RESEARCH ARTICLE

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Depression and cardiovascular risk factors: evidence from a large postmortem sample†

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Objectives: We aimed to investigate the association of depression with cardiovascular risk factors and diseases (CVRFD) in a large population-based sample.

Methods: This cross-sectional study included 1012 deceased individuals greater than 50 years of age from a general autopsy service located in São Paulo, Brazil. Demographics, socioeconomic profile, and CVRFD information were collected by caregivers from the deceased individuals from the Brain Bank of the Brazilian Aging Brain Study Group. Depression diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Mental Disorders was the main outcome.

Results: Depression was associated with female gender (odds ratio (OR) = 1.86; 95% confidence interval (CI) = 1.28–2.71, $p = 0.001$), widowhood (OR = 1.54; 95% CI = 1.03–2.32, $p = 0.04$), physical inactivity (OR = 1.61; 95% CI = 1.15–2.26, $p = 0.006$), and smoking (OR = 2.03; 95% CI = 1.40–2.95, $p < 0.001$) after multivariate logistic regression analysis. Other CVRFD were not associated with the presence of depression.

Conclusions: In our cross-sectional study, sedentary individuals and smokers showed a higher chance of depression during lifetime. Measures to control these common risk factors could decrease the incidence of depression. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

Depression is the most common psychiatric disorder. Its annual prevalence was 3.2% in a global survey of 245,404 individuals from 60 countries (Moussavi *et al.*, 2007). Moreover, depression is a leading cause of global burden of disease, being the third most common cause of disability-adjusted life year and affecting 121 million people worldwide (WHO, 2008). In a longitudinal cohort of older patients from primary care practices, depression contributed to mortality as much as diabetes and myocardial infarction did (Gallo *et al.*, 2005).

Cardiovascular risk factors and diseases (CVRFD) have been related to depression, particularly in older people (Carney and Freedland, 2003; Nicholson *et al.*,

2006; Rutledge *et al*., 2006; Sheline *et al*., 2010). The prevalence of depression was higher among individuals with cardiovascular diseases than in controls of the same age group, ranging from 20% to 25% (Carney and Freedland, 2003). Previous meta-analysis showed that depression is related to cardiovascular disease, particularly myocardial infarction (Van der Kooy *et al*., 2007). In addition, the presence of other clinical disorders is apparently synergistic, worsening the depression severity and prognosis (Moussavi *et al*., 2007). Almeida *et al*. found that diabetes, myocardial infarction, angina, stroke, hyperhomocysteine, high triglycerides, and smoking were related to depression in a large sample of men (Almeida *et al*., 2007). However, few studies have examined the association between several CVRFD and depression in large samples of both genders. We aimed to investigate further this association in a large population-based sample.

Methods

Participants

This cross-sectional study was conducted using data collected at the Brain Bank of the Brazilian Aging Brain Study Group (BB-BABSG), whose participants are sourced from the São Paulo Autopsy Service (SAS), University of São Paulo, Brazil. The SAS is the site of all autopsies of natural death from this city of 11 million inhabitants, performing about 13,000 autopsies per year. The BB-BABSG collects material from subjects autopsied between 8 AM to 12 PM from Monday to Friday, if a written consent is granted. During this period, data are obtained through a structured interview applied to an informant with a close relationship with the deceased (at least one visit/week in the last 6 months). This study used information collected from 2005 to 2008. Details regarding the structure of the BB-BABSG are described elsewhere (Grinberg *et al*., 2007). Briefly, individuals greater than 50 years of age were included after the next of kin agreed to participate and signed an informed written consent form approved by the local ethics committee. Subjects with acute cerebral lesions, including acute stroke, were excluded from the BABSG cohort because immediate brain examination is required to confirm the cause of death of these patients. Moreover, individuals with any potential acute conditions that could interfere with cognitive performance (e.g., anoxic encephalopathy) during the 6 months prior to death were also excluded.

Clinical postmortem evaluation

Demographics and clinical profile were evaluated during an interview with the informant of the deceased. Demographics included age, gender, race, marital status, years of education, and socioeconomic class. The classification suggested by ABIPEME (Brazilian Association of Market Research Institutes) was used to classify the participants in five possible socioeconomic classes (A–E) on the basis of the number of consumer goods and the years of formal education of the participant (Almeida and Wickerhauser, 1991). These five classes were grouped into two to facilitate statistical analysis: high socioeconomic class (A and B socioeconomic classes in ABIPEME classification) and low–middle socioeconomic class (C–E classes). History of CVRFD was assessed in detail during the interview with the informant, including history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, heart failure, and stroke. Habits including physical activity, smoking, and drinking were also assessed during the interview. Individuals were considered physically active if they had practiced at least 30 min of physical activity three times a week. Body mass index (BMI) was calculated using weight and height measured during the autopsy exam, and the results were expressed in kg/m^2.

