Late-life depression and mortality: influence of gender and antidepressant use

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Background: Depression may increase the risk of mortality among certain sub-groups of older people, but the role played by antidepressants in this association has not been thoroughly explored.

Aims: To identify the characteristics of older populations who are most at risk of dying, as a function of depressive symptoms, gender and antidepressant use.

Method: Adjusted Cox's proportional hazards models were used to determine the association between depression and/or antidepressant use, and 4-year survival of 7363 community-dwelling elderly. Major depressive disorder was evaluated using a standardised psychiatric examination based on DSM-IV criteria and depressive symptoms were assessed using the Centre for Epidemiological Studies Depression Scale.

Results: Depressed men using antidepressants had the greatest risk of dying, with increasing depression severity corresponding to a higher hazard risk. Among women, only severe depression in the absence of treatment was significantly associated with mortality.

Conclusions: The association between depression and mortality is gender dependent and varies according to symptom load and antidepressant use.

Declaration of interest: None.

INTRODUCTION

Late-life depression is often underdiagnosed and undertreated (Alexopoulos, 2005) or, when treatment is given, it is often inappropriate (Unutzer, 2002). Depression is associated with higher comorbidity (Tiemeier, *et al*, 2005), and may increase the risk of mortality (Adamson, *et al*, 2005; Anstey, *et al*, 2002; Penninx, *et al*, 1999; Schulz, *et al*, 2000; Vinkers, *et al*, 2004), although this has not been found consistently (Callahan, *et al*, 1998; Cuijpers, 2001; Hybels, *et al*, 2002; McCusker, *et al*, 2006; Thomas, *et al*, 1992). This variability can be partly explained by the large heterogeneity between the studies in terms of the populations (community vs. clinical samples), the method of depression assessment (clinical/standardised examination vs. self-evaluation) and the type of depression diagnosed (major or minor depression, depressive symptoms or "psychiatric distress"). The limited extent of covariate adjustment has also influenced the findings (Blazer, *et al*, 2001; Hybels, *et al*, 2002; McCusker, *et al*, 2006), with few community-based studies controlling for antidepressant use (Hybels, *et al*, 2002; McCusker, *et al*, 2006).

The objective of this study was to examine the association between depression and mortality in a large community-based elderly population, which permitted the examination of a wide range of clinical profiles and extensive adjustment for confounding factors. Analysis of gender-differences and the impact of antidepressant use were also considered.

METHOD

Study Population

The data used for this analysis were derived from the Three City Study (3C), an ongoing multi-centre longitudinal study involving the French cities of Bordeaux, Dijon and Montpellier (The 3C Study Group, 2003). Recruitment of the cohort took place between 1999 and 2001 with eligible participants (aged over 65 years and non-institutionalised) being randomly selected from the electoral rolls in the three cities. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre (France) and written informed consent was obtained from all participants. Participants were administered interviews by trained staff and underwent a number of clinical examinations at baseline and every two years thereafter.

Depression Measures

The Mini-International Neuropsychiatry Interview (M.I.N.I), a standardized psychiatric examination which has been validated in the general population (Sheehan, *et al*, 1998), was used for the diagnosis of current major depressive disorder (MDD), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Severity of depressive symptoms was assessed using the 20-item Centre for Epidemiology Studies Depression Scale (CES-D) (Radloff, 1977). Information was also gathered on the participant's history of major depressive episodes throughout their lifetime, to identify those with incident (one episode) versus recurrent depression (two or more episodes).

For the analysis participants were classified into one of three groups. "Severe depression" included participants with a current MDD or a CES-D score of 23 or over, allowing for the fact that some participants with very severe symptoms did not reach DSM classification criteria, most commonly due to the duration of symptoms. "Mild depression" was defined as a CES-D score between 16 and 22 and "no depression" included participants with a CES-D score lower than 16.

Current use of antidepressants was validated either by presentation of the prescription or the medication itself and the type of medication was noted according to the World Health Organisation's ATC classification (WHO., 2000).

Mortality

The follow-up time for this analysis was 4 years, with a median of 3.7 years for both men and women. For the participants who died during this period, information on the exact date and cause of death was determined respectively from death registries and medical records (based on the International Classification of Diseases: ICD-10). All-cause mortality was the principal outcome defined for this analysis, however cause-specific mortality was also examined.

