The effect of gender, age, and symptom severity in late-life depression on the risk of all-cause mortality: The Bambuí Cohort Study of Aging

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Abstract

Background—Increased mortality risk and its moderators is an important, but still under recognized, negative outcome of Late-Life Depression (LLD). Therefore, we aimed to evaluate whether LLD is a risk factor for all-cause mortality in a population-based study with over ten years of follow-up, and addressed the moderating effect of gender and symptom severity on mortality risk.

Methods—This analysis used data from the Bambuí Cohort Study of Aging. The study population comprised 1.508 (86.5%) of all eligible 1.742 elderly residents. Depressive symptoms were annually evaluated by the GHQ-12, with scores of 5 or higher indicating clinically significant depression. From 1997 to 2007, 441 participants died during 10,648 person-years of follow-up. We estimated the hazard ratio for mortality risk by Cox regression analyses.

Results—Depressive symptoms were a risk factor for all-cause mortality after adjusting for confounding lifestyle and clinical factors (adjusted HR=1.24 $CI_{95\%}$ [1.00–1.55], p=0.05). Mortality risk was significantly elevated in men (adjusted HR=1.45 $CI_{95\%}$ [1.01 – 2.07], p=0.04), but not in women (adjusted HR=1.13 $CI_{95\%}$ [0.84 – 1.48], p=0.15). We observed a significant interaction between gender and depressive symptoms on mortality risk ((HR= 1.72 $CI_{95\%}$ [1.18 – 2.49], p=0.004).

Conclusion—The present study provides evidence that LLD is a risk factor for all-cause mortality in the elderly, especially in men. The prevention and adequate treatment of LLD may help to reduce premature disability and death among elders with depressive symptoms.

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Introduction

Major depression is a common psychiatric disorder in older adults. Recent studies show one-year prevalence rates ranging from 4% to 12% in developed and developing countries[1,2]. Late-life depression (LLD) is linked to negative health outcomes, including a higher risk of cognitive impairment[3], functional impairment[4], and development of Alzheimer's disease and vascular dementia[5]. LLD is also associated with a higher burden of medical illnesses and comorbid psychiatric disorders, independent of lifestyle factors[6,7].

An important negative outcome of LLD may be the risk of death associated with this condition. Previous studies have shown an increased risk of all-cause mortality, including deaths due to suicide, in community-dwelling older adults with LLD, independent of comorbid medical conditions, lifestyle, health behavior, and cognitive decline[8–10]. Other studies, however, have not found an association between LLD and mortality and even found that mild depressive symptoms may protect against mortality in the elderly [11–13]. Several reasons may help to explain these discrepant results. First, the studies used different instruments to evaluate depressive symptoms, and most did not carry out structured psychiatric interviews. Measurement variability could have led to differences in rates of depression caseness. Sample clinical (e.g. presence of medical comorbidities) and other socio-demographic characteristics differ among studies. In addition, varying follow-up periods may lead to differences in the estimation of mortality risk between studies. Finally, LLD is a heterogeneous disorder and may be related to distinct risk factors and neurobiological changes in different populations; therefore, subgroups of LLD subjects may be more prone to dying. Such differences in underlying neurobiology may not be captured in population-based studies.

Another reason for inconsistent findings of the association between depression and mortality in the elderly may be related to the presence of moderators of this association that have not been consistently evaluated in population-based studies. Gender may be an important moderator of mortality risk in LLD. Some studies suggest higher mortality risk in men compared to women[14,15]; though the opposite pattern has also been observed[12]. Severity of depressive episode may also moderate mortality risk. Community-based studies have shown that older adults with major depression or with more severe depressive episodes have higher mortality risk[16,17]. A recent meta-analysis including depressed and non-depressed participants across the lifespan showed that the mortality risk was significantly higher in individuals with subthreshold depression (RR=1.31) and with major depression (RR=1.58) compared to non-depressed individuals. Nonetheless, the relative risk of mortality between major and subthreshold depression was not different[18]. Why gender and depression severity may moderate the relationship between depression and mortality in the elderly is not clear. Nonetheless, differences in lifestyle, health behavior (including willingness to seek help for depression), and biological differences between gender, as well as the clinical and

neurobiological correlates of depression severity may, in part, help to explain their potential moderating effects[19–21]. Age may also be a significant moderator of the relationship between LLD and mortality risk. Nonetheless, no study thus far has specifically addressed whether age is a significant moderator of mortality risk among individuals with LLD.

