ABSTRACT

**Importance:** Depression is associated with increased mortality, but it is unclear if this relationship is truly causal.

**Objectives:** To determine the relative mortality associated with past and current depression taking into account the effect of frailty.

**Design, Setting and Participants:** Prospective longitudinal cohort study of 2565 men aged 75 years or over living in metropolitan Perth, Western Australia, who completed the third wave of assessments of the Health In Men Study throughout 2008.

**Main outcome and measures:** All cause mortality data were derived from Australian death records up to the 17th June 2013. History of past depression and age of onset of symptoms were obtained from direct questioning and from electronic health record linkage. Diagnosis of current major depressive symptoms followed DSM-IV-TR guidelines. We considered that participants were frail if they showed evidence of impairment in 3 or more of the 5 domains on the FRAIL scale: i.e. fatigue, resistance, ambulation, illnesses and loss of weight. Other measured factors included age, education, living arrangements, smoking and alcohol history, and physical activity.

**Results:** 558 participants died during mean period of follow-up of 4.2±1.1 years. The annual death rate per thousand was 50 for men without depression, 52 for men with past depression, and 201 for men with major depressive symptoms at baseline. The crude mortality hazard (MH) was 4.26 (95%CI=2.98, 6.09) for men with depression at baseline compared with never depressed men, and 1.79 (95%CI=1.21, 2.62) after adjustment for frailty. Further decline in MH was observed after adjustment for other measured factors.

**Conclusion:** Current, but not past, depression is associated with increased mortality, and this excess mortality is strongly associated with frailty. Interventions designed to decrease depression-related mortality in later life may need to focus on ameliorating frailty in addition to treating depression.

**Key-words:** depression, mortality, frailty, cohort study, elderly.
INTRODUCTION

Depression is a common mental disorder that affects about 10% of those older than 60 years of age.\textsuperscript{1,2} People with depression are subject to deteriorating quality of life, as well as to increased disability, morbidity and mortality compared with their non-depressed peers.\textsuperscript{3-5} The mechanisms linking depression to negative health outcomes such as death are not clear, but unhealthy lifestyle practices, high disease burden and decreased heart rate variability may all play a part.\textsuperscript{6-8}

There is also some evidence, albeit inconclusive, that the risk of death increases with the severity of the depressive episode.\textsuperscript{9,10} Antidepressants are effective at reducing the severity of symptoms,\textsuperscript{11} but seem to have an equivocal impact on long term mortality, particularly later in life.\textsuperscript{12,13} There are three possible ways of explaining this observation. Firstly, depression (or its treatment) could be associated with damaging physiological changes that extend beyond those involved in the expression of depressive signs and symptoms, and those changes might fail to normalize with antidepressant treatment. For example, depression is associated with decreased heart rate variability, but effective antidepressant treatment does not reverse these changes.\textsuperscript{13} Secondly, older adults with depression include a group of people with recurrent or chronic depressive episodes, and this could lead to a pattern of repetitive exposure to stress and deteriorating health.\textsuperscript{14,15} In this case, the increased risk of death associated with depression could be due to the presence of recurrent rather than simply the current depressive episode. Finally, it is conceivable that the excess mortality associated with depression in later life is due to the presence of comorbid physical illnesses that trigger both depressive symptoms and a cascade of events that ultimately result in death.\textsuperscript{16}

If depression increases mortality, one might expect older people exposed to depression earlier in life to have greater absolute risk of death than late onset cases, as the former would have been exposed for longer to the conceivably damaging physiological changes associated with depression. Alternatively, if depression later in life is a marker of frailty, current rather than past depression
would be associated with increased risk of death. Clarifying this issue is important because if longstanding history of depression increases mortality, then developing effective secondary preventive strategies should be highlighted as research and public health priorities. Conversely, if depression in late life is a marker of frailty, death might only be successfully delayed if the factors that contribute to increasing frailty can be identified and ameliorated.

We designed this study to determine the mortality associated with remote and recent past depression, as well as with current depression, in a cohort of community-dwelling men older than 75 years. The null hypotheses of the study were that the mortality hazard of men with past (recent or remote) and current depression would be similar to that of men who had never been depressed before study entry.

METHODS

Study design and setting: This was a prospective cohort study of community-dwelling men living in the Perth metropolitan region, Western Australia.

