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Generalised anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam Experience Study

Short title: Anxiety, depression and mortality in veterans

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Abstract

Objective: To examine whether or not the one-year prevalence of major depressive disorder (MDD), generalised anxiety disorder (GAD), and their comorbidity were associated with subsequent all-cause and cardiovascular disease mortality over 15 years in Vietnam veterans. **Methods**: Participants (N = 4256) were from the Vietnam Experience Study. Service, socio-demographic, and health data were collected from service files, telephone interviews, and a medical examination. One-year prevalence of MDD and GAD was determined through a diagnostic interview schedule based on the DSM-IV criteria. Mortality over the subsequent 15 years was gathered from US army records. **Results**: MDD and GAD were positively and significantly associated with all-cause and CVD mortality. The relationships between MDD and GAD and CVD mortality were no longer significant following adjustment for socio-demograhics, health status at entry, health behaviours, and other risk markers. Income was the covariate with the strongest impact on this association. In analyses comparing comorbidity and GAD and MDD alone, to neither diagnosis, comorbidity proved to be the strongest predictor of both all-cause and CVD mortality. **Conclusion**: GAD and MDD predict all-cause mortality in a veteran population after adjusting for a range of covariates. However, those with both GAD and MDD were at greatest risk of subsequent death, and it would appear that these disorders may interact synergistically to affect mortality. Future research on mental disorders and health outcomes, as well as future clinical interventions, should pay more attention to comorbidity.

Key words: comorbidity, generalised anxiety disorder, major depressive disorder, mortality, veterans.

GAD = generalised anxiety disorder, **MDD** = major depressive disorder, **PTSD** = post-traumatic stress disorder, **HR** = hazard ratio, **CVD** = cardiovascular disease, **SBP** = systolic blood pressure, **DBP** = diastolic blood pressure, **BMI** = body mass index, **IQ** = intelligence quotient.

Mental health disorders in the general population are relatively common (1, 2). In fact, an estimated 14% of the global disease burden has been attributed to mental health disorders (3), and this figure is likely to be an underestimate as it fails to take into consideration the association between mental health and other health conditions (4). Populations who have been exposed to traumatic events, such as war veterans, have an even higher prevalence of Major Depressive Disorder (MDD) and Generalised Anxiety Disorder (GAD) (5-7). For example, soldiers assessed a few months after returning from deployment to Afghanistan and Iraq had a GAD prevalence of around 14% and 15%, respectively, and prevalence of MDD of around 17% and 16% (8). Others have reported depressive symptom rates as high as 19% in veterans based on prior diagnosis records (9), and 31% using self-report measures (10), although some studies have shown lower rates of 6.9% and 1.7% for MDD and GAD, respectively (11). Little has been reported about the consequences for survival of these mental health disorders in veterans.

In the general population, MDD has been associated with increased mortality rates (see e.g. (12, 13). Although much of this excess is attributable to non-medical causes of death such as injury and suicide, it is becoming clear that MDD also increases the risk of death from common chronic diseases such as cardiovascular disease (CVD) (14). There is now substantial evidence linking depression with CVD morbidity and mortality (see e.g. (15, 16). However, much of this research has examined the impact of depressed mood rather than a diagnosis of MDD. In a recent meta-analysis of 11 studies of coronary heart disease (CHD), MDD, which had been measured in only three studies, was a much stronger predictor of CHD outcomes than depressed mood (17). Few studies have examined GAD as a risk factor for all-cause mortality, although two population studies suggest that, for causes of death other than suicide, GAD does not present a significant risk (18, 19). However, other manifestations of anxiety have been associated with an increased risk of CVD morbidity and/or mortality (see e.g. (20-22). To our knowledge, no study has measured the relationship between diagnosed GAD and CVD mortality.

The bulk of research examining the consequences of mental health disorders for chronic disease in veterans has concentrated on post-traumatic stress disorder (PTSD). For example, lifetime prevalence of PTSD was linked with an increased mortality rate (23, 24). In addition, PTSD in veterans has also been associated with cardiovascular, digestive, musculoskeletal, endocrine-nutritional-metabolic, nervous system, respiratory, and nonsexually transmitted infectious diseases (25), chronic changes in immunity (26), and markers of inflammatory disorders (27). However, there appear to be few studies examining the influence of other major mental health disorders on mortality risk in veterans. In a study of PTSD and MDD in veterans, MDD was related to increased mortality following adjustment for age, demographic variables, health behaviours, and medical co-morbidities (9). As far as we are aware, the association between GAD and mortality in veterans has not been studied.