Despite a large number of studies linking depression and higher mortality risk in older adults, most of population-based studies were conducted in high-income countries and there are few population-based studies in low- and middle-income countries[10,22,23]. The latter studies found a marginal increase in the mortality risk in older adults with depression, but they did not evaluate the influence of moderators, like gender, age, and depression severity in LLD-related mortality risk. We expect an exponential rise of the elderly population in these countries in the coming decades, which will probably be accompanied by increased prevalence of age-related disorders as well as of depressive symptoms. Thus, given the paucity of evidence linking depression and mortality, and its moderators in older adults from low and middle-income countries[22,23], this study aimed to assess whether LLD is a risk factor for all-cause mortality in a population-based study of elderly subjects with low socioeconomic status. We also addressed whether gender, age, and the intensity of depressive symptoms moderated the association with all-cause mortality risk in this population. Understanding whether depression is associated with increased mortality risk, and the potential moderators of this relationship in low and middle-income countries is important for the development of more specific interventions to prevent death in this population. In this study, we analyzed data from the Bambuí Cohort Study of Aging (BCSA), a large longitudinal population-based study, with over ten years of follow-up, which aimed to evaluate health outcomes in an elderly population with low socioeconomic status from Brazil[24].

Methods

The Bambuí Cohort Study of Aging (BCSA)

Study area and population

This analysis used data from a population-based prospective cohort study of aging, which was carried out in Bambuí city (approximately 15,000 inhabitants), situated in southeastern Brazil. The local Human Development Index was 0.70, which implies moderate development. The original goal of the BCSA was to investigate the incidence and predictors of health outcomes in an elderly population with low social economic level[24].

The BCSA recruitment and procedures have been described in detail elsewhere[25]. Briefly, the baseline cohort population comprised all residents aged 60 and over on January 1st, 1997, who were identified by a population census carried out in November and December of 1996, by the BCSA team. From a total of 1,742 older residents in Bambui, 1,606 (92.2%) participated in the baseline survey. Baseline data collection was carried out from February to May 1997. All interviews were carried out in participants' homes. Neither interviewers nor respondents were aware of clinical results at the time of the interview.

A standardized survey questionnaire was administered to all participants and included information on: (1) social and demographic characteristics; (2) self-perceived health conditions and history of selected diseases; (3) medication use; (4) health service utilization and source of medical care; (5) lifestyle (physical activities, smoking, drinking and eating habits); (6) psychosocial aspects (personality traits, social support and life events); (7) reproductive history; (8) physical functioning and (9) mental health (depressive symptoms, cognitive functioning and sleeping habits), including the administration of the General Health Questionnaire-12, Mini-Mental State Examination. A laboratory work-up was also done in all participants and included the following blood tests: (1) biochemical assays (glucose, creatinine, urea, total protein, albumin, uric acid, calcium, phosphorus, magnesium, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides); (2) haematological assays (red blood cell count, haemoglobin, hematocrit, red blood cell indices, white blood cell count, and platelet count); and (3) Chagas' disease serological tests.

Participants (and their family members, if available) underwent annual follow-up evaluation and responded to the same survey questionnaire administered at the baseline assessment.