Immediate cause of death was determined during autopsy examination. We grouped the cause of death in "cardiovascular cause of death" and "noncardiovascular cause of death". Immediate cause of death was considered as cardiovascular cause if it is included in the "Diseases of the circulatory system" (chapter IX) of the International Classification of Disease, 10th edition (WHO, 2010).

Depressive symptoms evaluation

The presence of depressive symptoms was defined by a previous episode of major depression during life assessed by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (Spitzer *et al*., 1995), according to information provided by an informant close of the deceased. The SCID is based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994). Depression was diagnosed when at least one of the two main depressive symptoms was present, depressed mood or markedly decreased interest or pleasure in activities, along with at least four additional symptoms for a duration of at least 2 weeks: alterations in weight, sleep, psychomotor activity, decreased

energy, concentration and reasoning problems, feelings of worthlessness or guilt, or recurrent thoughts of death or suicide. Individuals were classified as control group if they did not have any of the two core depressive symptoms. Individuals that had one main depressive symptom and less than four secondary symptoms were excluded from this analysis.

Statistical analysis

Participants were classified into two groups according to the presence of depressive symptoms assessed by SCID: depression and control group (binary outcome). Differences between the two groups regarding categorical variables were examined using chi-squared tests. For quantitative variables, unpaired *t*-tests were used.

In previous studies, individuals with more CVRFD had higher incidence of depression during follow up (Mast *et al*., 2008; Kivimäki *et al*., 2012). To test the impact of the overall vascular burden in our sample, an index of cumulative vascular risk was created by coding each factor (hypertension, diabetes mellitus, coronary artery disease, heart failure, arrhythmia, dyslipidemia, stroke, physical inactivity, smoking, drinking) as "1" if present and "0" if absent. After that, they were summed into an overall composite index score, ranging from 0 to 10. This index score was compared between individuals with and without depression using unpaired *t*-tests.

The variables that showed a *p*-value equal or less than 0.15 were included in a multivariate stepwise forward logistic regression model to investigate which variables were related to the outcome. The level of significance was set at 0.05 in two-tailed tests. The software SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis.

Results

From 2005 to 2008, the SAS performed 52,455 autopsies. During the BB-BABSG office hour, 4850 autopsies were performed. From them, 3175 subjects (65.5%) could not be included in our series because they were retained by the attending pathologist because of suspicion of acute brain lesions. Out of the 1675 remaining subjects, 128 (7.6%) next of kin did not agree to participate in the study and another 493 (29.4%) were excluded because of processes that could interfere with cognitive performance. Therefore, data from a total of 1054 individuals were included in the BB-BABSG from 2005 to 2008. Twelve individuals were excluded because of incomplete clinical information, and 30 participants were excluded because they had one main depressive symptom but less than four secondary ones. Therefore, data from 1012 participants were analyzed: 181 (17.9%) had depressive symptoms compatible with the diagnosis of previous major depression during life and 831 (82.1%) were classified as controls (Figure 1). The mean age at death was 69.8 ± 11.7 years old, 52.5% were men, 66.4% were Caucasians, and 44.5% were married. Regarding socioeconomic level, 72.9% were from low–middle socioeconomic classes, and the mean number of years of education of the sample was 4.4 ± 3.7 years. Overall prevalence of hypertension was 64.9%, followed by diabetes mellitus (30.4%), coronary artery disease (27.9%), heart failure (20.0%), stroke (14.0%), and dyslipidemia (10.2%). Regarding habits during life, 59.4% were physically inactive, 26.1% were smokers, and 24.5% were alcohol drinkers. The mean BMI was $23.4 \pm 4.2\,kg/m^2$.

