |
| Female, no (%) | 1,784 (39.7) | 171,943 (54.3) | <0.0001 |
| Neuroticism, mean (SD) | 3.89 (3.23) | 4.06 (3.24) | 0.0005 |
| Fair or poor self-rated health, no (%) | 1,829 (40.7) | 69,144 (21.8) | <0.0001 |
| Current smoker, no (%) | 801 (17.8) | 30,471 (9.61) | <0.0001 |
| <5 portions of fruit/vegetables per day, no (%) | 1,599(35.6) | 123,748 (39.0) | <0.0001 |
| Drinks alcohol daily or almost daily, no (%)  | 1,119 (24.5) | 68,188 (21.2) | <0.0001 |
| Types of physical activity in last 4 weeks, mean (SD) | 1.96 (1.17) | 2.31 (1.16) | <0.0001 |
| BMI (kg/m2), mean (SD) | 28.0 (5.24) | 27.3 (4.66) | <0.0001 |
| Systolic blood pressure (mm Hg), mean (SD) | 139.2 (19.9) | 135.3 (18.4) | <0.0001 |
| Grip strength (kg), mean (SD) | 32.7 (11.0) | 33.0 (11.3) | 0.022 |
| FEV1 (liter), mean (SD) | 2.62 (0.84) | 2.85 (0.80) | <0.0001 |
| Reaction time, mean (SD) | 587.0 (126.8) | 553.7 (113.1) | <0.0001 |
| Vascular or heart problems, no (%) | 1,946 (43.3) | 87,348 (27.6) | <0.0001 |
| Diabetes, no (%) | 507 (11.3) | 14,432 (4.55) | <0.0001 |
| Asthma, no (%) | 441 (9.81) | 34,428 (10.9) | 0.024 |
| Chronic lung disease, no (%) | 175 (3.89) | 3,547 (1.12) | <0.0001 |
| Cancer, no (%) | 1,141 (25.4) | 22,655 (7.15) | <0.0001 |
| Deep vein thrombosis, no (%) | 162 (3.60) | 5,644 (1.78) | <0.0001 |
| Pulmonary embolism, no (%) | 67 (1.49) | 2,181 (0.69) | <0.0001 |
| Has degree, no (%) | 1,169 (26.0) | 109,818 (34.7) | <0.0001 |
| Townsend index, median (Interquartile range) | -1.93 (-3.55 to 1.01) | -2.29 (-3.70 to 0.19) | <0.0001 |

**Neurotism and mortality**

Table 2 shows hazard ratios and 95% confidence intervals for all-cause and cause-specific mortality according to a SD increment in Neuroticism. In total, 4497 people died during the follow-up period. In age- and sex-adjusted analyses, all-cause mortality was higher in study participants with higher levels of Neuroticism, HR [95% CI] = 1.06 [1.03, 1.09]. In additional models, we made further separate adjustments for health behaviors, physical attributes, reaction time, markers of socioeconomic position, existing illness, and self-rated health to gauge the impact of each on the association between Neuroticism and mortality. Adjustment for health behaviors had the strongest attenuating effect on the association, reducing it by 100%. Adjustment for physical attributes, markers of socioeconomic position, and existing illness each attenuated the association by 50%. Adjustment for reaction time attenuated the association only by 17%. On adjustment for self-rated health, the association between Neuroticism and mortality reversed direction such that higher Neuroticism was significantly linked with lower mortality, HR [95% CI] = 0.93 [0.90, 0.96]. The size of this effect was little changed by simultaneously adjusting for all covariates: an SD increase in Neuroticism was associated with an 8% reduction in mortality risk, HR [95% CI] = 0.92 [0.89, 0.95]. After FDR correction, these latter two associations remained significant at *p* < 0.001.

**Table 2**

***Hazard ratios [95% confidence intervals] for all-cause and cause-specific mortality for a SD increment in Neuroticism (n=321 456)***