Mortality data source

Deaths occurring up to June 30th 2007 were included in this analysis. Deaths were reported by next of kin during the annual follow-up interview and verified through the Brazilian System of Information on Mortality, available with the permission of the Ministry of Health. Death certificates were obtained for 98.9% of individuals. The endpoint in this analysis was all-cause death, including deaths due to suicide. Due to lack of standardised report of specific death causes in death certificates, we did not evaluate specific causes of death in this study.

Depressive symptoms assessment

Symptoms of depression were assessed by the General Health Questionnaire-12 (GHQ-12). Originally the GHQ was designed for the assessment of common mental disorders in the general population[26]. Shorter versions of this scale were developed, and the GHQ-12 version has been shown to have similar accuracy as the Geriatric Depression Scale (GDS) for the identification of depression in the elderly[27]. We used a cut-off score of 5 or more points in the GHQ-12 to define major depression ("LLD group"), based on a previous validation study in this population[27]. Otherwise, participants were included in the "non-depressed group".

Covariates

Information on socio-demographic variables was obtained in the baseline BHAS interview. Monthly income was determined according to the Brazilian Minimum Wage at the time of assessment. Subjects were classified according to size of monthly minimum wage between 1 and 1.99 times monthly minimum wage; between 2 and 3.99 times monthly minimum wage; between 4 to 5.99 times monthly minimum wage; between 6 and 9.99 monthly minimum wage; between 10 to 19.99 monthly minimum wage; and more than 20 times monthly minimum wage. Body mass index (weight (kg) divided by height $(m)^2$) was calculated from

height and weight measurements. Activities of daily living were ascertained by the Katz Index of Activities of Daily Living[28]. Participants were questioned about the following lifestyle characteristics: alcohol consumption (drinking at least one glass of alcohol per week in the previous 12 months), smoking habits, and regular physical activity, and use of psychotropic medication in the past 90 days. Smoking habits were defined as never smoked, past smoker, and current active smoker. Regular physical activity was defined as any exercise during leisure time for at least 20–30 minutes at least three times a week in the previous 90 days. Diabetes mellitus was defined as fasting blood glucose equal to or greater than 126 mg/dl and/or current treatment for diabetes[29]. Blood hypertension was defined as systolic blood pressure equal to or greater than 140 mmHg, and/or diastolic blood pressure equal to or greater than 90 mmHg and/or the use of antihypertensive drugs[30]. Myocardial infarct was ascertained by self-report and defined as physician diagnosis of myocardial infarct. Infection with *T. cruzi* was defined by seropositivity in both indirect hemagglutination assay and enzyme-linked immunoabsorbent assay (Biolab-Mérieux and Abbott, respectively). The scores on the MMSE were corrected for educational levels, according to previously published Brazilian norms[31]. The BCSA was approved by the Ethics Committee of the Oswaldo Cruz Foundation. All participants were informed about the objectives and procedures of the project and gave full-informed written consent.

Statistical analysis

Baseline differences between depression groups were tested by t-tests for continuous and Chi-square tests for categorical variables. We carried out Kaplan-Meyer survival analysis with log-rank tests to ascertain differences in survival between depressed and non-depressed elderly at baseline on annual follow-up assessments. The association between depression and risk of all-cause mortality was tested with Cox proportional hazard regressions, yielding hazard ratios (HR) and the corresponding 95% confidence interval ($CI_{95\%}$). All analysis were adjusted for gender, baseline age, baseline monthly income, marital status, use of psychotropic medication, retirement, educational level, activities of daily living, baseline MMSE scores, drinking and smoking habits, hypertension, myocardial infarction, Chagas disease, physical activity, BMI, diabetes mellitus 2. The proportionality assumption for the Cox regression models was assessed by checking the Kaplan-Meyer survival curves. All analyses were carried out for the whole sample and then stratified according to gender, age (below or equal 70 years-old or greater than 70 years-old), and intensity of depressive symptoms.