Other measures

At inclusion, information was obtained on socio-demographic and lifestyle characteristics, as well as overall health. Participants were classified as disabled if they were unable to complete at least two tasks from either the Instrumental Activities of Daily Living (IADL) (Lawton, *et al*, 1969) or the Activities of Daily Living (ADL) (Katz, *et al*, 1963) scales. Cognitive function was assessed using the Mini-Mental State Examination (MMSE; (Folstein, *et al*, 1975)). Within each centre, participants scoring less than the10th percentile for their age (4 groups) and education level (4 groups), were classified as cognitively impaired. This method of classifying cognitive impairment, compared with that based on an unadjusted MMSE score <26, did not change the results of the study.

Detailed medical questionnaires were used to obtain information on history of vascular diseases (including angina pectoris, myocardial infarction, stroke, cardiovascular surgery, bradycardia or palpitations), other chronic illnesses (asthma, diabetes (fasting glucose≥7.2mmol/l or reported treatment), hypercholesterolemia (total cholesterol ≥6.2mmol/l), hypertension (resting blood pressure ≥160/95mm Hg or treated) and thyroid problems) and diagnoses of cancer within the last 2 years. Participants were classified as having comorbidity if they suffered from one or more of these illnesses. Hospitalisation for a non-traumatic illness within the last 2 years was also used as a measure of health status.

The multivariate analysis controlled for all covariates which have been described in the literature as confounding factors in relation to depression and mortality (Anstey, *et al*, 2002; Blazer, *et al*, 2001; Hybels, *et al*, 2002; Penninx, *et al*, 1999); age (continuous), education level (≥12 years of schooling), living situation (alone vs. with others), current high alcohol consumption (binary: <24 vs.

≥24g/day), current smoking status (binary: <10 vs. ≥10 pack-years), body mass index (BMI; ≤18, 18-30 or ≥30 kg/m²), disability (yes/no), cognitive impairment (yes/no), comorbidity (yes/no) and recent hospitalisation (yes/no).

Statistical Analysis

Two-tailed chi-squared tests were used to compare the baseline characteristics between men and women and to determine differences in unadjusted characteristics between participants with and without depressive symptoms, or between antidepressant users and non-users. Cox Proportional Hazard analysis was used to model the risk of mortality during the follow-up period. The age of participants at inclusion was taken as the basic time scale (Commenges, *et al*, 1998) to account for the non-proportionality in risk of mortality with age among the elderly (Blazer, *et al*, 2001; Penninx, *et al*, 1999), and Cox models with delayed entry were used. To estimate the risk associated with current depression or antidepressant use, models were generated with reference to non-depressed (no MDD and CES-D<16) or non-treated participants, respectively. When the combined effect of depression and antidepressant treatment were examined, participants that were neither depressed nor using treatment were the reference group.

Unadjusted models were initially constructed for each of the factors of interest, controlling only for study centre. Due to the statistically significant interactions between gender and both depression (mild: z=-0.76, df=1, p=0.004; severe: z=-1.34, df=1, p<0.001) and antidepressant use (z=-1.44, df=1, p<0.001), all subsequent analysis was undertaken separately for men and women. Multivariate analysis was used to determine the hazard associated with depression and/or antidepressant treatment, while adjusting for the potential confounding factors and stratifying by gender. There was no indication of collinearity between any of the covariates and no statistically significant interaction terms in the adjusted models. SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina) was used for all of the statistical analysis and the significance level was p<0.05.

RESULTS

Study population

Of the 9294 participants initially recruited in the 3C Study, 1922 participants were excluded from this analysis because they had missing data for some of the depression and/or confounding variables. A further nine participants were lost to follow-up, leaving 7363 for this analysis. Compared to the analysed sample, those not included in this analysis were more likely to be older (χ^2=162, df=1, p<0.001), live alone (χ^2=39.8, df=1, p<0.001), have lower education (χ^2=3.99, df=1, p=0.05), be underweight (χ^2=8.9, df=1, p=0.003), have disabilities (χ^2=398, df=1, p<0.001) and cognitive impairment (χ^2=63.9, df=1, p<0.001), have comorbidity (χ^2=12.9, df=1, p<0.001) and to have been hospitalised recently (χ^2=12.4, df=1, p<0.001). They were also more likely to use antidepressants (χ^2=25.8, df=1, p<0.001), to be depressed (χ^2=11.1, df=2, p=0.004) and to have died during the follow-up period (χ^2=156, df=1, p<0.001). There were however, no differences in the sex ratio of participants included in the analysis and those that were not.

Baseline characteristics of the 7363 participants in the analyzed sample are summarized in Table 1. The majority were female (60.8%) with a mean age of 74 years, ranging from 65 to 93 years. With the exception of centre, obesity and adjusted MMSE, men and women differed significantly in all of the covariates examined.