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All causes****(4497 deaths)** | ***p******p*FDR** | **Cancer****(2912 deaths)** | ***p******p*FDR** | **Cardiovascular****disease****(925 deaths)** | ***p******p*FDR** | **Respiratory disease** **(688 deaths)** | ***p******p*FDR** | **External causes****(422 deaths)** | ***p******p*FDR** |
| Age & Sex | 1.06 [1.03, 1.09] | < 0.001< 0.001 | 1.00 [0.97, 1.04]  | 0.7760.887 | 1.08 [1.01, 1.15] | 0.0270.072 | 1.11 [1.03, 1.20] | 0.0070.028 | 1.20 [1.09, 1.32] | < 0.001< 0.001 |
| Age, Sex, & … |  |  |  |  |  |  |  |  |  |  |
|  Health behaviors | 1.00 [0.98, 1.04] | 0.6420.660 | 0.96 [0.93, 1.00] | 0.0650.173 | 1.00 [0.94, 1.07] | 0.9500.975 | 1.03 [0.95, 1.11] | 0.4910.650 | 1.14 [1.04, 1.26] | 0.0050.003 |
|  Physical attributes | 1.03 [1.00, 1.06] | 0.0490.057 | 0.99 [0.95, 1.03] | 0.6290.841 | 1.03 [0.97, 1.10] | 0.3370.449 | 1.05 [0.97, 1.13] | 0.2250.257 | 1.17 [1.06, 1.28] | 0.0010.003 |
|  Reaction time | 1.05 [1.02, 1.08] | 0.0010.002 | 1.00 [0.96, 1.04] | 0.9070.907 | 1.07 [1.00, 1.14] | 0.0540.108 | 1.10 [1.01, 1.18] | 0.0170.034 | 1.19 [1.08, 1.30] | < 0.0010.001 |
|  SEP | 1.03 [1.00, 1.06] | 0.0500.057 | 0.99 [0.95, 1.02] | 0.6310.841 | 1.03 [0.97, 1.11] | 0.5630.643 | 1.06 [0.98, 1.15] | 0.2030.257 | 1.16 [1.06, 1.28] | 0.0020.003 |
|  Existing illness | 1.03 [1.00, 1.06] | 0.0330.053 | 0.99 [0.95, 1.03] | 0.5080.841 | 1.02 [0.96, 1.09] | 0.3140.449 | 1.05 [0.97, 1.13] | 0.1270.203 | 1.16 [1.06, 1.27] | 0 0020.003 |
|  Self-rated health | 0.93 [0.90, 0.96] | < 0.001< 0.001 | 0.90 [0.87, 0.94] | < 0.001< 0.001 | 0.91 [0.85, 0.98] | 0.0460.024 | 0.90 [0.83, 0.98][ | 0.0110.029 | 1.07 [0.97, 1.18] | 0.1480.169 |
|  All covariates | 0.92 [0.89, 0.95] | < 0.001< 0.001 | 0.90 [0.86, 0.93] | < 0.001< 0.001 | 0.89 [0.83, 0.95] | 0.0010.008 | 0.87 [0.80, 0.94] | 0.0010.008 | 1.04 [0.95, 1.15] | 0.3830.383 |

*Note*. Effect estimates are shown adjusted first for only age and sex, then further adjusted separately for other types of covariates at baseline: health behaviors (smoking status, frequency of alcohol intake, number of types of exercise taken, and five or more portions of fruit and vegetables per day), physical attributes (body mass index, forced expiratory volume in 1 second, systolic blood pressure, and grip strength), reaction time, existing illness (diagnoses of vascular/heart problems, diabetes, cancer, asthma, chronic lung disease, deep vein thrombosis, or pulmonary embolism at baseline), SEP = socioeconomic position (Townsend index score and highest educational qualification), self-rated health, and finally for all covariates simultaneously. *p* = uncorrected *p*-value; *p*FDR = *p*-value corrected for the false discovery rate.

Cancer was the most common cause of death in the study sample. There was no significant association between Neuroticism and risk of death from cancer in age- and sex-adjusted analyses. Further separate adjustment for health behaviors, physical attributes, reaction time, markers of socioeconomic position, or existing illness had little effect on the association between Neuroticism and cancer mortality and it remained non-significant. On adjustment for self-rated health, higher Neuroticism became significantly linked with lower risk of death from cancer, HR [95% CI] = 0.90 [0.87, 0.94]. The size of this effect was unchanged by simultaneous adjustment for all covariates: an SD increase in Neuroticism was associated with a 10% reduction in risk, HR [95% CI] = 0.90 [0.86, 0.93]. After FDR correction, these latter two associations remained significant at *p* < 0.001.

In the case of mortality from cardiovascular disease and respiratory disease, people who were higher in Neuroticism tended to have an increased risk in age- and sex-adjusted analyses, although neither of these associations was statistically significant at *p* < 0.001 either before or after FDR correction. As with all-cause mortality, we observed a reversal of the Neuroticism-death gradient specifically on adjustment for self-rated health. After separate adjustment for self-rated health, Neuroticism was associated with a reduced risk of death from cardiovascular disease, HR [95% CI] = 0.91 [0.85, 0.98], and respiratory disease, HR [95% CI] = 0.90 [0.83, 0.98]. The effect sizes increased slightly after simultaneous adjustment for all covariates: a SD increment in Neuroticism was associated with reductions in risk of 11% and 13%, respectively, with HRs [95% CIs] = 0.89 [0.83, 0.95] and 0.87 [0.80, 0.94]. These latter models were statistically significant at *p* < 0.001 level before FDR correction; after FDR correction, the all covariates models were non-significant, both *p*s = 0.008.