We then estimated the population attributable risk (PAR) of dying due to depression according to the following formula:

$$PAR = \frac{p(HR-1)}{p(HR-1)+1}$$

Where p is the prevalence of the condition in the population, HR is the adjusted hazard ratio for all-cause mortality due to LLD. The PAR was calculated only in case the HR for mortality was statistically significant.

Statistical significance was set at α 5%. All analyses were conducted with the Statistical Package for Social Science (SPSS), v18 for Windows.

Results

At baseline assessment, 1606 older adults were evaluated. Ninety-eight were excluded due to absent information or incomplete data for depressive symptoms at baseline. Thus, the final baseline sample included in the analysis was 1508 subjects (922 women and 586 men). At baseline 581 subjects (38.5%) had GHQ-12 scores equal to or greater than 5 and were considered to be in a major depressive episode ("LLD group"). Table 1 shows the baseline socio-demographic and clinical characteristics according to depression status. The median follow-up period was 8.9 years, interquartile range [6.3 years – 9.2 years]. Four hundred and forty one deaths occurred during 10,648 person-years of follow-up. Men showed a significant higher proportion of death compared to women (women, 27.1% vs. men, 32.4%, X^2=5.02, df=1, p=0.02).

Baseline depressive symptoms and mortality risk

Kaplan-Meyer survival analysis showed shorter survival in subjects in the LLD group (Log-rank Chi^2 = 27.28, df=1, p<0.001). Cox regression analysis showed a significant association between GHQ-12 scores (as a continuous measure) and mortality risk (adjusted HR = 1.05 $CI_{95\%}$ [1.02 – 1.08], p=0.003) (table 2). We dichotomized the sample according to the GHQ-12 score and those participants in the LLD group (GHQ-12 scores 5) at baseline showed a higher mortality risk (adjusted HR = 1.24 $CI_{95\%}$ [1.00 – 1.54], p=0.05) (table 2).

The PAR of death due to LLD was 8.5% ($CI_{95\%}$: 0% – 17.2%).

We conducted additional analyses to assess whether the higher depressive symptoms was associated with differential risk of mortality. Although the cut point of 5 of the GHQ-12 is based on previous validation, there is no cut point available in the literature to distinguish among lower vs. higher levels of depressive symptoms based on the GHQ-12 scores. We therefore used the quartiles of the distribution of GHQ-12 scores among LLD participants in the sample to form two groups: "higher depressive symptoms" group (participants with scores above the third quartile (i.e. scores 9), and "lower depressive symptoms" (defined as scores below the third quartile (i.e. scores between 5 and 8).

Cox regression analysis showed that participants in the "higher depressive symptoms" group showed an increased mortality risk compared to the non-depressed group (i.e. those with GHQ-12 scores below 5) (adjusted HR=1.44 $CI_{95\%}$ [1.07 – 1.93], p=0.01) (table 2). Participants in the "lower depressive symptoms" group did not show a higher mortality risk relative to the non-depressed group after adjustment for confounding variables (table 2). Mortality was higher in the "higher depressive symptoms" group compared to the "lower depressive symptoms" group (adjusted HR 1.39 $CI_{95\%}$ [1.01 – 1.91], p=0.04).

The PAR of due in the "higher depressive symptoms" group was 14.5% ($CI_{95\%}$ 2.6% – 26.4%).

The moderating effect of gender and age on LLD-related mortality

Gender may be an important moderator in the association between LLD and mortality risk. Therefore, we stratified all analysis according to gender. Kaplan-Meyer survival analysis showed that men and women with LLD differed with respect to survival. In the Cox regression analysis, participants with LLD showed a higher mortality risk in men (adjusted HR=1.45 CI$_{95\%}$ [1.01 – 2.07], p=0.04), but not in women (adjusted HR=1.13 CI$_{95\%}$ [0.84 – 1.48], p=0.15) (table 3).

The PAR of dying due to depression in men was 12% (CI$_{95\%}$ 0.3% – 24.4%).