TABLE 1 HERE

Prevalence and correlates of depression

The prevalence of severe depression (MDD or CES-D≥23) was 10.2%, including 1.8% diagnosed with MDD and that of mild depression (CES-D 16-22) was 12.1% (Table 2). Women had a significantly higher prevalence of depression than men and were more than twice as likely to use antidepressants. Among the antidepressant users, over half were taking selective serotonin re-uptake inhibitors (SSRIs) and a relatively high number used tricyclic antidepressants (TCAs).

Compared to the non-depressed, those with either mild or severe depression were more likely to live alone (χ^2=139, df=2, p<0.001), have disability (χ^2=46.5, df=2, p<0.001), cognitive impairment (χ^2=43.6, df=2, p<0.001) and comorbidity (χ^2=14.3, df=2, p<0.001). Depressed women were also of

lower education (χ^2=15.4, df=2, p<0.001) and were more likely to have been hospitalised recently (χ^2=9.24, df=2, p=0.01), while depressed men were older (χ^2=10.5, df=2, p=0.005).

TABLE 2 HERE

Incidence and correlates of mortality

The total follow-up time for the study was 26,165 person-years and during this period 380 participants (5.2%) died, with a higher proportion of the deaths among men (7.5%) than women (3.7%). Recent hospitalisation (χ^2=37.9, df=1, p<0.001), co-morbidity (χ^2=24.6, df=1, p<0.001) and disability (χ^2=83.9, df=1, p<0.001)) were all significantly associated with mortality in both sexes, as was increasing age (χ^2=82.4, df=1, p<0.001). Cognitive impairment (χ^2=8.8, df=1, p=0.003) and current smoking (χ^2=8.05, df=1, p=0.005) were associated with mortality in men only. Alcohol consumption, education level, living alone and BMI were not significantly associated with mortality, however they were retained in the adjusted models due to their correlation with mortality at the 20% significance level and because previously reports suggest they confound the depression-mortality association.

TABLE 3 HERE

Associations between mortality and depression severity or antidepressant use

We first evaluated the separate effects of depression and antidepressant use on 4-year survival. For men, there was an apparent severity-dependent association between depression and mortality (Table 3). Compared to non-depressed men at inclusion, a higher percentage of men with mild depressive symptoms died during follow-up and the percentage of those dying with severe depression was even higher. In site-adjusted Cox models depression severity was positively associated with mortality risk. In models adjusted for a range of covariates, a similar trend was seen, however only severe depression remained significantly associated with mortality. For men taking antidepressants, the percentage of deaths was almost three times that of men not on treatment. This corresponded with a significantly increased mortality risk for antidepressant users in the univariate Cox analysis, which remained

significant after adjustment for covariates. There was no difference in mortality risk according to type of antidepressant treatment.

By contrast, among women the overall risk associated with depression was less marked, and very similar effects were seen regardless of depression severity (Table 4). Mild and severe depression were significantly associated with mortality in univariate analysis, with women having approximately one and a half times the risk of dying during follow-up compared to non-depressed women. After multivariate adjustment, the risk associated with depression remained similar in strength, although reduced in significance for both mild and severe depression. Antidepressant use was not associated with 4-year survival in either univariate or multivariate analysis, with a similar percentage of women dying in the group taking antidepressants and amongst those that did not.

TABLE 4 HERE

Combined effects of depression and antidepressant use

To investigate further the association between depression and mortality, participants were then grouped according to depression severity and use of antidepressants (Table 5). Overall there was little change in the significance of the associations found between the univariate and multivariate analysis, with relatively minor differences in the hazard ratios.

Among men, the largest mortality risk was seen in the group with severe depression who were taking antidepressants and there was also an increased mortality risk for antidepressant users with mild depressive symptoms. By contrast, non-depressed men using antidepressants did not have an increased mortality risk. For the men who were not using antidepressants, minor depression was not associated with 4-year survival, but severe depression appeared to increase risk, just failing to reach significant.

When we considered separately the small number of men with current MDD (diagnosed using the MINI), similar results were obtained to those with the severe depression group. Men taking antidepressants had a significantly increased risk of dying (adjusted HR=6.2, 95%CI: 2.2-17.3, x^2=12.0, df=1, $p<0.001$) and there was also a trend for increased risk among men without treatment, but this did not reach the threshold for significance (adjusted HR=2.3, 95%CI: 0.5-9.9, x^2=1.28, df=1, p=0.2).