Participants: This investigation included 2565 men aged 75 years or over who took part in the third wave of assessments of the Health In Men Study (HIMS) throughout 2008. HIMS is an ongoing longitudinal study of a community-representative sample of 12203 men aged 65-84 years recruited via the Australian Electoral roll during 1996-98. In order to take part in HIMS, participants had to be willing to complete a structured health questionnaire and to undergo an ultrasound for abdominal aortic aneurysm. During 2001-4 5485 survivors were invited to complete a second wave of assessments. The third wave took place in 2008.
The Human Research Ethics Committees of the University of Western Australia and of the Department of Health of Western Australia approved the study protocol, which followed the principles of the Declaration of Helsinki. All men provided written informed consent to participate.

Outcome of interest

The outcome of interest in this study was death by any cause (specific causes of death were not available). We used the Western Australian Data Linkage System (WADLS) to retrieve information from death records across Australia, including the date of death. WADLS connects death and multiple health records, including all acute hospital admissions, hospital movements, cancer and mental health registries for residents of Western Australia. Data were censored on the 18th of June 2013.

Explanatory variables

Current and past depression were the exposures of interest in this study. We used the Patient Health Questionnaire (PHQ-9) to assess depressive symptoms during wave 3 of HIMS. To meet criteria for a current depressive episode, participants had to indicate that they had experienced ‘little pleasure in doing things’ and/or had been ‘feeling down, depressed or hopeless’ for a week or more during the previous two weeks. In addition, men had to report experiencing at least five of the nine symptoms described in the PHQ-9 for most days during the same 2-week period: (a) decreased interest or pleasure; (b) low mood; (c) sleep disturbance; (d) lack of energy; (e) disturbed appetite; (f) feelings of failure or guilt; (g) poor concentration; (h) psychomotor disturbance; and (i) suicidal thoughts. Men who fulfilled both requirements and indicated that these problems made working, taking care of things at home or getting along with other people ‘somewhat difficult’ or ‘extremely difficult’, received the diagnosis of a current major depressive episode.
In addition, during the third wave of assessments for HIMS, we asked participants if a doctor had ever told them that they had had a depressive episode (yes/no) and, for those who responded in the affirmative, we asked them to indicate how old they were at the time they were ‘first told’ they had depression. We used this information to indicate history of past depression and approximate age of onset of symptoms. We also used data retrieved from WADLS to ascertain the history of health contacts associated with diagnosis of a depressive episode according to ICD-9 codes 296.2, 296.3, 296.82, 296.90, 298.0 and 311, and ICD-10 codes F32, F33, F34.1 and F38.10. We used these data to estimate the age at the time of first contact. The final age of onset of depression represented the youngest age from either self-report or WADLS.

We then subtracted the age of onset of depression from the age of participants at the time of assessment at HIMS wave 3 to calculate the duration of the depressive disorder, and classified the history of depression as non-existent (never depressed), remote (>5 years), recent (≤5 years) or current.

Other study measures included age (in years), high school education (completed or not), marital status, living arrangements (alone or with others), smoking (never, past or current) and alcohol history (never or occasional, <15 drinks per week, 15-27 drinks per week, ≥28 drinks per week). Men who reported 150 minutes of more of weekly leisure or household activities that made them breathe harder and pant were considered physically active.

Finally, we used the IANA Task Force definition of frailty to guide our assessment of its five relevant domains: fatigue, resistance, ambulation, illness and loss of weight (the FRAIL Scale, 0/1 for each, maximum score=5).21 The first three items of the scale were derived from questions of the SF-36 Health Survey22 assessing fatigue (worn out or feeling tired most of the time), resistance (inability to climb a flight of stairs) and ambulation (inability to walk 100 metres). We also asked
participants if they had ever been told by a doctor that they had (yes/no): arthritis, osteoporosis, angina, stroke, myocardial infarction, heart failure, asthma, chronic bronchitis, emphysema, bowel cancer, prostate cancer, melanoma, other skin cancers, Alzheimer’s disease, leg ulcers, Parkinson’s disease, thyroid problems, hypertension or diabetes. Men who acknowledged having 6 or more conditions were ascribed one point for ‘illness’ on the FRAIL scale. Finally, we assessed changes in weight between the first and third HIMS assessments. Men who lost 10% or more of their weight between the two assessments were ascribed a score of 1 for weight loss. We considered that participants were ‘frail’ if they scored 3 or more on the FRAIL scale. We have previously validated this scale against new onset of disability and death in men23 and women.24