Depression was more common among women ($p < 0.001$) and widowers ($p = 0.008$). Considering habits, depression was more prevalent among individuals inactive physically ($p = 0.006$), and smoking was more common among the depression group than in individuals without depression ($p < 0.001$). Other CVRFD were not associated with depression (Table 1). The total numbers of CVRFD per individual were similar among subjects with and without depression (depression: 3.3 ± 1.5 vs. no depression: 3.3 ± 1.6, $p = 0.77$). Cardiovascular diseases were the most common cause of death in both groups ($p = 0.30$). The main causes of death among individuals with and without depression are described in Table 2.

When multivariate logistic regression model was applied, female gender showed a 1.9 times greater chance of depression compared with male participants (odds ratio (OR) = 1.86; 95% confidence interval (CI) = 1.28–2.71; $p = 0.001$). Compared with married individuals, widowed have higher risk of depression (OR = 1.54; 95% CI = 1.03–2.32, $p = 0.04$). Sedentary individuals had 1.6 times greater chance of depression compared with physical active persons (OR = 1.61; 95% CI = 1.15–2.26, $p = 0.006$). Similarly, a current habit of smoking was associated with a 2.0 times higher risk of depression than for former or non-smoking individuals (OR = 2.03; 95% CI = 1.40–2.95, $p < 0.001$) (Table 3).

Discussion

Depression was associated with physical inactivity and smoking in this cross-sectional population-based

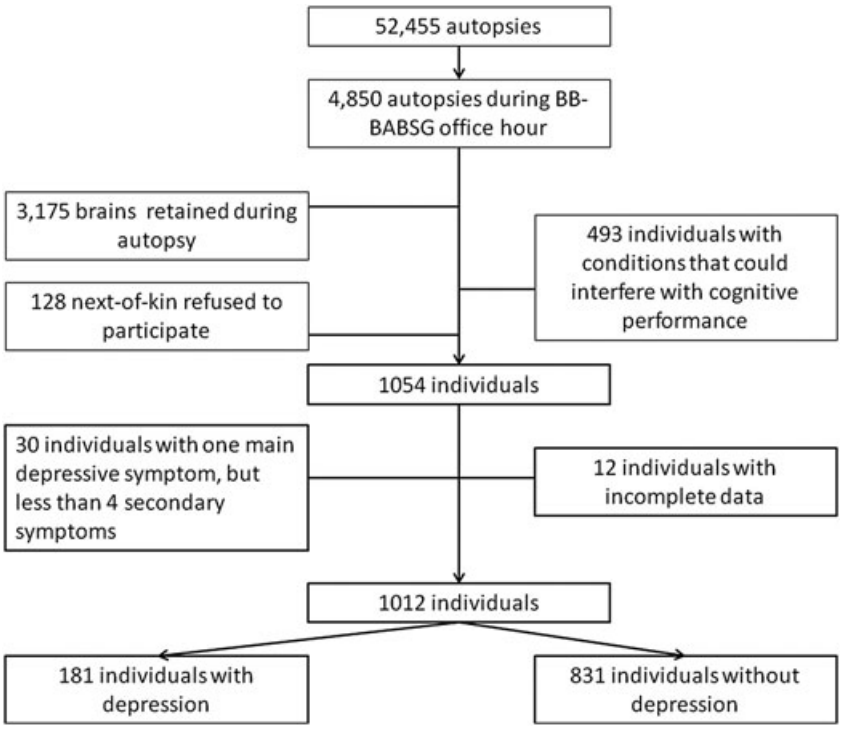

Figure 1 Flowchart of the participants of the study ($n = 1012$).

study. Other CVRFD were not associated with depression. The absolute number of CVRFD per individual was similar among individuals with and without depression. The prevalence of depression was 17.9% in our sample, and it was more common in women and in widowers compared with married subjects, as previously described (Belmaker and Agam, 2008; Yan *et al*., 2011).

Physical inactivity has already been related to depression. It has previously been shown that comorbid depression and physical inactivity increased the mortality by cardiovascular diseases (Geulayov *et al*., 2010). In a systematic review, depression and physical inactivity were associated in seven of the eleven studies that were included in the analysis (Teychenne *et al*., 2011). However, the causal relationship between these two variables is controversial. In a large sample of twins, an increase in exercise did not predict fewer depressive symptoms (Wolff and Strohle, 2010). In our cross-sectional study, the causal relationship between physical activity and depression could not be inferred. Physical inactivity may lead to depression, or the association found could be because depressed individuals present less psychomotor activity.