While similar hazard ratios were seen across the different groups of women (Table 5), the associations appeared strongest among the women who were depressed but not using antidepressants. In fact, in the adjusted models it was only severe depression in the absence of antidepressant treatment, which significantly increased mortality risk.

We examined separately the risk associated with incident and chronic major depressive episodes, which affected 5.4% (3.7% of men, 6.7% of women) and 4.5% (2.1% of men, 6.2% of women) of participants respectively (supplementary Table 1). For men with one depressive episode there was a trend for increased mortality risk, however no such increase in risk was observed for those with recurrent depression. In women, neither incident nor recurrent episodes were significantly associated with mortality. In addition, the number of depressive episodes did not predict mortality risk in men and women, when these factors where included in the multivariate models containing depression and antidepressant use (data not shown).

TABLE 5 HERE

Cause of death

The majority of participants died from causes related to cancer (men 33%, women 41%) or cardiovascular disease (men 24%, women 18%), with fewer dying from respiratory problems (men 7%, women 6%). A substantial number died from unknown causes (17%), which is probably the result of multiple pathologies and an overall decline in general health. There were very few suicides (4 in total) and only five deaths due to external causes such as accidents.

When examining a specific cause of death as the outcome variable in the multivariate adjusted Cox models (supplementary Table 2), mild depression in women significantly increased cardiac-related death. Severe depression in men resulted in an increased risk of death from all three causes that were examined (cardiac-related, tumour-related or unknown). Antidepressant treatment in men was associated with an increased risk of death from an unknown cause. The number of participants dying from other causes was too small to allow accurate analysis.

DISCUSSION

The most striking findings of this large community-based study were the difference in depression-related mortality risk depending on whether the participants were taking antidepressants and the divergent findings across the genders. The greatest risk was for depressed men who were also antidepressant users, with increasing depression severity corresponding to a higher hazard risk. In contrast, among women it was only severe depression in the absence of treatment that significantly increased risk.

Gender differences in depression-related mortality risk

Our study suggests that the relationship between depression and mortality is not only gender-dependent but also depends on the severity of depression. The findings of increased mortality risk among certain sub-groups remained significant even after controlling for a large number of variables including several measures of health status. Therefore our results do not support the suggestion that declining health explains in large part the association between depression and mortality (Blazer, *et al*, 2001).

It has been reported that increasing depressive symptoms (Adamson, *et al*, 2005; Wulsin, *et al*, 2005) are associated with incrementally higher mortality risk; however from our sex-stratified analysis we found that this was only the case for men. In women the overall association between depression and mortality was less marked, with non-significant adjusted associations and no apparent increase according to depression severity. These gender variations could be the consequence of differences in the nature or intensity of exposure to risk factors, or in the susceptibility to the same risk factors. They could result from cultural, social, behavioral or adaptive differences. Women tend to report a greater number of symptoms and a higher degree of distress (Kornstein, *et al*, 2002) and may differ from men in their perceived need and willingness to seek treatment. Depression is less likely to be recognized in men (Crawford, *et al*, 1998) and therefore, the presence of detectable depressive symptoms in elderly men could also signify a more extreme condition (Gorman, 2006), which might account for the stronger associations with mortality, even for mild depression. Another possibility is that in older people with

depression, men are more likely to die and women to be first disabled. This hypothesis could be tested with a longer follow-up.

Our finding that incident depression, but not chronic depression, increases mortality risk in men only, has been reported previously (Anstey, *et al*, 2002). However, our study suggests that this factor is secondary to the association between depression severity and/or antidepressant use, as it was not significantly associated with 4-year survival when included in the models presented. It should be noted though, that there was a higher rate of missing data regarding previous episodes in currently depressed participants, and therefore this finding requires further validation.

Gender differences in antidepressant-related mortality risk

Despite our finding that antidepressant use in depressed men was associated with increased mortality risk, no such association was found in non-depressed men who used antidepressants, arguing against the pharmacological adverse effects of the antidepressants as a potential cause. Assuming that these treated participants were formerly depressed, this would indicate rather that adequate treatment of depression results in a reduction in the increased mortality rate. Likewise, the presence of depressive symptoms despite treatment could be an indication of depression severity, rather than non-efficacy of treatment, and therefore this increased depression severity could account for the higher mortality risk among this group.