Statistical methods and bias

We used the statistical package Stata 13.1 (StataCorp, College Station, TX77845) to manage and analyse the data. Numerical variables were summarised by their mean and standard deviation (SD), and categorical variables by their count and proportion (%). We compared groups using the Pearson chi-square statistic ($\chi^2$) and reported the number of degrees of freedom (df) associated with the analyses. We investigated the association between history of depression and death (all causes) using Cox regression models, censoring data at the date of death or the 18th June 2013 (whichever occurred first). The Cox regression model was adjusted for the potential effect of confounding due to age, marital status, smoking, physical activity and frailty. The proportion of men deceased over time was then displayed in graphic form. Finally, we estimated the rate of death per thousand-person years for men who were never depressed, men with a recent and remote history of depression, and for men with current depression. All statistical tests were two-tailed and alpha was set at 5%. Ninety-five percent confidence intervals (95%CI) of risk estimates were also reported.

Previous analyses of the various waves of assessment for HIMS have shown that survivors who completed subsequent assessments were healthier than those who did not.25
RESULTS

The mean±SD age of the 2565 participants was 81.8±3.8 years (range: 76 to 94 years) at the beginning of the follow up period. Of these, 55 (2.1%) showed evidence of a major depressive episode at assessment, 240 (9.4%) reported history of past depression, and 2270 (88.5%) had never been clinically depressed. Table 1 summarises the sociodemographic, lifestyle and clinical characteristics of participants according to their history of depression. Older men who were depressed at the time of assessment were older and less likely to have completed high school education than those who had never been depressed. They were more likely to smoke, consume alcohol at harmful levels and to be physically inactive than men with no past history of depression. Finally, larger proportions of them were frail than their counterparts with positive and negative history of past depression.

TABLE 1

Participants were followed up for 4.2±1.1 years (range: 0.1 to 5.3 years). Table 1 shows that men who were depressed at the time of assessment were more likely to die during follow up (58.2%) compared with men who had a past history of depression (21.7%) and men with no history of depression (20.9%). Table 2 shows that the age-adjusted annual death rate per thousand older men was substantially higher amongst those with current than with past or with no history of depression. The age-adjusted annual mortality rates per thousand participants who did not fulfill the study criteria for frailty were 41 (95%CI=37, 46) for men who had never been depressed, 46 (95%CI=24, 88) for men with history of recent depression, 35 (95%CI=23, 54) for those with remote history of depression, and 141 (95%CI=53, 376) for men who were currently depressed. Similarly, the respective mortality rates for men who were frail at baseline and who had never been depressed
were 136 (95%CI=113, 164), 65 (95%CI=24, 172), 120 (95%CI=76, 191) and 214 (95%CI=148, 310).

Participants with current depression had a mortality hazard four times greater than older men who had never been depressed (HR=4.26; 95%CI=2.98, 6.09), although the magnitude of the association decreased markedly when adjusted for frailty (adjusted HR=1.78, 95%CI=1.21, 2.62), and decreased further when age, marital status, smoking, physical activity and frailty were taken into account (adjusted HR=1.66, 95%CI=1.08, 2.56). History of remote or recent past depression did not increase the mortality hazard (Figure 1).

TABLE 2

FIGURE 1

DISCUSSION

The results of this study showed that men older than 75 years with current major depressive symptoms had a four-fold increase in annual mortality compared with men who had never been depressed or who had been depressed in the past. History of recent or remote clinically significant depressive symptoms did not increase mortality hazard or rates. The association between current depression and increased risk of death was largely explained by the presence of frailty, although some residual increased mortality associated with current, but not past, major depressive symptoms could not be explained by other measured factors.

Before discussing the implications of these findings, we wish to consider the limitations and strengths of the approach we used to address the aims of the study. This cohort survey reports data on a large community-derived sample of older men for whom past and current health data were available. In addition, participants were derived from a sample of men at risk of depression, frailty
and death, thereby enhancing our ability to investigate the association between these variables. Our access to data about the history of past depression from various sources (self-report and health data linkage) is a strength, although we concede that the validity of this assessment is yet to be established. In addition, the use of the PHQ-9 enabled us to ascertain the presence of major depressive symptoms at the start of the follow up. This approach has merit, but it does not necessarily equate to a DSM diagnosis of major depressive episode derived from structured psychiatric interview, although our prevalence estimates of depression are consistent with those reported by other studies in Europe and North America. Finally, as the recording of death is mandatory and universal in Australia, valid outcome data were available for all participants.