Given the reported high prevalence of GAD and MDD in army veterans and the significant prevalence of these disorders in the general population, their individual and combined impact merits research attention. Consequently, the present analyses examined the associations between GAD, MDD

and their comorbidity and all-cause and CVD mortality in a substantial cohort of US veterans from the Vietnam Experience Study. Based on the balance of evidence from general population studies, it was hypothesised that a diagnosis of GAD and/or MDD would be associated with an increased mortality risk over the subsequent 15 years.

Methods

Participants and procedure

Participants were identified retrospectively from data gathered as part of the Vietnam Experience Study; an epidemiological study commissioned by the US congress to investigate the health consequences of the military experiences of Vietnam veterans. These were male military personnel drawn from approximately five million US Vietnam-era army veterans whose service files were stored at the National Personnel Records Center (28). The Centers for Disease Control, Atlanta, had access to U.S. Veteran Administration records and provided the authors with a fully anonymised dataset. Details of sampling at each stage of data collection are shown in Figure 1. Ethical approval for the study protocol was given by the US Office for Technology Assessment; the Department of Health and Human Sciences Advisory Committee; the Agent Orange Working Group Science Panel; and a review panel from the US Centers for Disease Control. Those who entered military service between January 1, 1965 and December 31, 1971; served only one term of enlistment; served at least 16 weeks of active duty; earned a military specialty other than "trainee" or "duty soldier"; at discharge from active duty had a military pay grade no higher than sergeant; and had not died during military duties were eligible for inclusion. On reviewing a random sample of 48 513 records, 1355 were found to be incomplete, 28 577 did not meet study entry criteria and 268 men died during military duties, so the final cohort included 18,313 former military personnel (28-30).

[Insert Figure 1 about here]

The vital status of men between army discharge and December 31st 1983 (the date the cohort was established) was ascertained by cross-checking against a variety of mortality databases supplied by the US army, the Veterans Administration (Beneficiary Identification and Records Locator Subsystem), the Social Security Administration, the Internal Revenue Service, and the National Center for Health Statistics (National Death Index). Of those included in the original cohort, 17,867 were considered to be alive on December 31st 1983 and therefore eligible for active follow-up. In 1985 these participants were invited to participate in a telephone interview. Telephone directories, credit bureau searches, driver's license and motor vehicle registration records, city directories, local records and personal field visits were all utilized to locate the whereabouts of apparently surviving men. Of those traced (N = 16 349), an

interview was not possible for reasons of incarceration (N = 63), physical or mental disability (N = 20), refusal (N = 949), death during the tracing process (N = 53), or 'other' (N = 6). This resulted in a sample of 15,288 men (85.6% of those alive on December 31st 1983) who participated in the 1985 telephone survey (30).

In 1986, a random sample of telephone interview respondents (N=6443) were invited to attend a three day medical examination with orientation at a single facility in Albuquerque, New Mexico, for which travel expenses and a nominal stipend were met; 4462 attended (69.3% of those invited). The mean age at medical examination was 38.3 years (range: 31.1 to 49.0). Of those invited, medical examination was not possible for reasons of incarceration (N = 26), physical or mental disability (N = 10), refusal (N = 949), death before invitation (N = 10), or 'refusal' (N = 372). The main reasons for refusing to participate at this stage of data collection were: work related, e.g. unable to get leave with pay; a lack of interest in the study, e.g. unable to see how it would benefit them; or personal, e.g. did not like to travel. The final number of participants with complete data after the medical examination was 4256. This group represents 23.3% of persons originally enrolled in the study. Although this analytical sample is based on the recruitment of a random sample of surviving men, concerns about selection bias are nonetheless possible; that is, if the reported results differ markedly between persons included in the analyses and those not. Differences between the excluded and included participants were in fact very small: in comparison to the excluded group, men in the analytical sample had higher IQ test scores (means of 101.3 versus 100.4, $p = .001$) and a greater proportion had service experience in Vietnam (55% versus 51%, $p < .001$). The fact that these marginal differences reached statistical significance can be ascribed to the large sample size. Vital status post-medical exam continued to be ascertained until 31st December 2000 using the mortality databases described above. Mortality due to major CVD was classified using the International Classification of Diseases (ICD) (31) codes: ICD-9: 390–434,436–448, and ICD-10: I00–I78 which comprised: acute rheumatic fever; chronic rheumatic heart diseases; hypertensive diseases; ischaemic heart diseases; pulmonary heart disease and diseases of pulmonary circulation; other forms of heart disease; cerebrovascular diseases; diseases of arteries, arterioles and capillaries. The CVD mortality variable thus encompasses death from a variety of disorders.