In the case of death from external causes, the pattern as regards Neuroticism was different. Higher Neuroticism was associated with increased risk of death from external causes in age- and sex-adjusted analysis, and this association was significant at the *p* < 0.001 level both before and after FDR correction. Separate adjustment for health behaviors, physical attributes, reaction time, markers of socioeconomic position, and existing illness, each attenuated this association, by between 30% (health behaviors) and 5% (reaction time). Separate adjustment for self-rated health attenuated the association by 65% and it was non-significant at *p =* 0.148. Simultaneous adjustment for all covariates attenuated the relationship still further.

In summary, age- and sex-adjusted analyses showed that higher Neuroticism was associated with a slight increase in mortality. However, after adjustment for self-rated health, higher Neuroticism was associated with reduced mortality from all causes and cancer (both *p*s < 0.001) and a non-significant reduction in mortality from cardiovascular disease and respiratory disease (both *p*s = 0.008 after FDR correction). Higher Neuroticism ceased to be associated with mortality from external causes after adjustment for self-rated health and other covariates.

**Neuroticism and mortality according to self-rated health**

We next examined whether the associations between Neuroticism and mortality from all-causes, cancer, cardiovascular disease or respiratory disease varied according to levels of self-rated health. Tests of the Neuroticism and self-rated health interaction met our imposed level of significance (*p* < 0.001) in the case of mortality from cancer (*p*=0.0007), but were not significant in the case of mortality from all causes *(p* = 0.003), cardiovascular disease (p = 0.806, respiratory disease (p = 0.362), or external causes (p = 0.734). Comparison of the models of mortality from all causes or cancer that included the interaction with the model without the interaction showed that in the case of cancer mortality only, the bigger model with the interaction fitted the data better than the smaller model which did not include the interaction. The likelihood ratio test statistics (distributed as a chi-square) with three degrees of freedom were 13.81 for all-cause mortality (p = 0.003) and 17.14 for cancer mortality, (*p* = 0.0007). Likelihood ratio tests are sensitive to sample size so these results should be viewed with caution. In view of these findings, we carried out exploratory analyses in which we examined the associations between Neuroticism and mortality, stratifying by self-rated health.

 Table 3 shows hazard ratios and 95% confidence intervals for death from all causes and specific causes according to a SD increment in Neuroticism, stratified by self-rated health. For all causes of death, Neuroticism was significantly protective against mortality in participants who rated their health as fair or poor (*p* < 0.001), but not in those who rated their health as excellent or good. The age- and sex-adjusted HR [95% CI] was 0.89 [0.83, 0.94] in participants who rated their health as fair and 0.83 [0.76, 0.90] in participants who rated their health as poor. After adjustment for all covariates, the HRs were 0.89 [0.83, 0.94] in those who rated their health as fair and 0.86 [0.79, 0.94] in those who rated their health as poor. Both associations were statistically significant at conventional levels, but only the association in those with fair self-rated health met our alpha criterion for significance (*p* < 0.001) after FDR correction. For cancer mortality, too, Neuroticism was significantly protective in participants who rated their health as fair or poor. The age- and sex-adjusted HR [95% CI] for death from cancer per SD increment in Neuroticism was 0.87 [0.80, 0.94] in those who rated their health as fair and 0.73 [0.65, 0.82] in those who rated their health as poor. Further adjustment for all covariates had little or no attenuating effects on these associations: the multivariable-adjusted HRs were 0.87 [0.80, 0.94] in those who rated their health as fair and 0.80 [0.71, 0.90] and both associations remained statistically significant (*p* < 0.001) after FDR correction.

 Associations between Neuroticism and mortality from cardiovascular disease, respiratory disease, and external causes, stratified by self-rated health, are included in Table 3 to provide full results, but, as noted above, the relationship between Neuroticism and these causes of death did not vary by levels of self-rated health.