We observed an increase in the mortality risk among men with baseline GHQ scores of 9 or higher (HR=1.90 CI$_{95\%}$ [1.19 – 3.04], p=0.007), but not in women (HR=1.38 CI$_{95\%}$ [0.93 – 2.06], p=0.15) (table 3). Low depressive symptoms were not associated with increased risk of mortality in either men or women after adjustment for confounding variables (table 3).

The PAR of dying due to depression in men with severe depressive symptoms was 21.4% (CI$_{95\%}$ 5.4% – 38.1%).

We conducted additional analyses to further address the moderating effect of gender and age on mortality risk due to depression. We tested the interaction between gender, age, and depressive symptoms in the risk of death in this cohort. We found a significant interaction between gender and clinically significant depressive symptoms (HR= 1.72 CI$_{95\%}$ [1.18 – 2.49], p=0.004). We did not find a significant interaction between age and clinically significant depressive symptoms (HR= 1.16 CI$_{95\%}$ [0.75 – 1.79], p=0.5), or and interaction between gender, age and clinically significant depressive symptoms (HR=1.03 CI$_{95\%}$ [0.59 – 1.82), p=0.9).

Discussion

In this population-based prospective cohort study, GHQ-12 scores of 5 or greater constituted a risk factor for mortality in older adults. The attributable risk of dying due to LLD was high (8.5%). Additional analyses revealed that the mortality risk was more pronounced in older adults with GHQ-12 depression scores of 9 or higher (indicating a higher level of depressive symptoms). We found a significant gender and depression interaction on mortality risk and the relationship between mortality risk and depression is considerably stronger in men compared to women after controlling for confounding variables. Thus, the present study provides additional evidence that depression is an important risk factor for mortality in older adults with low socioeconomic status and illustrates the moderating role of gender and intensity of depressive symptoms in depression-related mortality risk.

Late-life depression is usually associated with negative health behaviors (e.g. smoking, low physical activity level), worse physical health (e.g. obesity, hypertension, cardiovascular disease, diabetes), as well as adverse socioeconomic condition[7,32–34]. These are well-known risk factors for death in older adults and may explain in part the relationship between depression and mortality in these subjects. Nonetheless, we found that the mortality risk

persisted after adjustment for lifestyle factors; therefore, other systemic biological factors may be related to the increased mortality risk in older subjects.

Abnormalities in inflammatory control, with persistent low-grade pro-inflammatory activity, is a common feature of several medical illness, such as diabetes, dyslipidemia, hypertension, obesity and is associated with higher risk of death in these patients[35–36]. Several lines of evidence suggest that depression in older adults is also associated with low-grade pro-inflammatory status with a similar pattern observed in the latter disorders[37–39]. Therefore, inflammatory abnormalities may help to explain the independent, higher risk of mortality in LLD.

Other mechanisms may also play an important mediating role in depression-related mortality in the elderly. Depressed older adults, especially those with more severe depressive episodes, show significant HPA axis dysfunction[40], increased oxidative stress[41], reduced neurotrophic support[42], increased GSK-3β[19], and reduced telomere length and increased telomerase activity[43]. These abnormalities may result in higher systemic allostatic load, leading to accelerating normal aging processes and, finally, to premature death in these individuals[44,45]. In addition, recent studies showed that cardiovascular, endocrine-metabolic and depressive disorders share biological, genetic, and environmental susceptibility factors that may increase the risk of death in these conditions[46,47]. Therefore, studies are needed to better understand the neurobiologic and systemic mediators of higher risk of mortality in older adults with depression.