Data collection in late adolescence/early adulthood

Information pertaining to place of service, military rank, ethnicity, and cognitive ability scores from the Army General Technical Test (hereafter referred to as "IQ") was extracted from the military archives. Participants were designated as being Vietnam veterans if they had served at least one tour of duty in Vietnam, and as non-Vietnam veterans if they did not (this group included men who served one or more tours of duty in Korea, Germany or the US). The ethnic origin of the study members were classified as 'white', 'black', or 'other'; the latter group comprising Hispanics, Asians, Pacific Islanders, American Indians, and Alaskan Natives.

Data collection in middle-age – telephone survey

During the telephone survey, enquiries were made about the study participants' socio-economic characteristics, health behaviours, and health. Socio-economic position was measured using household income in midlife. Frequency of alcohol consumption was classified as number of units consumed per week. Smoking habits and marital status were ascertained using standard questions. Participants were also asked whether or not they had a range of somatic physician-diagnosed health problems which included hypertension, cancer, diabetes and coronary heart disease (32, 33).

Data collection in middle-age – medical examination

Mean age at medical examination was 38.3 yr. (range: 31.1 to 49.0). All men were requested to fast from 19.00 the evening before medical testing. Following the drawing of blood the following morning, cholesterol level was ascertained using a Kodak Ektachem 700 autoanalyzer (32, 33). Serum glucose level was determined with a standard adaptation of the glucose oxidase-peroxidase-chromogen-coupled system for glucose determination in biologic fluids (32, 33). Blood pressure, while seated, was measured twice in the right arm using a standard mercury sphygmomanometer; for the purposes of analyses, an average was computed. Height and weight, measured using standard protocols, were used to calculate body mass index (BMI) (kg/m^2).

Psychological morbidity was assessed using the Diagnostic Interview Schedule (version 3A) as administered by a trained psychological technician. The Diagnostic Interview Schedule is a standardized questionnaire that is designed to assess the prevalence of certain psychiatric conditions according to the Diagnostic and Statistical Manual of Mental Disorders (version III) criteria of the American Psychiatric Association (34, 35). Study participants were considered positive for GAD and MDD if they reported a pattern of symptoms in the previous 12 months that satisfied full Diagnostic and Statistical Manual of Mental Disorders (version III) criteria.

Data Analysis

Baseline demographic, service-related, and health-related variables were compared between those with and without MDD and GAD, and those who had or had not died from all-cause or cardiovascular mortality using chi-square and ANOVAs. Cox's proportional hazards regression was used to examine the relationships between MDD, GAD, and both all-cause and cardiovascular mortality. Follow-up time was the underlying time scale. In these analyses, both MDD and GAD were utilized as binary variables (diagnosis or no diagnosis). Follow-up time was taken from the date of the telephone survey until censoring, death or December 31st 2000, which ever came first (mean follow-up time 14.6 (SD = 1.76) years). In these analyses we adjusted first for age at telephone survey, and then additionally for variables that we conceptualised as potential confounding factors (place of service, ethnicity, marital status,

smoking habit, alcohol consumption, IQ at enlistment, household income in midlife, body mass index, total cholesterol, systolic blood pressure, blood glucose, and somatic illness). These covariates were chosen *a priori* as they have all been associated with mortality in this dataset (23, 36) and others (37). In the event that controlling for covariates attenuated the significance of relationships between the independent and dependent variables, we estimated the percentage effect of controlling for the covariates using the following formulae as we have elsewhere (38) (HR=hazards ratio): $([HR_{age\text{-}adjusted} - 1] - [HR_{risk\ factor\text{-}adjusted} - 1] / [HR_{age\text{-}adjusted} - 1]) * 100$. In order to examine the effect of having both disorders as opposed to a single disorder or neither, the above analyses predicting all-cause and cardiovascular mortality, with adjustment for age and then for all covariates, were repeated using a variable which compared those with psychiatric comorbidity against those with GAD alone, those with MDD alone, and those with neither diagnosis. Finally, in order to examine whether MDD and GAD were having additive or synergistic effects on mortality, an interaction term was created from the product of MDD and GAD (resulting in a further binary variable consisting of individuals with both MDD and GAD versus the remainder of the sample). Further age-adjusted and fully adjusted hazard models were then tested.