**Table 3**

***Hazard ratios [95% confidence intervals] for all cause and cause-specific mortality for a SD increment in Neuroticism stratified by levels of self-rated health (n=321 456)***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Excellent** **(n=59,305)** | ***p******p*FDR** | **Good****(n=191,178)** | ***p******p*FDR** | **Fair****(n=60,095)** | ***p******p*FDR** | **Poor****(n=10,878)** | ***p******p*FDR** |
| **All causes** | 483 deaths |  | 2185 deaths |  | 1265 deaths |  | 564 deaths |  |
| Adjustments: |  |  |  |  |  |  |  |  |
|  Age & sex | 0.97 [0.88, 1.07] | 0.5580.710 | 0.97 [0.94, 1.02] | 0.2920.508 | 0.89 [0.83, 0.94] | < 0.001< 0.001 | 0.83 [0.76, 0.90] | < 0.001< 0.001 |
|  All covariates | 0.97 [0.88, 1.07] | 0.5210.695 | 0.96 [0.92, 1.01] | 0.0680.169 | 0.89 [0.83, 0.94] | < 0.001< 0.001 | 0.86 [0.79, 0.94] | 0.0010.004 |
|  |  |  |  |  |  |  |  |  |
| **Cancer** | 340 deaths |  | 1497 deaths |  | 758 deaths |  | 317 deaths |  |
| Adjustments: |  |  |  |  |  |  |  |  |
|  Age & sex | 0.94 [0.84, 1.06] | 0.3190.507 | 0.96 [0.91, 1.01] | 0.1010.212 | 0.87 [0.80, 0.94] | < 0.001< 0.001 | 0.73 [0.65, 0.82] | < 0.001< 0.001 |
|  All covariates | 0.94 [0.84, 1.06] | 0.3130.507 | 0.94 [0.89, 1.00] | 0.0010.001 | 0.87 [0.81, 0.94] | < 0.001< 0.001 | 0.80 [0.71, 0.90] | < 0.001< 0.001 |
|  |  |  |  |  |  |  |  |  |
| **Cardiovascular disease** | 75 deaths |  | 402 deaths |  | 313 deaths |  | 135 deaths |  |
| Adjustments: |  |  |  |  |  |  |  |  |
|  Age & sex | 0.99 [0.78, 1.27] | 0.9600.985 | 0.94 [0.84, 1.04] | 0.2220.404 | 0.87 [0.77, 0.98] | 0.0220.068 | 0.87 [0.73, 1.03] | 0.1070.214 |
|  All covariates | 1.00 [0.78, 1.28] | 0.9870.986 | 0.91 [0.82, 1.01] | 0.0720.169 | 0.86 [0.77, 0.90]) | 0.0160.049 | 0.85 [0.71, 1.0] | 0.0770.171 |
|  |  |  |  |  |  |  |  |  |
| **Respiratory disease** | 56 deaths |  | 257 deaths |  | 247 deaths |  | 128 deaths |  |
| Adjustments: |  |  |  |  |  |  |  |  |
|  Age & sex | 0.96 [0.72, 1.28] | 0.7890.852 | 0.95 [0.83, 1.08] | 0.4510.644 | 0.81 [0.71, 0.93] | 0.0030.011 | 0.93 [0.78, 1.11] | 0.4140.613 |
|  All covariates | 0.91 [0.68, 1.21] | 0.5110.695 | 0.92 [0.81, 1.05] | 0.2220.404 | 0.79 [0.68, 0.90] | 0.0010.004 | 0.91 [0.76, 1.09] | 0.3300.508 |
|  |  |  |  |  |  |  |  |  |
| **External causes** | 54 deaths |  | 205 deaths |  | 103 deaths |  | 60 deaths |  |
| Adjustments: |  |  |  |  |  |  |  |  |
|  Age & sex | 0.98 [0.74, 1.30] | 0.8790.925 | 1.20 [1.05, 1.27] | 0.0080.027 | 0.95 [0.78, 1.17] | 0.6460.760 | 0.95 [0.73, 1.23] | 0.6840.782 |
|  All covariates | 0.96 [0.72, 1.07] | 0.7600.844 | 1.17 [1.02, 1.33] | 0.0270.072 | 0.95 [0.77, 1.16] | 0.6060.735 | 0.93 [0.71, 1.20] | 0.5680.710 |

*Note*. Effect estimates are shown adjusted first for only age and sex, then further adjusted for other covariates at baseline: health behaviors (smoking status, frequency of alcohol intake, number of types of exercise taken, and five or more portions of fruit and vegetables per day), existing illness (diagnoses of vascular/heart problems, diabetes, cancer, asthma, chronic lung disease, deep vein thrombosis, or pulmonary embolism at baseline), physical attributes (body mass index, forced expiratory volume in 1 second, systolic blood pressure, and grip strength), and markers of socioeconomic position (Townsend index score and highest educational qualification). *p* = uncorrected *p*-value; *p*FDR = *p*-value corrected for the false discovery rate.