It is widely accepted that gender modulates the expression of affective disorders. The prevalence and incidence of major depression and distress is higher in women than in men; men tend not to report milder symptoms or seek treatment until depressive symptom are more severe[20,48]. In addition, men have higher prevalence and risk of death due to cardiovascular disease and endocrine-metabolic disorders; though these differences attenuate with aging[21,49]. These factors may explain in part the higher risk of death in men compared to women in the present study. Biological differences between men and women, in particular hormonal differences can also contribute to the differences in the mortality risk between men and women. It is worth noting that a previous study found that older women with subthreshold depressive symptoms had a significant lower risk of dying compared to men[13]. The authors hypothesized that subthreshold depression may be an adaptive state in women that protects against death. Methodological differences as well as differences in the socio-demographic characteristics of the samples between these studies may help to explain the observed differences in mortality risk between men and women. Nonetheless, no study thus far has specifically addressed depression-related biological mechanisms that confer a higher mortality risk in men compared to women. A better understanding of the mechanisms by which gender moderates the mortality risk in LLD is of utmost importance to develop personalized preventive and therapeutic interventions aiming the reduction of mortality in these subjects.

Late-life depression is a treatable and potentially preventable medical condition[50,51], and may be a modifiable risk factor for preventing premature death in older adults. A recent analysis of long-term outcomes of a clinical trial for LLD treatment showed that the risk of

death, in particular due to cancer, was reduced by approximately 24% in older adults in full remission after antidepressant treatment[52]. This result suggests that the adequate and long-term treatment of depression and maintenance of remission of depressive episode can reduce mortality risk in LLD. However, no clinical trial to date has evaluated whether the prevention of depression in the elderly can also reduce the mortality associated with this disorder. Given the high attributable risk of dying due to LLD, and the expected increase in LLD cases due to the increasingly older population, it is necessary to conduct novel clinical trials to investigate the potential impact of prevention and treatment of depression on risk of death in elderly people. Finally, given the moderating effect of gender on mortality risk, these interventions should be tailored to gender to maximize their effectiveness.

The present results should be viewed in light of some study limitations. Diagnosis of LLD and of depression severity was based on pre-defined cut-off scores of the GHQ-12, and no structured psychiatric interview was carried out with cohort members. Therefore, some participants with milder symptoms might have been misclassified as non-depressed. On the other hand, this cut-off value yielded a very high prevalence of clinically significant depressive symptoms in this population (38.5%). Therefore, some non-depressed participants may have been misclassified as presenting clinically significantly depressive symptoms, yielding a very high prevalence of depression caseness (38.5%)[27,53]. The assessment of depressive symptoms at baseline may reflect either a temporary or acute state, or may reflect the presence of more chronic depressive symptoms. Therefore, we cannot determine with the current data whether the mortality risk is due to the effect of acute and/or persistent depressive symptoms. Given this limitation, we have tried to evaluate the relationship between late-life depression through different perspectives, in order to show how approaches to measurement and ascertainment of caseness can influence estimates of mortality risk, and the results were robust across several analyses. We did not have information on past psychiatric history and on whether participants were under treatment for depression. Thus, we were not able to evaluate the impact of either variable on mortality risk. Finally, this study was conducted in one small city in Brazil and we did not address the relationship between depressive symptoms and specific causes of death, including deaths due to suicide or trauma. These factors may limit the generalizability of these results and should be replicated in other population-based studies.

In conclusion, in the present study we found that LLD is associated with increased risk for all-cause mortality in the elderly, in particular in those with more severe depressive symptoms. In addition, gender may moderate mortality risk, being elevated in men more so than in women. Therefore, it is necessary to carry out long-term clinical trials to investigate the potential impact of treatment and prevention of depression on the risk of all-cause mortality in this population.