Results

Major depressive disorder and generalised anxiety disorder

Of the 4256 participants, 6.5% met diagnostic criteria for MDD, and 9.7% for GAD. The characteristics of the participants, from data collected in early adulthood from military records, and in middle age from the telephone survey and the medical examination, are presented in Table 1, according to whether or not they met diagnostic criteria for MDD and GAD. MDD was significantly associated with serving in Vietnam, younger age at the time of the medical examination, not being married and a greater likelihood of being divorced/separated/widowed than never married. They also had lower IQ scores, and lower household income in mid life. Finally, they were more likely to be a current smoker and to drink more units of alcohol per week; had lower total cholesterol, and were more likely to have a physical illness. A recent meta-analysis also found that low cholesterol levels have been observed in those with depression, perhaps as a result of candidate mechanisms such as suppressed appetite, cytokine activation, and reduced availability of serotonin (39). The same differences emerged for those with and without GAD except there were no differences in total cholesterol. Those with GAD were significantly less likely to be white, and equally likely to be divorced/separated/widowed as never married.

All-cause mortality

During the 15 years of follow-up there were 236 deaths. Table 2 summarises the differences between those who had died and those who survived. Higher mortality was associated with service in Vietnam, not being married, being non-white, having lower household income in midlife, higher blood pressure and

blood glucose level, smoking; higher alcohol consumption, and reported physical illness at examination. Age-adjusted analyses revealed that those diagnosed with MDD were at a significantly greater risk of mortality, HR = 2.56, 95%CI = 1.78 – 3.68, $p < .001$; and those diagnosed with GAD were also at an increased risk of death, HR = 2.70, 95%CI = 1.98 – 3.68, $p < .001$. Following adjustment for age and the other covariates collectively, the associations between MDD, HR = 1.55, 95%CI = 1.06 – 2.26, $p = .02$, GAD, HR = 1.68, 95%CI = 1.22 – 2.33, $p = .002$, and all-cause mortality remained significant.

[Insert Tables 1 and 2 about here]

Cardiovascular disease mortality

Of the 236 deaths, 63 were due to major cardiovascular diseases. Table 2 shows the differences between those who had died due to cardiovascular disease and those who had not. Those who had died of cardiovascular causes were significantly more likely to have served in Vietnam, were older at the time of the medical examination, were less likely to be white, had lower household income in midlife, had lower BMI, higher blood pressure, were more likely to be a current smoker than a non-smoker, had higher total cholesterol and blood glucose, and were more likely to have a physical illness. In age-adjusted analyses, those diagnosed with MDD were at a significantly increased risk of death, HR = 2.31, 95%CI = 1.10 – 4.86, $p = .03$; and those diagnosed with GAD were also at an increased risk of cardiovascular mortality, HR = 2.89, 95%CI = 1.59 – 5.23, $p < .001$. Following adjustment for both age and all of the other covariates, the association between MDD and cardiovascular mortality was weakened by 61% and became non-significant, HR = 1.51, 95%CI = 0.70 – 3.25, $p = .30$. The association between GAD and cardiovascular mortality was weakened by 55% and was attenuated to a non-significant trend, HR = 1.84, 95%CI = 0.98 – 3.45, $p = .06$. The covariate which weakened the association between MDD and CVD mortality most strongly was household income in midlife.