We acknowledge, however, that recruitment into our study has been subject to healthy participant bias. The implication of such bias would be a reduction in the prevalence of depression and frailty in the study sample. Consequently, it is possible that the mortality potentially attributable to depression could be higher, although the loss of frail men from the study population might have limited our ability to adjust the analyses appropriately. Thus, the residual association between current depression and mortality that we did observe could potentially be attributable to severe frailty (and non-participation in the study). We are also mindful of the fact that our pragmatic definition of frailty would benefit from external validation by others, even though it is a robust predictor of death, and the observed prevalence of 13% is in the same range as that of other community derived samples of older people living in North America and Europe. Moreover, the observational design of the study limits our ability to infer causality for the association between depression and subsequent death, although our results are consistent with those of previous reports. Finally, we cannot be certain that our findings would apply equally to women.

Given the context and characteristics of our investigation, how should its results be interpreted? Numerous previous studies have found that people presenting with clinically significant symptoms
of depression have greater annual mortality than those without depression.\textsuperscript{3,29,30} The impact of history of past depression on mortality seems less clear. Evidence from randomised controlled trials indicates that people offered active antidepressant treatment have lower mortality than controls,\textsuperscript{31} while observational data of older adults treated with antidepressants who are free of clinically significant depressive symptoms show that their mortality is comparable to that of subjects without depression.\textsuperscript{12} These findings could be interpreted as indicating that people who experience an episode of depression and recover have no greater mortality than those who have never been depressed. Our results are broadly consistent with this conclusion: older men with past depressive episodes, either recent or remote, were no more likely to die than older men who had never been depressed. In other words, past depressive episodes do not seem to trigger potentially lethal physiological changes that persist once symptoms remit.

In contrast, current major depressive symptoms were associated with a marked increase in mortality over a period of up to five years, which was largely explained by the concurrent presence of frailty. Frailty is a threshold state characterised by increasing inability to adequately address physiological demands. Not surprisingly, the progressive accumulation of deficits observed among frail individuals\textsuperscript{32} is associated with high mortality risk.\textsuperscript{33} A staggering 85\% of older men with major depressive symptoms in our sample were also frail, suggesting that frailty may contribute to the onset of major depressive symptoms in the very old or, alternatively, that depression in very late life is an expression of frailty.

Mezuk and colleagues used latent class analysis to determine whether depression and frailty were overlapping concepts for older participants of the Baltimore Epidemiologic Catchment Area Study.\textsuperscript{34} They found that these constructs were not identical, but showed a high degree of overlap.\textsuperscript{34} Unlike our study, however, their sample of 683 people was relatively young (40+ years) and used ‘lifetime’ rather than current major depression in the analyses. Other observational studies have
shown that depressive symptoms are common among frail older people, and non-lethal outcomes associated with frailty in later life, such as falls, are also more frequent amongst those with depression. Therefore, the presence of major depressive symptoms in very late life should alert health practitioners to the possible presence of frailty. Indeed, it is conceivable that the excess mortality associated with depression in this age group may be more responsive to the reversal of frailty than to the isolated treatment of depressive symptoms.

Singh and colleagues randomly assigned 124 frail older adults who underwent surgical repair for hip fracture to a twelve-month program of physical resistance training, nutrition, sensory enhancement and the active management of other risk factors. Compared with controls, the intervention reduced admission to residential care and mortality by 80%. In addition to physical activity, vitamin D and testosterone may also have a role to play in decreasing frailty, but their effectiveness has not been consistently supported by the findings of randomised controlled trials.

In conclusion, the results of our study indicate that current, but not past, depression in older men is associated with increased mortality, and that this excess mortality is largely associated with frailty. Interventions designed to decrease depression-associated death rates in later life may need to focus on ameliorating the frailty of this population in addition to treating depressive symptoms.
ACKNOWLEDGEMENTS