Acknowledgments

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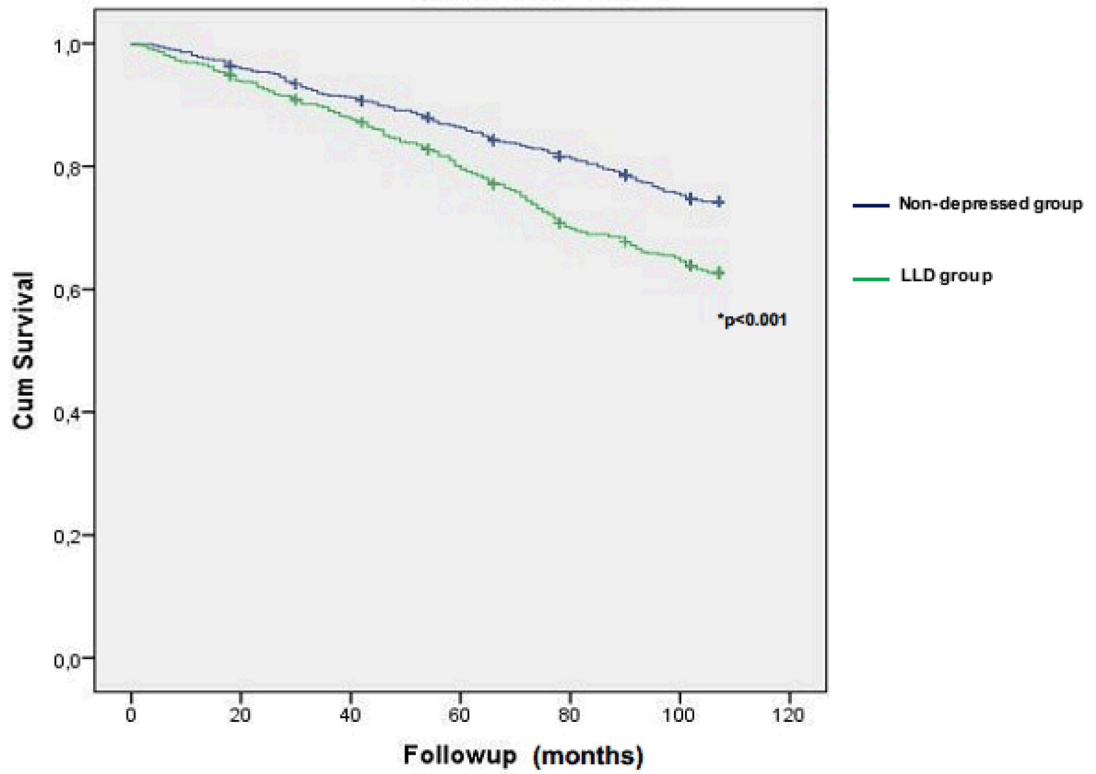
Figure 1.
Survival curve for mortality for participants with clinically significant depressive symptoms (LLD group) vs. non-depressed group.

Table 1

Baseline socio-demographic and clinical characteristics of the sample.

	Controls (N=927)	LLD (N=581)	Statistics	df	p
Baseline age (years)	68.6 ± 6.8	69.6 ± 7.6	t= 2.85	1506	0.005
Gender					
Females	55.9%	69.5%	X^2=28.03	1	<0.001
Males	44.1%	30.5%			
Marital status					
Married	54%	42%	X^2=18.86	1	<0.001
Not married *	46%	58%			
Retirement					
No	41%	35%	X^2=6.88	1	0.009
Yes	59%	65%			
Schooling					
4 years	39.5%	30.1%	X^2=13.6	1	<0.001
< 3 years	60.5%	69.9%			
Physical exercise					
No	15.7%	9.1%	X^2=13.7	1	<0.001
Yes	84.3%	90.9%			
BMI	25.1 ± 4.8	25.3 ± 5.3	t=−0.703	1506	0.5
Hypertension					
No	38.3%	37.5%	X^2=0.1	1	0.7
Yes	61.7%	62.5%			
Diabetes					
No	84.7%	85.3%	X^2=0.1	1	0.7
Yes	15.3%	14.7%			
Chagas disease					
No	67.2%	54.4%	X^2=23.3	1	<0.001
Yes	32.8%	45.6%			
Previous MI					
No	96.3%	93.3%	X^2=6.78	1	0.009