We examined the extent to which higher Neuroticism might compensate for the adverse influence of poor self-rated health on mortality by comparing the main effect of poor self-rated health and the effect of its interaction with Neuroticism. In the case of all-cause mortality, after adjustment for all covariates, the main effect of poor self-rated health was a more than 3-fold increase in risk of death, HR [95% CI] = 3.27 [2.84, 3.77]; the effect of its interaction with Neuroticism was to reduce this risk only slightly, HR [95% CI] = 2.99 [95% CI] [2.28, 4.04]. In the case of cancer mortality, the main effect of poor self-rated health was also a more than 3-fold increase in risk of death, HR [95% CI] = 3.26 [2.74, 3.89]; the effect of its interaction with Neuroticism was a little larger than that observed with all-cause mortality, but again the reduction in risk was small, HR [95% CI] = 2.77 [2.35, 3.27].

In summary, exploratory analyses suggested that the relationships between Neuroticism and mortality from all-causes and cancer, but not those between Neuroticism and mortality from cardiovascular disease, respiratory disease or external causes, varied by level of self-rated health. Higher Neuroticism was protective against mortality from all causes and from cancer only in those who rated their health as fair or poor. After FDR correction, higher Neuroticism remained significantly associated with reduced risk of death from cancer in participants who rated their health as fair or poor, but was associated with reduced risk of death from all causes only in those who rated their health as fair. Comparison of the main effect of poor self-rated health with the effect of its interaction with Neuroticism on mortality risk suggests that higher Neuroticism reduces risk of death from all causes and cancer in participants with poor self-rated health by only a small amount.

**Neuroticism facets and mortality**

 At the suggestion of a referee, we explored the apparent protective association between Neuroticism and mortality that was revealed after adjustment for self-rated health. The full exploratory structural equation model results of Neuroticism items are presented in Table S1 in the Supplementary Material available online. This structure consisted of a general Neuroticism factor, onto which all items loaded and two facets that were orthogonal to the general Neuroticism factor and correlated with each other at 0.312, *p* < .0001. The general Neuroticism factor correlated 0.96 with score on the full Neuroticism scale. The three highest loading items on the first facet, which we labeled “anxious/tense”, were: “Would you call yourself a nervous person?” (loading = 0.608); “Do you suffer from ‘nerves’?” (loading = 0.490); and “Would you call yourself tense or ‘highly strung’?” (loading = 0.352). The four highest loading items on the second facet, which we labeled “worried/vulnerable”, were: “Do you worry too long after an embarrassing experience?” (loading = 0.568); “Are your feelings easily hurt?” (loading = 0.399); “Are you ever troubled by feelings of guilt?” (loading = 0.315); and “Are you a worrier?” (loading = 0.309). The factor determinacies for the general factor and two facets were 0.919, 0.790, and 0.721, respectively. For the factor scores extracted from this analysis, anxious/tense facet and the worried/vulnerable facet correlated 0.26 and 0.38, respectively, with scores on the full Neuroticism scale, both *p*s < .0001. Scores on the anxious/tense and worried/vulnerable facets correlated 0.07 and 0.12, respectively, with scores on the general factor, and 0.43 with each other, all *p*s < .0001.

 Table 4 shows the association between a standard deviation increment in the anxious/tense facet and the worried/vulnerable facet (entered simultaneously, along with the general Neuroticism factor), and all-cause, and cause-specific mortality. The anxious/tense facet was not significantly associated with all-cause or cause-specific mortality risk. Higher scores on the worried/vulnerable facet were associated with a significantly reduced risk of death from all causes in age- and sex-adjusted analysis, HR [95% CI] = 0.88 [0.86, 0.91]. After further