In quite a different manner, only untreated women with severe depression had an increased risk, suggesting a positive impact of treatment even if women have residual symptoms. These results could highlight sex differences in the prescription and utilization of antidepressants, or in treatment compliance. It may also be that women respond better to specific types of antidepressant treatment than men (Khan, *et al*, 2005) (although this has rarely been reported in the case of post-menopausal women) and therefore depressed women on treatment may be better off than their male counterparts. Even when individuals respond to antidepressant treatment, they can still maintain clinically diagnosable depression (Gorman, 2006). The treatment may be effective but needs to be given for a longer period of time or the depression may be resistant to treatment. This raises the question of the dose and/or

reduction in depression symptoms required for both sexes. Overall these results emphasis the importance of stratifying the analysis by gender, with clear sex-differences in mortality risks.

Interestingly, we found no significant difference in mortality risk when we compared the difference types of antidepressants, despite suggestions that SSRIs and TCAs have differential effects on cardiovascular health (Cohen, *et al*, 2000). Benzodiazepine-related medications, which are used to treat anxiety and are often administered in combination with or in place of antidepressants (van Rijswijk, *et al*, 2007), were not associated with mortality risk in either men or women. In addition, this factor did not confound the associations reported here (data not shown).

Why is depression associated with increased mortality?

The relationship between depression and mortality is thought to result from a combination of factors. Depression appears to exacerbate the outcome of medical illness (Alexopoulos, 2005), even in appropriately adjusted analysis and it is possible that depression acts as a proxy marker for the severity of physical health. Psychological well-being also plays a role, with loss of motivation and social isolation enhancing the effect of depression on mortality (Stek, *et al*, 2005). Finally, several behavioral mechanisms could help explain the risk associated with depression. Depressed participants are less likely to comply with their medications (Ciechanowski, *et al*, 2000; Vinkers, *et al*, 2004), affecting other illnesses they may have. They may also behave in ways which are detrimental to their overall health, particularly men (Ciechanowski, *et al*, 2000), however the associations found in this analysis remained even after controlling for "self-care" variables (i.e. smoking, alcohol, BMI). Further work is needed to determine why the prognosis of depression appears to differ between men and women and why it is worse among male antidepressant users.

Cause of deaths

Our results showed that the increased mortality risk associated with severe depression in men, was in part due to an increase in cardiac-related mortality, as reported previously (Vinkers, *et al*, 2004). In women mild but not severe depression appeared to increase cardiac death. Men with severe depression had an increased risk of death from "unknown" causes, which could reflect the helplessness of severely

depressed men, who may just give-up on life and die from multiple conditions and dwindling health. Other studies have suggested that depression and antidepressant use increases the risk of suicides (Kivimaki, *et al*, 2006) and may increase deaths by unnatural causes, such as accidents, particularly among men. However, as found in other community-based studies of older people, external causes of death were rare in our population (Penninx, *et al*, 1999).

Limitations

This study has several limitations. The data concerning some of the covariates were self-reported which may be subject to recall bias with depressed participants responding more negatively about their health. However, as these self-report measures concern the covariates, and since similar associations were seen in the unadjusted and adjusted analysis, it would appear that any bias did not have a substantial influence on the results. Bias could also be introduced from the exclusion of participants with missing data, who were more likely to be depressed or from the participants lost to follow-up, who were more likely to have died. Thus people with the strongest potential depression-mortality associations may have been selectively excluded so that associations between depression and mortality were underestimated. Assessment of depression and collection of information on antidepressant use were carried out at inclusion and therefore the status of these participants at the time of their deaths is unknown. In addition, we did not consider treatment compliance, which may have caused classification bias, or the history and duration of antidepressant use which could have influenced the results. In particular for males it would be interesting to asses whether there was a differential effect of short-term vs. long-term antidepressant treatment on mortality. Finally, it is possible that there are other unknown factors including subclinical disease (in addition to that detectable through the analysis of lipids, glycemia and hypertension), which may confound the association between depression and mortality.

Strengths

The study has a number of strengths. The data used in the analysis comes from a large multicentre population-based prospective study of people aged 65 years and over. Depression was assessed by trained staff using two distinct measures validated in the general population, including a structured

diagnostic interview (Radloff, 1977; Sheehan, *et al*, 1998) and antidepressant use was verified by examining the prescriptions and medications themselves, thus minimizing exposure misclassification. In addition, being based on a large community sample we were able to cover a wide range of depression profiles, from sub-clinical symptoms to major depression, thus addressing the problem of the varying definitions of depression in previous research. In this study we obtained comprehensive information on the mortality status of the participants, using death registries and medical records, with only nine participants lost to follow-up. We controlled for a large number of covariates, particularly measures of physical health (comorbidity, physical incapacities, recent hospitalization, health behaviors), and cognitive impairment, which reportedly explain in large part the reported depression-mortality link (Blazer, *et al*, 2001; McCusker, *et al*, 2006). Despite this, there were only minor changes in the hazard ratios between the unadjusted and adjusted analysis, suggesting independence of associations. Finally, in contrast to the majority of community-based studies, we have explored the role played by antidepressants in the depression-mortality association, which has enabled us to better characterize the profile of the elderly participants who are most at risk of dying.