	Controls (N=927)	LLD (N=581)	Statistics	df	p
Yes	3.7%	6.7%			
Drinking habits					
No	79%	85%	X²=9.64	1	0.002
Yes	21%	15%			
Smoking					
Never	58.8%	58.7%			
Past smoking	22.4%	23.8%	X²=0.56	2	0.7
Current smoking	18.8%	17.6%			
Use of psychoactive drugs					
No	84%	30%	X²=41.24	1	<0.001
Yes	16%	70%			
Katz ADL	0.07 ± 0.008	0.18 ± 0.16	T=5.82	1506	<0.001
Baseline MMSE	25.3 ± 3.9	23.7 ± 4.6	t=6.94	1506	<0.001
Baseline GHQ-12	1.5 ± 1.4	7.7 ± 2.1	t=68.11	1506	<0.001
Follow-up (months)	91.0 ± 28.3	85.1 ± 31.7	t=3.76	1506	<0.001
Death **					
No	75.1%	63.9%	Log-rank χ²=27.28	1	<0.001
Yes	24.9%	36.1%			

BMI: body mass index; MI: myocardial infarction; MMSE: Mini-mental State Examination; GHQ-12: General Health Questionnaire-12;

*
Not married: single, divorced, widowed

**
Kaplan-Meyer survival analysis.

Table 2

Hazard ratio for mortality risk.

Comparisons	Unadjusted			Adjusted[*]		
	HR	95% CI	p	HR	95% CI	p
GHQ-12 scores (continuous measure)	1.07	1.05 – 1.10	<0.001	1.05	1.02 – 1.08	0.003
LLD group *vs.* non-depressed group	1.56	1.30 – 1.88	<0.001	1.24	1.00 – 1.55	0.05
Depression severity						
"low depressive symptoms" group vs. non-depressed group	1.41	1.14 – 1.75	0.002	1.03	0.81 – 1.33	0.77
"high depressive symptoms" groups vs. non-depressed group	1.87	1.46 – 2.41	<0.001	1.44	1.07 – 1.93	0.01

[*]
gender, baseline age, baseline monthly income, marital status, use of psychoactive drugs, retirement, educational level, activities of daily living, MMSE scores, drinking and smoking habits, hypertension, myocardial infarct, Chagas disease, physical activity, BMI, diabetes mellitus 2

Table 3

Effect of gender on mortality risk.

Comparisons	Men					
	Unadjusted			**Adjusted***		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**P**
GHQ-12 scores (continuous measure)	1.05	1.02 – 1.09	0.004	1.09	1.04 – 1.14	0.001
LLD group vs. non-depressed group	1.90	1.43 – 2.54	<0.001	1.45	1.01 – 2.07	0.04
Depression severity						
"low depressive symptoms" group vs. non-depressed group	1.60	1.13 – 2.26	0.008	1.23	0.80 – 1.87	0.34
"high depressive symptoms" groups vs. non-depressed group	2.56	1.74 – 3.76	<0.001	1.90	1.19 – 3.04	0.007

Comparisons	Women					
	Unadjusted			**Adjusted***		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**P**
GHQ-12 scores (continuous measure)	1.12	1.08 – 1.16	<0.001	1.01	0.97 – 1.06	0.5
LLD group vs. non-depressed group	1.48	1.16 – 1.90	0.002	1.13	0.84 – 1.48	0.45
Depression severity						
"low depressive symptoms" group vs. non-depressed group	1.40	1.06 – 1.85	0.02	1.01	0.73 – 1.39	0.9
"high depressive symptoms" groups vs. non-depressed group	1.66	1.18 – 2.32	0.003	1.38	0.93 – 2.06	0.11

*
baseline age, baseline monthly income, use of psychoactive drugs, marital status, retirement, educational level, activities of daily living, MMSE scores, drinking and smoking habits, hypertension, myocardial infarct, Chagas disease, physical activity, BMI, diabetes mellitus 2