Analysis of comorbidity

One hundred and fifty-three (3.6%) participants had a diagnosis of both MDD and GAD in the past year; there were 124 with only MDD and 258 with only GAD. The diagnoses of MDD and GAD were significantly correlated, C(1) = .38, $p < .001$. In age-adjusted analyses, comorbidity of these two disorders was a very strong predictor of all-cause mortality, HR = 4.29, 95%CI = 2.90 – 6.36, $p < .001$. MDD was not associated with mortality in this model, HR = 0.85, 95%CI = 0.35 – 2.07, $p = .72$, although GAD was, HR = 1.80, 95%CI = 1.16 – 2.80, $p = .009$. When this analysis was repeated, adjusting for all covariates in addition to age, neither MDD or GAD were related to all-cause mortality, but comorbidity remained strongly associated, HR = 2.29, 95%CI = 1.51 – 3.48, $p < .001$. Only comorbidity was associated with CVD mortality in the age-adjusted analysis, HR = 4.55, 95%CI = 2.15 – 9.61, $p < .001$. In analyses with all covariates, comorbidity emerged again as the only significant predictor, HR = 2.68,

95%CI = 1.22 – 5.88, p = .01. Percentages who died of all-causes or cardiovascular disease with comorbidity, MDD only, GAD only, or neither are shown in Figure 2.

[Insert Figure 2 about here]

A further model was run where, with adjustment for age, both MDD, GAD, and the MDD x GAD interaction variable were entered. These were then repeated with full adjustment for all covariates. In the age-adjusted model, MDD was not a significant predictor of all-cause mortality, HR = 0.85, 95%CI = 0.35 – 2.07, p = .72, but GAD was, HR = 1.80, 95%CI = 1.16 – 2.80, p = .009, and the interaction term was not quite significant, HR = 2.81, 95%CI = 0.99 – 8.01, p = .053. However, in the fully adjusted model, neither MDD, HR = 0.59, 95%CI = 0.24 – 1.45, p = .25, or GAD, HR = 1.22, 95%CI = 0.78 – 1.91, p = .39, were significantly associated with all-cause mortality, whereas the interaction term was, HR = 3.18, 95%CI = 1.11 – 9.15, p = .03. Models for CVD mortality could not be computed since the coefficients did not converge. This probably reflected the small numbers in the cells including zero deaths from CVD in the MDD group once comorbidity is controlled for.

Supplementary analyses: PTSD comorbidity

As PTSD is prevalent (N = 313) and has been found to predict mortality previously in this population (23, 24), we examined its association with MDD and GAD. PTSD was significantly associated with both MDD, C(1) = .25, p < .001, and GAD, C(1) = .19, p < .001. Consequently, we conducted age-adjusted and fully adjusted analyses for all-cause mortality, where those with comorbidity of all three disorders are compared against those with comorbidity of two disorders (GAD and MDD, GAD and PTSD, and MDD and PTSD) against those with either disorder alone against those with none of the disorders. We then repeated these models with CVD mortality as the outcome variable. For all-cause mortality, GAD, HR = 1.80, 95%CI = 1.11 – 2.94, p = .02, and PTSD, HR = 1.82, 95%CI = 1.07 – 3.085, p = .03, significantly predicted mortality, as did comorbidity of MDD and GAD as above, HR = 4.18, 95%CI = 2.54 – 6.90, p < .001, and comorbidity of all three disorders, HR = 4.61, 95%CI = 2.50 – 8.49, p < .001. In the fully adjusted model, only comorbidity of MDD and GAD, HR = 2.46, 95%CI = 1.45 – 4.16, p = .001, and comorbidity of all three disorders, HR = 2.06, 95%CI = 1.09 – 3.91, p = .03, predicted mortality. For CVD mortality in the age-adjusted model, only comorbidity of MDD and GAD, HR = 3.74, 95%CI = 1.36 – 10.41, p = .01, and comorbidity of all three disorders, HR = 6.56, 95%CI = 2.36 – 18.26, p < .001, were significant predictors. Finally, in the fully adjusted model, only the comorbidity of all three disorders, HR = 3.34, 95%CI = 1.12 – 10.01, p = .03, predicted CVD mortality. Statistics for the non-significant associations in these analyses are available on request from the corresponding author.

Discussion

The one-year prevalence of MDD and GAD in this population of veterans was 6.5 and 9.7, respectively. This is higher than general population estimates (2). However, even higher prevalence has been observed in other veteran groups when mental disorders were measured more proximally to combat exposure (8). In individual analyses, both MDD and GAD were positively associated with all-cause mortality in age-adjusted analyses. When adjustment was made for a whole range of covariates, these associations were attenuated but both remained statistically significant. In further age-adjusted individual analyses, both MDD and GAD were positively associated with CVD mortality, although the association for MDD was no longer significant following adjustment for other covariates and the association for GAD was attenuated to a trend. The covariate with the largest impact on its association with CVD mortality was household income in midlife. Undoubtedly the most compelling and robust associations with mortality, both all-cause and CVD, emerged for MDD and GAD comorbidity. These associations withstood adjustment in the covariate analyses. Interaction analyses appeared to show that MDD and GAD work synergistically to increase risk of all-cause mortality.