Our findings suggest that the relationship between depression and mortality in older populations is gender-dependent and also varies according to symptom load. This association is modified when the use of antidepressants is also taken into consideration, which indicates the importance of including this factor when investigating mortality risk. Findings from this study suggest an increased risk of mortality for men with even sub-clinical depression and highlight the importance of detecting depressive symptoms, most notably by the general practitioner during routine medical visits. This study suggests that inadequate treatment of late-life depression may reduce long-term survival and that resistance to treatment in men could have a detrimental effect on their survival.

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TABLE 1. Comparison between the baseline characteristics of 7363 elderly community dwelling men and women, who participated in the 3C Study.

Characteristic	%		Test for gender difference	
	Men (n = 2886)	Women (n = 4477)	X^2 (d.f.)	p-value
≥ 75 years old	39.2	42.8	9.2 (1)	0.002
≥12yrs schooling	46.1	34.3	102.6 (1)	< 0.001
Living alone	13.1	47.8	940.1 (1)	< 0.001
Recently hospitalised	13.6	10.8	13.1 (1)	< 0.001
Disability	1.5	2.7	10.4 (1)	0.001
Comorbidity[a]	47.5	45.1	4.0 (1)	0.05
Cognitive impairment (MMSE<10th percentile)	7.1	7.0	0.01 (1)	0.9
Current heavy drinker (≥24grams each day)	33.6	4.1	1156.2 (1)	< 0.001
Current regular smoker (≥10 pack-years)	48.4	9.5	1424.9 (1)	< 0.001
Underweight (BMI ≤ 18)	0.4	1.7	26.0 (1)	< 0.001
Obese (BMI ≥ 30)	12.4	13.6	2.3 (1)	0.1
Centre			3.1 (2)	0.2
Bordeaux	24.9	25.0		
Dijon	50.6	52.2		
Montpellier	24.5	22.8		

[a] Includes a chronic disease (cardiovascular disease, other heart problems, high blood pressure, high cholesterol, diabetes, thyroid problems), or cancer diagnosed within the last 2 years.

TABLE 2. Comparison between the baseline depression characteristics of 7363 elderly community-dwelling men and women who participated in the 3C Study.

Depression Characteristics	%		Test for gender difference	
	Men (n = 2886)	Women (n = 4477)	X^2 (d.f.)	p-value
Depression Severity [a]			236.6 (2)	< 0.001
No depression	86.9	71.9		
Mild depression	8.1	14.6		
Severe depression	5.0	13.5		
Uses antidepressants	3.7	8.5	64.8 (1)	< 0.001
Depression Severity and Antidepressant use			269.1 (5)	< 0.001
No depression / antidepressants -	84.8	68.1		
No depression / antidepressants +	2.1	3.8		
Mild depression / antidepressants -	7.4	12.9		
Mild depression / antidepressants +	0.7	1.7		
Severe depression / antidepressants -	4.0	10.4		
Severe depression / antidepressants +	1.0	3.1		
Type of Antidepressant	**(n =108)**	**(n =382)**	1.21 (2)	0.6
Tricyclic antidepressants (TCAs)	24.1	19.4		
Selective serotonin re-uptake inhibitors (SSRIs)	50.9	55.2		
Other antidepressants	25.0	25.4		

[a] Participants with "severe" depression were identified as having a current major depressive disorder (MDD) according to the M.I.N.I., or current severe depressive symptoms according to the CES-D (CES-D score ≥23). Participants with a CES-D score below 23, but above the cut-off for clinically significant depressive symptoms (CES-D≥16) were classified as having "mild" depressive symptoms.

TABLE 3. Cox proportional hazard models for the risk associated with depression or antidepressant use among elderly men (n=2886).