**Table 4**

***Hazard ratios [95% confidence intervals] for all-cause and cause-specific mortality for a SD increment in the anxious/tense and worried/vulnerable facets examined simultaneously (n=321 456)***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Anxious/tense** | ***p******p*FDR** | **Worried/vulnerable** | ***p******p*FDR** |
| **All causes (4497 deaths)**  |  |  |  |  |
| Adjustments: |  |  |  |  |
|  Age, sex & general Neuroticism factor | 1.00 [0.98, 1.03] | 0.9050.937 | 0.88 [0.86, 0.91] | < 0.001< 0.001 |
|  All covariates | 0.99 [0.96, 1.03] | 0.6520.819 | 0.94 [0.90, 0.97] | < 0.001< 0.001 |
|  |  |  |  |  |
| **Cancer (2912 deaths)** |  |  |  |  |
| Adjustments: |  |  |  |  |
|  Age, sex & general Neuroticism factor | 0.96 [0.92, 1.00] | 0.0650.180 | 0.93 [0.89, 0.97] | <0.001<0.001 |
|  All covariates | 0.96 [0.92, 1.00] | 0.0720.180 | 0.97 [0.92, 1.01] | 0.0970.194 |
|  |  |  |  |  |
| **Cardiovascular disease (925 deaths)** |  |  |  |  |
| Adjustments: |  |  |  |  |
|  Age, sex & general Neuroticism factor | 1.00 [0.93, 1.07] | 0.9200.935 | 0.84 [0.78, 0.91] | < 0.001< 0.001 |
|  All covariates | 0.99 [0.92, 1.06] | 0.7080.833 | 0.93 [0.86, 1.00] | 0.0450.150 |
|  |  |  |  |  |
| **Respiratory disease (688 deaths)** |  |  |  |  |
| Adjustments: |  |  |  |  |
|  Age, sex & general Neuroticism factor | 1.02 [0.94, 1.11] | 0.5880.819 | 0.84 [0.77, 0.91] | < 0.001< 0.001 |
|  All covariates | 0.98 [0.90, 1.06] | 0.5810.819 | 0.93 [0.85, 1.01] | 0.0810.180 |
|  |  |  |  |  |
| **External causes** **(422 deaths)** |  |  |  |  |
| Adjustments: |  |  |  |  |
|  Age, sex & general Neuroticism factor | 1.03 [0.90, 1.13] | 0.6550.819 | 0.92 [0.82, 1.02] | 0.1140.207 |
|  All covariates | 1.00 [0.90, 1.10] | 0.9370.937 | 0.97 [0.87, 1.08] | 0.6310.819 |

*Note*. Effect estimates are shown adjusted first for age, sex and the general Neuroticism factor, then further adjusted for other covariates at baseline: health behaviors (smoking status, frequency of alcohol intake, number of types of exercise taken, and five or more portions of fruit and vegetables per day), existing illness (diagnoses of vascular/heart problems, diabetes, cancer, asthma, chronic lung disease, deep vein thrombosis, or pulmonary embolism at baseline), physical attributes (body mass index, forced expiratory volume in 1 second, systolic blood pressure, and grip strength), and markers of socioeconomic position (Townsend index score and highest educational qualification). *p* = uncorrected *p*-value; *p*FDR = *p*-value corrected for the false discovery rate.

adjustment for all covariates, the effect size was attenuated but remained significant, even after FDR correction, HR [95% CI] = 0.94 [0.90, 0.97]. Higher worried/vulnerable scores were also associated with a significantly reduced risk of death from cancer (HR [95% CI] = 0.93 [0.89, 0.97]), cardiovascular disease (HR [95% CI] = 0.84 [0.78, 0.91]), and respiratory disease (HR [95% CI] = 0.84 [0.77, 0.91]), but not from external causes, in age- and sex-adjusted models but none of these associations remained significant after adjustment for all covariates and correction for multiple testing.

**The role of health behaviors**

To explore whether physical activity, fruit and vegetable consumption, smoking or alcohol use might help explain the protective effect of higher Neuroticism on mortality from all causes and cancer in those with fair or poor self-rated health, we examined whether the correlations between Neuroticism and these health behaviors differed according to whether participants rated their health as fair or poor rather than excellent or good. Before stratifying by self-rated health, after adjusting for age and sex, higher Neuroticism was modestly but significantly correlated (*p* < .0001) with less healthy behaviors: eating at least five pieces of fruit and vegetable daily (*r* = -0.042), being a current smoker (*r* = 0.050), drinking alcohol daily or nearly daily (*r* = 0.015), and taking part in fewer types of physical activity (*r* = -0.100). Comparing these correlations and their 95% confidence intervals in participants who rated their health as excellent or good to those in participants who rated their health as fair or poor showed that there was no significant difference between these groups of participants in any of these behaviors. Consistent with this, when we compared multivariable models of all-cause and cancer mortality, with and without these health behavior covariates, the effect sizes for Neuroticism were essentially the same (data not shown), suggesting that these factors do not account for the association between higher Neuroticism and mortality risk in those with fair or poor self-rated health.