These findings are consistent with the results of previous research linking MDD with all-cause mortality in the general population (e.g. (12, 13) and in veterans (9). Although many studies have considered depression as a predictor of CVD mortality, surprisingly few have examined diagnosed MDD. Of those available, both positive (14) and null (40, 41) findings have been reported. In the present analysis, a positive association with CVD mortality was found but this was attenuated to non-significance with full adjustment. Although little attention has been paid to MDD and all-cause mortality in veterans, our findings are consistent with those of one recent study in which individuals with a diagnosis of depression were at increased risk of death over an average of two years (9). The present analysis is the first to examine MDD and CVD mortality in veterans. Our results regarding GAD contrast with those from the two previous studies on GAD and all-cause mortality, which suggest that GAD does not present a significant risk (18, 19). However, this discrepancy might be due to the difference in populations examined: older adults (18) and the general population (19). It is also possible that anxiety may only predict mortality in men, as in one previous study where an association between anxiety disorders and mortality was found for men but not women (42). GAD has not been previously studied in terms of CVD mortality in the general population, or in the context of mortality *per se* in veterans. This seems unfortunate given that it is a strong predictor of all-cause mortality in the present analyses.

Some studies have examined the prognostic importance of both symptoms of anxiety and depression and mortality in cardiac patient groups. In a review of 25 studies of chronic heart failure patients, anxiety symptoms were measured along with depression in just three studies (43). Anxiety symptoms were not associated with mortality, whereas depressive symptoms significantly predicted death (43). A number of studies have examined both anxiety and depression symptoms and mortality in myocardial infarction patients. High depression and anxiety scores have both been found to predict all-cause mortality (44), and cardiac death (45). However, in three studies, symptoms of depression but not

anxiety in multivariate models predicted all-cause or cardiac mortality (46-48). Finally, neither depression nor anxiety symptoms were found to predict mortality in myocardial infarction patients (49). Thus, in prognostic studies, it would appear that depressive symptoms may be a more stable predictor of mortality than anxiety. However, it is unclear the extent to which the results of these studies of patients with chronic inflammatory disease relate to the present aetiological study where only 1% had a diagnosis of coronary heart disease at the medical examination. It is possible that the effects of depression on mortality and the underlying mechanisms may not be identical in patient versus population-based studies. Further, none of the prognostic studies that we know of have examined psychiatric comorbidity effects on mortality.

MDD and GAD are highly comorbid psychiatric conditions (2). In the present study, 3.6% of participants had a diagnosis of both MDD and GAD. More strikingly, 55% of those with a diagnosis of MDD also had GAD. Patients with comorbid MDD and GAD have been found to have poorer functional status than those with either condition alone (50) and it has been proposed that they are at increased risk for CVD (51). However, we know of no previous studies that have examined the mortality risk associated with this comorbidity. The present study indicates that comorbid MDD and GAD confers a stronger mortality risk than either condition alone. Indeed, in the fully adjusted interaction analysis, only comorbidity was significant, suggesting that these disorders act synergistically rather than additively in their effect on death.

The importance of comorbidity is further demonstrated in the supplementary analyses of the effects of comorbidity with PTSD where it was the comorbidity of MDD and GAD, and of PTSD, MDD, and GAD that emerged as the most consistent predictors of mortality. Consequently, this argues that comorbidity should receive considerably more attention in future research on mental disorders and health outcomes, at least in studies of non-patient groups. Further, clinical interventions have tended to concentrate on single mental health diagnoses; our findings suggest that targeting comorbidity might be a fruitful new approach.