Depression Variables	% deaths (n = 215)	Unadjusted[a] Hazard Ratio (95% CI)	X^2 stat. (1 d.f.)	p	Adjusted[b] Hazard Ratio (95% CI)	X^2 stat. (1 d.f.)	p
Depression Severity[c]							
No depression	6.7	1			1		
Mild depression	11.1	1.5 (1.0-2.3)	3.65	0.05	1.5 (1.0-2.2)	3.03	0.09
Severe depression	15.3	2.8 (1.8-4.4)	20.34	<0.001	2.5 (1.6-4.0)	15.40	<0.001
Antidepressant Use							
No	7.0	1			1		
Yes	20.4	2.8 (1.8-4.4)	18.56	<0.001	2.2 (1.4-3.5)	10.88	0.001
Antidepressant type							
No treatment	7.0	1			1		
TCAs	30.8	2.6 (1.1-6.4)	4.56	0.03	2.4 (1.0-6.0)	3.76	0.05
SSRIs	16.4	2.3 (1.2-4.4)	6.54	0.01	1.9 (1.0-3.7)	3.70	0.05
Other	18.5	2.8 (1.3-5.9)	7.89	0.005	2.5 (1.2-5.3)	5.51	0.02

[a] Adjusted for centre.

[b] Adjusted for centre, education, living status, cognitive impairment, high alcohol consumption, regular smoking, disability, recent hospitalization, comorbidity, underweight and obesity.

[c] Participants with "severe" depression were identified as having a current major depressive disorder (MDD) according to the M.I.N.I., or current severe depressive symptoms according to the CES-D (CES-D score ≥23). Participants with a CES-D score below 23, but above the cut-off for clinically significant depressive symptoms (CES-D≥16) were classified as having "mild" depressive symptoms.

TABLE 4. Cox proportional hazard models for the risk associated with depression or antidepressant use among elderly women (n=4477).

Depression Variables	% deaths (n = 165)	Unadjusted[a] Hazard Ratio (95% CI)	Unadjusted[a] X^2 stat. (1 d.f.)	Unadjusted[a] p	Adjusted[b] Hazard Ratio (95% CI)	Adjusted[b] X^2 stat. (1 d.f.)	Adjusted[b] p
Depression Severity[c]							
No depression	3.2	1			1		
Mild depression	4.8	1.5 (1.2-3.0)	3.94	0.05	1.4 (0.9-2.1)	2.86	0.09
Severe depression	5.0	1.6 (1.1-2.4)	5.02	0.03	1.4 (0.9-2.2)	2.95	0.09
Antidepressant Use							
No	3.6	1			1		
Yes	4.7	1.2 (0.8-2.0)	0.73	0.4	1.1 (0.7-1.8)	0.20	0.7
Antidepressant Type							
No treatment	3.6	1			1		
TCAs	1.4	1.7 (0.8-3.9)	1.81	0.2	1.7 (0.7-3.7)	1.45	0.2
SSRIs	5.2	1.3 (0.7-2.4)	0.67	0.4	1.2 (0.6-2.2)	0.31	0.6
Other	6.2	0.7 (0.2-2.7)	0.31	0.6	0.5 (0.1-2.2)	0.75	0.4

[a] Adjusted for centre.

[b] Adjusted for centre, education, living status, cognitive impairment, high alcohol consumption, regular smoking, disability, recent hospitalization, comorbidity, underweight and obesity.

[c] Participants with "severe" depression were identified as having a current major depressive disorder (MDD) according to the M.I.N.I., or current severe depressive symptoms according to the CES-D (CES-D score ≥23). Participants with a CES-D score below 23, but above the cut-off for clinically significant depressive symptoms (CES-D≥16) were classified as having "mild" depressive symptoms.

TABLE 5. Cox proportional hazard models for the combined effect of depression severity with or without antidepressant treatment, separately in elderly men (n=2886) and women (n=4477).