We explored the relationship between Neuroticism and health behaviors further by investigating whether the presence of disease at baseline (diagnosis of vascular/heart problems, diabetes, cancer, asthma, chronic lung disease, deep vein thrombosis, or pulmonary embolism) moderated the relationship. Age- and sex-adjusted correlations between Neuroticism and eating five or more pieces of fruit and vegetable daily, being a current smoker, drinking alcohol daily or nearly daily, and number of types of physical activity undertaken were very similar in those with and without diagnosed disease. Comparison of these correlations and their confidence intervals showed they did not differ significantly between those with and without diagnosed disease.

**The role of diagnosed disease**

People who had diagnosed disease at baseline were more likely to rate their health as fair or poor, and they were more likely to have died during follow-up. We examined whether having any diagnosis, i.e., a diagnosis of vascular/heart problems, diabetes, cancer, asthma, chronic lung disease, deep vein thrombosis, or pulmonary embolism, at baseline moderated the associations between Neuroticism and mortality from all causes or from cancer in those who viewed their health as fair or poor. The *p*-values for the interaction terms were not statistically significant (*p*s = 0.749 and 0.942, respectively).

**The effect of missing covariate data**

The analyses described above were based on 321 456 participants (64% of the 502 655 people recruited to UK Biobank) who had complete data on Neuroticism, self-rated health, and the other covariates at baseline. To explore whether excluding people with missing covariate data biased our findings, we carried out a sensitivity analysis in the 401 265 people who had data on Neuroticism and self-rated health. The associations were similar to those described above. For example, the age- and sex-adjusted HR [95% CI] for death from all causes per SD increment in Neuroticism was 1.10 [1.08, 1.13]; after further adjustment for self-rated health, this changed to 0.94 [0.91, 0.96]. In our analytical sample, the equivalent effects were 1.06 [1.03, 1.09] and 0.93 [0.90, 0.96], respectively.

**Discussion**

In this prospective study, age- and sex-adjusted analyses showed that higher Neuroticism was associated with a slight increase in mortality risk. However, after adjustment for other covariates, and specifically self-rated health, higher Neuroticism was associated with reduced mortality from all causes, cancer, cardiovascular disease, and respiratory disease, but not external causes. The relationships between Neuroticism and mortality from all causes and cancer varied according to self-rated health. Tests of the overall interaction between Neuroticism and self-rated health interaction did not meet our imposed alpha criterion (*p* < 0.001) in the case of mortality from all causes(*p* = 0.003) and were significant in the case of mortality from cancer (*p* = 0.0007). Exploratory analyses, in which we stratified the sample by self-rated health, showed that higher Neuroticism was associated with reduced mortality from all causes and from cancer in participants who rated their health as fair or poor. The compensatory effect of higher Neuroticism on risk of death from all causes or cancer in those with poor self-rated health was small.

We examined whether two Neuroticism facets—anxious/tense and worried/vulnerable—that were independent of the common Neuroticism variance, were associated with mortality. Higher scores on the worried/vulnerable facet were associated with a reduced risk of death from all-causes. This effect persisted after adjustment for all covariates and survived correction for multiple testing. Higher scores on the worried/vulnerable facet were also associated with lower mortality from cancer, cardiovascular disease, and respiratory disease, but only in age- and sex-adjusted models. The anxious/tense facet was not associated with mortality.

 Although higher Neuroticism has been linked with poorer subjective health (Goodwin & Engstrom, 2002; Watson & Pennebaker, 1989), it might be protective against earlier death if it leads individuals to vigilant in taking care of their health (Friedman, 2000). We found some support for that notion: among people who rated their health as poor or fair, higher Neuroticism was associated with a reduced mortality from all causes and cancer. No such effect was observed in those with excellent self-rated health. We found no indication to suggest that diet, exercise, smoking, or drinking explained the association seen in those with poorer self-rated health, but our data was restricted to behavior at the start of the study so may not reflect changes in these behaviors made subsequently. Higher Neuroticism was associated with poorer health behaviours, although the size of all these correlations was small. We found no evidence that these correlations differed between participants with excellent or good self-rated health and participants with fair or poor self-rated health. There was also no evidence that these correlations differed between participants who had diagnosed disease at baseline and those who had not. If concerns about health underlie our finding that higher Neuroticism is linked with lower mortality from all causes and cancer in those with poorer self-rated health, it does not appear to be manifested via the health behaviors we examined at baseline.