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REFERENCES


<table>
<thead>
<tr>
<th>Depression History</th>
<th>Never N=2270 (%)</th>
<th>Past N=240 (%)</th>
<th>Current N=55 (%)</th>
<th>Statistic (df)</th>
<th>p-value</th>
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<td>Age group (years)</td>
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<td>75-79</td>
<td>901 (39.7)</td>
<td>88 (36.7)</td>
<td>16 (29.1)</td>
<td>$\chi^2(6)=13.69$</td>
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<tr>
<td>80-84</td>
<td>944 (41.6)</td>
<td>100 (41.7)</td>
<td>22 (40.0)</td>
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<td>85-89</td>
<td>355 (15.6)</td>
<td>41 (17.1)</td>
<td>11 (20.0)</td>
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<td>≥90</td>
<td>70 (3.1)</td>
<td>11 (4.6)</td>
<td>6 (10.9)</td>
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<tr>
<td>Completed high school</td>
<td>1172 (51.6)</td>
<td>130 (54.2)</td>
<td>19 (34.5)</td>
<td>$\chi^2(2)=7.03$</td>
<td>0.030</td>
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<tr>
<td>Currently married</td>
<td>1733 (77.6)</td>
<td>167 (71.7)</td>
<td>41 (77.4)</td>
<td>$\chi^2(2)=4.26$</td>
<td>0.119</td>
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<tr>
<td>Living alone</td>
<td>452 (20.3)</td>
<td>58 (24.7)</td>
<td>13 (26.5)</td>
<td>$\chi^2(2)=3.39$</td>
<td>0.183</td>
</tr>
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<td>Smoking:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>891 (41.8)</td>
<td>85 (37.1)</td>
<td>19 (38.8)</td>
<td>$\chi^2(4)=20.26$</td>
<td>&lt;0.001</td>
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<td>past</td>
<td>1188 (55.8)</td>
<td>135 (58.9)</td>
<td>24 (49.0)</td>
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</tr>
<tr>
<td>current</td>
<td>51 (2.4)</td>
<td>9 (3.9)</td>
<td>6 (12.2)</td>
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<tr>
<td>Alcohol:</td>
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<tr>
<td>never/occasional</td>
<td>118 (5.2)</td>
<td>13 (5.4)</td>
<td>4 (7.3)</td>
<td>$\chi^2(6)=14.53$</td>
<td>0.024</td>
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<tr>
<td>&lt;15 drinks/week</td>
<td>1098 (48.5)</td>
<td>100 (41.7)</td>
<td>17 (30.9)</td>
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<td>15-27 drinks/week</td>
<td>177 (7.8)</td>
<td>18 (7.5)</td>
<td>2 (3.6)</td>
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<tr>
<td>≥28 drinks/week</td>
<td>873 (38.5)</td>
<td>109 (45.4)</td>
<td>32 (58.2)</td>
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<tr>
<td>Physically inactive</td>
<td>808 (35.6)</td>
<td>111 (46.2)</td>
<td>46 (83.6)</td>
<td>$\chi^2(2)=61.21$</td>
<td>&lt;0.001</td>
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<td>Frail</td>
<td>230 (10.1)</td>
<td>56 (23.3)</td>
<td>47 (85.4)</td>
<td>$\chi^2(2)=294.79$</td>
<td>&lt;0.001</td>
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<td>Died during follow up</td>
<td>474 (20.9)</td>
<td>52 (21.7)</td>
<td>32 (58.2)</td>
<td>$\chi^2(2)=43.89$</td>
<td>&lt;0.001</td>
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$\chi^2$: Pearson chi-square statistic; df: degrees of freedom.
Table 2. Annual death rate of older men according to their depression history.

<table>
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<tr>
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<th>Person-years</th>
<th>Death Rate per 1000</th>
<th>95%CI</th>
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<tr>
<td>Never depressed</td>
<td>9565</td>
<td>50</td>
<td>45 to 54</td>
</tr>
<tr>
<td>Depression &lt; 5 years</td>
<td>258</td>
<td>50</td>
<td>29 to 87</td>
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<td>Depression ≥ 5 years</td>
<td>747</td>
<td>52</td>
<td>38 to 71</td>
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<tr>
<td>Currently depressed</td>
<td>159</td>
<td>201</td>
<td>142 to 284</td>
</tr>
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95%CI: 95% confidence interval of the death rate.
**FIGURE LEGEND**

**Figure 1.** The figure shows the proportion of men deceased over time according to their depression history. The hazard ratio (HR) of death was 1.02 (95% confidence interval, 95%CI=0.59, 1.77), 1.06 (95%CI=0.76, 1.46) and 4.26 (95%CI=2.98, 6.09) for men with depression for < 5 years, depression for ≥ 5 years and with current depression, respectively. The respective adjusted HRs were 0.72 (95%CI=0.39, 1.31), 0.87 (95%CI=0.62, 1.23) and 1.66 (95%CI=1.08, 2.56) (adjusted for age, marital status, smoking, physical activity and frailty).