Variables	% deaths	Unadjusted[a] Hazard Ratio (95% CI)	X^2 stat. (1 d.f.)	p	Fully Adjusted[b] Hazard Ratio (95% CI)	X^2 stat. (1 d.f.)	p
MEN							
Depression & Antidepressants							
No depression / antidepr. -	6.5	1			1		
No depression / antidepr. +	13.1	1.6 (0.8-3.3)	1.68	0.2	1.3 (0.6-2.7)	0.41	0.5
Mild depression / antidepr. -	10.2	1.4 (0.9-2.2)	2.15	0.1	1.3 (0.9-2.1)	1.57	0.2
Mild depression / antidepr. +	21.1	3.0 (1.1-8.2)	4.66	0.03	2.8 (1.0-7.7)	4.03	0.04
Severe depression / antidepr. -	10.3	1.9 (1.1-3.5)	4.84	0.03	1.8 (1.0-3.3)	3.57	0.06
Severe depression / antidepr +	35.3	6.5 (3.4-12.5)	32.41	<0.001	5.3 (2.7-10.5)	23.64	<0.001
WOMEN							
Depression & Antidepressants							
No depression / antidepr. -	3.1	1			1		
No depression / antidepr. +	5.9	1.6 (0.8-3.1)	2.01	0.2	1.5 (0.8-2.9)	1.54	0.2
Mild depression / antidepr. -	4.7	1.5 (1.0-2.3)	3.38	0.07	1.4 (0.9-2.2)	2.46	0.1
Mild depression / antidepr. +	5.4	2.2 (0.8-6.0)	2.34	0.1	2.0 (0.7-5.4)	1.77	0.2
Severe depression / antidepr. -	5.6	1.9 (1.2-3.0)	8.21	0.004	1.8 (1.1-2.8)	6.18	0.01
Severe depression / antidepr +	2.9	0.9 (0.3-2.5)	0.04	0.8	0.8 (0.3-2.1)	0.33	0.6

[a] Adjusted for centre.

[b] Adjusted for centre, education, living status, cognitive impairment, high alcohol consumption, regular smoking, disability, recent hospitalization, comorbidity, underweight and obesity.

SUPPLEMENTARY TABLE 1. Cox proportional hazard models for the risk associated with the number of lifetime depressive episodes, among elderly men (n=2723) and women (n=3891)[a].

Depression History	% Deaths	Unadjusted[b] Hazard Ratio (95% CI)	z (1 d.f.)	p	Adjusted[c] Hazard Ratio (95% CI)	z (1 d.f.)	p
Men	***n=215***						
No depressive episodes	7.4	1			1		
One depressive episode	10.9	1.9 (1.0-3.5)	3.63	0.06	1.9 (1.0-3.6)	3.60	0.06
At least two depressive episodes	3.5	0.6 (0.2-2.5)	0.51	0.5	0.4 (0.1-1.8)	1.32	0.3
Women	***n=165***						
No depressive episodes	4.0	1			1		
One depressive episode	2.7	0.7 (0.3-1.6)	0.55	0.5	0.7 (0.3-1.6)	0.60	0.4
At least two depressive episodes	3.7	1.0 (0.5-1.9)	0.02	0.9	0.9 (0.5-1.8)	0.1	0.8

[a] Due to the missing data concerning the number of lifetime depressive episodes, the analysis was based on a smaller number of participants.

[b] Adjusted for centre.

[c] Adjusted for centre, education, living status, cognitive impairment, high alcohol consumption, regular smoking, disability, recent hospitalization, comorbidity, underweight and obesity.

SUPPLEMENTARY TABLE 2. Cox proportional hazards models for the adjusted[a] association between depression and cause-specific mortality.

Gender	Variables	Cardiac-related death			Tumor-related death			Unknown cause of death		
		HR (95% CI)	z (1 d.f.)	p	HR (95% CI)	z (1 df)	p	HR (95% CI)	z (1 df)	p
Men	*Depression Severity*									
	No Depression	1			1			1		
	Mild Depression	1.4 (0.6-3.4)	0.54	0.5	1.0 (0.4-2.5)	0.01	0.9	1.0 (0.3-3.2)	0.006	0.9
	Severe Depression	2.8 (1.1-6.9)	4.87	0.03	2.0 (1.0-3.4)	4.32	0.05	4.1 (1.5-11.1)	7.47	0.006
	Antidepressants									
	No	1			1			1		
	Yes	2.1 (0.8-5.4)	2.60	0.1	0.7 (0.2-3.0)	0.21	0.6	3.7 (1.4-9.9)	6.9	0.009
Women	*Depression Severity*									
	No Depression	1			1			1		
	Mild Depression	2.8 (1.2-6.5)	5.57	0.02	1.1 (0.6-2.2)	0.06	0.8	1.7 (0.7-4.4)	1.19	0.3
	Severe Depression	1.5 (0.5-4.2)	0.48	0.5	1.2 (0.6-2.4)	0.26	0.6	1.9 (0.8-4.7)	0.71	0.2
	Antidepressants									
	No	1			1			1		
	Yes	2.2 (0.9-5.5)	2.60	0.1	0.8 (0.3-2.1)	0.14	0.7	0.6 (0.1-2.5)	0.53	0.5

[a] Adjusted for centre, education, living status, cognitive impairment, high alcohol consumption, regular smoking, disability, recent hospitalization, comorbidity, underweight and obesity.