There is evidence that higher Neuroticism is associated with greater use of health care services (Cuijpers et al., 2010). This propensity to seek medical help in response to worries about health could plausibly result in earlier identification of cancer, and greater likelihood of survival. We were unable to investigate whether the protective effect of higher Neuroticism in this group was due to better self-care in terms of seeking professional advice in response to symptoms or compliance with medical treatment, but our finding that higher Neuroticism among those with poor self-rated health was associated with a reduction in risk of death from cancer is consistent with that explanation, as is our observation that higher scores on the worried/vulnerable facet were associated with reduced mortality from all causes. It is worth noting that higher scores on the worried/vulnerable facet were associated with lower mortality without the need to adjust for self-rated health.

 Strengths of our study include the number of deaths in our large sample and the data on a range of potential confounding factors. One limitation is that no data were available on other personality traits. We could not examine whether Conscientiousness, for example, moderated Neuroticism’s relationship with mortality. Being high in Conscientiousness may lead individuals who are high in Neuroticism to live a healthier lifestyle, possibly in response to health concerns (Vollrath & Torgersen, 2002; Weston & Jackson, 2015). Weston and Jackson (2015) found that after the onset of chronic physical disease, people who were high in Neuroticism and high in Conscientiousness, so-called “healthy neurotics”, smoked less. This Neuroticism-Conscientiousness combination was only associated with smoking after disease onset. Weston and Jackson therefore suggested that high Conscientiousness may enable individuals high in Neuroticism to act on their anxiety when confronted by disease by making behavioral changes (Weston & Jackson, 2015). We found no evidence that the relationship between Neuroticism and health behaviors differed in those with or without physical illness at baseline, but were unable to examine the potential impact of Conscientiousness on this relationship. Another limitation of our study is that our follow-up period was relatively short, on average 6.25 years. We therefore cannot gauge whether the association between higher Neuroticism and reduced mortality in those with poorer self-rated health persists over the longer term. One final limitation of this study is that the analyses concerning the interaction were exploratory as we found a significant interaction effect only in the case of mortality from cancer. This is probably attributable to a combination of our very conservative criterion for significance and the fact that the power to detect interaction effects is considerably lower than that to detect main effects (McClelland & Judd, 1993). Future studies should thus try to replicate these findings, and use an alpha criterion that better balances the power to detect interaction effects and to avoid a high type 1 error rate.

The findings of this study raise the question of why does Neuroticism become protective against mortality from all causes and cancer in those with fair or poor self-rated health? These protective effects were not explained by healthier behavior in terms of smoking, exercise, fruit and vegetable intake or alcohol consumption, and did not vary according to the presence of diagnosed disease. It may be that individuals with higher Neuroticism are vigilant about their health if they perceive it to be less than excellent. Such individuals may be more aware of bodily, including autonomic, symptoms and may be more likely to consult their doctor, perhaps increasing the likelihood of earlier diagnosis and prompt treatment. As we noted above, our findings on the Neuroticism facets provide some evidence in support of this: the lower risk of all-cause mortality seen in individuals who score highly on the worried/vulnerable facet could be due to a greater propensity to seek medical advice. Future analysis of primary care records in this cohort—not currently available—would lend further support to this explanation. If prompt seeking of medical advice is indeed a mechanism underlying the covert protective effect of higher Neuroticism, we may need to re-evaluate the evidence on the economic costs of Neuroticism in terms of use of health service resources (Cuijpers et al., 2010).

The present results suggest that perhaps the most promising avenue for future research would be a closer examination of the role of Neuroticism’s facets, for example the six---anxiety, angry-hostility, depression, self-consciousness, impulsiveness, and vulnerability---operationalized by the Revised NEO Personality Inventory (Costa & McCrae, 1992). A study of the association between “nuances” (Mõttus, Kandler, Bleidorn, Riemann, & McCrae, 2017) of Neuroticism, e.g., the 8 items from the Revised NEO Personality Inventory, no doubt will also yield insights into when and why being higher in Neuroticism might harm or protect health.

**Author Contributions**

CRG and IJD planned the study. AW conducted the bi-factor exploratory structural equations models and extracted the facet scores. CRG performed all other statistical analyses in discussion with IJD and drafted the manuscript. All authors provided critical revisions and approved the final version of the manuscript.

**Acknowledgment**

This research has been conducted using the UK Biobank Resource under application 10279. The work was undertaken in The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1) which supports IJD. Funding from the BBSRC and the Medical Research Council (MRC) is gratefully acknowledged. IJD, CRG and IC are supported by the MRC (MR/K025023/1). IJD and AMM are supported by the Wellcome Trust (104036/Z/14/Z).

**Conflict of Interest**

The authors declare no conflict of interest.

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