It should be conceded that there are a number of limitations to this analysis and its interpretation. First, the weaker effects for CVD in comparison to all-cause mortality, and the attenuation to non-significance in the fully adjusted models, may reflect the small number of deaths due to CVD in this sample resulting in lower power to detect significant associations, particularly when adjusting for a large number of covariates. Support for this assertion can be found in the hazard ratios which were of comparable size in the fully adjusted models for both all-cause and CVD mortality, but only attained significance when all-cause mortality was the outcome. Second, as associations were attenuated for both all-cause and CVD mortality following adjustment for various covariates, this raises the issue of whether or not mental disorders are causally related to mortality, particularly CVD mortality. It is worth noting that some researchers remain sceptical regarding causality in this context (49, 52). In addition, residual confounding as a consequence of un-measured variables, such as sleep duration (53) and birthweight (54),

cannot be wholly discounted. The present analysis, however, did adjust for a large number of potential confounding variables. Third, as this sample was exclusively male, there is the issue of generalisation. It should be noted that the previous studies with null results tested women only in one case (40) and both sexes in the other (41). It is also worth noting, though, that these studies had much smaller samples, reducing their power to detect effects on mortality. In addition, it is possible that veterans differ in other ways from the broader population. For example, one study of stable coronary heart disease that included veterans found no evidence that depression was associated with elevated levels of inflammation (55); a finding opposite to that of many studies in non-cardiac disease patients. However, not all the patients in this study were veterans (55). Fourth, it has been suggested that the prevalence of mental health disorders in the Vietnam Experience Study are underestimated (56, 57). However, this criticism has mainly been levelled at estimations of PTSD prevalence. Nevertheless, it is possible that severely depressed veterans were less likely to participate in the medical examination, which may have accounted for the attenuated associations for major depression in the present analyses. However, this seems unlikely given that only 10 (<2%) veterans were unable to attend on the basis of physical/mental disability, and only 372 (<6%) refused to attend, with the main reasons being a lack of interest or unwillingness to travel. Moreover, underestimation in the present study would make the associations demonstrated between MDD, GAD, their comorbidity and mortality more compelling. Fifth, given that a diagnosis of MDD only requires two weeks of symptoms, whereas GAD requires symptoms for at least six months, it is possible that MDD diagnoses were less trustworthy. However, evidence indicates that the DSM-III criteria for diagnosis of both MDD and GAD are highly reliable (58). Finally, it should be conceded that we are unable to fully explore the nature of the comorbidity effect for CVD mortality in this sample, due to the small numbers precluding interaction analyses.

In conclusion, the present analysis in Vietnam veterans showed that MDD and GAD were positively associated with all-cause and CVD mortality. However, the relationships with CVD mortality were non-significant following adjustment for a range of covariates, possibly due to low statistical power. A diagnosis of both MDD and GAD proved much the strongest predictor of all-cause and CVD mortality. The effects of comorbidity of MDD and GAD, and with PTSD would suggest that future research on mental health disorders and physical health outcomes, as well as future clinical interventions, should pay more attention to comorbidity. In addition, future studies should attempt to measure and take account of a full range of factors likely to be associated with both mental and physical health.

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Table 1: Descriptive statistics and frequencies for each variable by major depressive disorder status and generalised anxiety disorder status

			Major Depressive Disorder (N = 277)		No Major Depressive Disorder (N = 3979)		*p*	Generalised Anxiety Disorder (N = 411)		No Generalised Anxiety Disorder (N = 3845)		*p*
			Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Standardised IQ score from enlistment			97.9	15.42	101.6	15.15	<.001	96.5	16.18	101.9	14.99	<.001
Units of alcohol per week			10.7	24.8	6.8	13.4	<.001	10.6	22.87	6.7	13.15	<.001
Age at medical examination (years)			37.8	2.67	38.4	2.50	.001	38.0	2.65	38.4	2.50	.003
Total cholesterol (mmol/l)			5.4	1.00	5.5	1.08	.03	5.5	1.01	5.5	1.09	.42
Blood glucose (mg/dL)			94.6	20.6	94.3	16.8	.77	95.6	20.44	94.2	16.66	.10
SBP (mmHg)			123.1	12.54	123.0	12.01	.90	123.8	13.06	122.9	11.93	.17
BMI (kg/m^2)			25.9	3.72	25.8	3.96	.69	25.9	3.70	25.9	4.12	.88
			N (%)		N (%)		*p*	N (%)		N (%)		*P*
Place of service	Ever in Vietnam		186 (68)		2163 (54)		<.001	267 (65)		2082 (54)		<.001
	Other overseas		51 (18)		1044 (26)			85 (21)		1010 (26)		
	US only		40 (14)		772 (20)			59 (14)		753 (20)		
Ethnicity:	White		218 (79)		3272 (82)		.31	311 (76)		3179 (83)		.001
	Black		37 (13)		459 (12)			61 (15)		435 (11)		
	Other		22 (8)		248 (6)			39 (9)		231 (6)		
Household income in midlife		<$20,000	130 (47)		1072 (27)		<.001	184 (45)		1018 (26)		<.001
		-$40,000	110 (40)		2019 (51)			171 (42)		1958 (51)		
		>$40,000	37 (13)		888 (22)			56 (13)		869 (23)		
Smoking Status:	Non smoker		50 (18)		1035 (26)		<.001	79 (19)		1006 (26)		<.001
	Ex smoker		57 (21)		1152 (29)			90 (22)		1119 (29)		
	Current smoker		170 (61)		1792 (45)			242 (59)		1720 (45)		
Marital Status:	Married		151 (55)		2980 (75)		<.001	244 (59)		2887 (75)		<.001
	Divorced/separated/widowed		94 (34)		673 (17)			116 (28)		651 (17)		
	Never married		32 (11)		326 (8)			51 (12)		307 (8)		
Physical Illness		Yes	220 (79)		3463 (87)		<.001	335 (82)		3349 (87)		.002
diabetes/hypertension/cancer or CHD		No	57 (21)		515 (13)			76 (18)		496 (13)		

Table 2: Descriptive statistics and frequencies for each variable by all-cause and CVD-specific mortality status

			Died: All-cause (N = 236)		Surviving (N = 4020)		*p*	Died: CVD (N = 63)		Surviving (N = 4193)		*p*
			Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Standardised IQ score from enlistment			96.5	15.2	101.6	15.14	< .001	97.4	14.41	101.4	15.19	.04
Units of alcohol per week			11.9	23.00	6.8	13.7	< .001	8.8	16.97	7.1	14.38	.34
Age at medical examination (years)			38.6	2.68	38.3	2.51	.15	39.1	2.14	38.3	2.52	.02
Total cholesterol (mmol/l)			5.6	1.35	5.5	1.06	.45	6.1	1.52	5.49	1.07	<.001
Blood glucose (mg/dL)			102.6	40.75	93.8	14.38	< .001	110.1	51.61	94.1	15.88	<.001
SBP (mmHg)			125.4	15.65	122.9	11.79	.001	128.3	20.04	122.9	11.87	<.001
BMI (kg/m^2)			25.9	3.69	26.2	4.50	.20	25.9	3.73	27.6	4.18	<.001
			N (%)		N (%)		*p*	N (%)		N (%)		*p*
Place of service	Ever in Vietnam		148 (63)		2201 (55)		.06	42 (67)		2307 (55)		.09
	Other overseas		49 (21)		1046 (26)			9 (14)		1086 (26)		
	US only		39 (17)		773 (19)			12 (19)		800 (19)		
Ethnicity:	White		162 (69)		3328 (83)		< .001	44 (70)		3446 (82)		.04
	Black		51 (21)		445 (11)			12 (19)		484 (12)		
	Other		23 (10)		247 (6)			7 (11)		263 (6)		
Household income in midlife		<$20,000	110 (47)		1092 (27)		<.001	28 (44)		1174 (28)		.005
		-$40,000	105 (44)		2024 (50)			29 (46)		2100 (50)		
		>$40,000	21 (9)		904 (23)			6 (10)		919 (22)		
Smoking Status:	Non smoker		42 (18)		1043 (26)		< .001	10 (16)		1075 (26)		.06
	Ex smoker		44 (19)		1165 (29)			15 (24)		1194 (28)		
	Current smoker		150 (64)		1812 (45)			38 (60)		1924 (46)		
Marital Status:	Married		129 (55)		3002 (75)		< .001	39 (62)		3092 (74)		.07
	Divorced/separated/widowed		71 (30)		696 (17)			18 (29)		749 (18)		
	Never married		36 (15)		322 (8)			6 (10)		352 (8)		
Physical Illness		Yes	62 (26)		3510 (87)		< .001	41 (65)		3643 (87)		<.001
diabetes/hypertension/cancer or CHD		No	174 (74)		510 (13)			22 (35)		550 (13)		

Figure 1: Sampling in the Vietnam Experience Study

Figure 2: Percentage dead within each diagnosis group for all-cause and cardiovascular disease mortality