A higher prevalence of depression among smokers has also been described previously (Almeida *et al*., 2007; Korhonen *et al*., 2011). Smoking was related to the presence of late-life depression, sleep disturbances, sexual dysfunction, and increases in fatigue. A causal relationship between symptoms of nicotine dependence and depression was suggested by a prospective study (Boden *et al*., 2010). It has been proposed that smoking causes changes in neurotransmitter levels in the brain, leading to an increased risk of depression (Haustein *et al*., 2002). Similar to physical inactivity, the causal relationship between smoking and depression could not be inferred in our study.

We did not find an association between depression and other CVRFD besides physical inactivity and smoking. However, previous studies have shown an association between depression and different CVRFD, such as hypertension, diabetes, coronary artery disease, heart failure, and stroke (Carney and Freedland, 2003; Hackett *et al*., 2005; Rutledge *et al*., 2006; Moussavi *et al*., 2007; Grimsrud *et al*., 2009; Nouwen *et al*., 2010; Celano and Huffman, 2011). The prognosis of patients with cardiovascular diseases was worse when depression was present (Carney and Freedland, 2003; Nicholson *et al*., 2006; Moussavi *et al*., 2007). Moreover, depression was more common in individuals with multiple comorbidities (Moussavi *et al*., 2007). Although we found that cardiovascular diseases were the main cause of death in our sample, we found that the number of CVRFD and factors were similar between individuals with and without depression.

Table 1 Demographics, cardiovascular risk factors, and diseases among individuals with depression and control group ($n = 1012$)

Variable	Depression	No depression	p
Age at death, mean (SD)*	69.9 (11.9)	69.8 (11.7)	0.89
Gender, %#			<0.001
Female	59.7	44.9	
Male	40.3	55.1	
Caucasian, %#	70.2	656.6	0.24
Marital status, %†			0.008
Married	34.4	46.7	
Single	13.9	14.3	
Widower	45.6	32.9	
Divorced	6.1	6.2	
Years of education, mean (SD)*	4.3 (3.5)	4.5 (3.8)	0.26
Socioeconomic class, %#			0.60
High	25.4	27.3	
Middle and low	74.6	72.7	
Cardiovascular cause of death, %	76.8	73.0	0.30
Hypertension, %#	69.1	64.0	0.20
Diabetes mellitus, %#	27.1	31.1	0.29
Dyslipidemia, %#	6.6	11.0	0.08
Coronary artery disease, %#	26.5	28.2	0.66
Heart failure, %#	21.5	19.6	0.56
Stroke, %#	14.9	13.8	0.70
Physical Inactivity, %#	68.5	57.5	0.006
Smoking, %#	34.3	24.3	0.006
Drinking, %#	24.9	24.5	0.806
Body mass index (kg/m^2), %#			0.23
<18.5	11.2	7.7	
18.5–24.99	65.9	65.6	
25–29.99	18.4	19.1	
≥30	4.5	7.7	
Number of CVRFD per individual, mean (SD)*	3.3 ± 1.5	3.3 ± 1.6	0.77
Total, n (%)	181 (17.9)	831 (82.1)	

SD, standard deviation; CVRFD, cardiovascular risk factor and diseases.
*Unpaired t-test.
#Chi-square test.
†Missing data.

Our study has advantages compared with previous studies. We analyzed a wide range of information from a large population-based sample. Moreover, immediate cause of death in both groups could be accessed during the autopsy examination. The diagnosis of depression was based on the DSM-IV criteria verified through the application of a structured interview with a close informant of the deceased.

Table 2 Leading causes of death confirmed by autopsy examination, among individuals with and without depression ($n = 1012$)

Depression	No depression
Heart failure (27.1%)	Myocardial infarction (31.4%)
Myocardial infarction (26.0%)	Heart failure (20.8%)
Aortic aneurysm (9.4%)	Pneumonia (10.7%)
Pneumonia (8.8%)	Aortic aneurysm (8.8%)
Pulmonary thromboembolism (7.7%)	Pulmonary thromboembolism (7.6%)

Moreover, we used a more conservative criterion, as only individuals with one main depressive symptom and at least four minor symptoms were considered to be depressed, and individuals without depression did not have any main depressive symptoms during life.

However, this study also has some limitations. The diagnosis of CVRFD was based solely on the information provided by the informant. Previous medical records and laboratory tests were not available in our postmortem study. The diagnosis of depression was also based on caregiver information, and it was not possible to determine the exact age of onset of the depression. It is expected that late-onset depression would be more related to cardiovascular disease, and the lack of association could be due to the inability to separate the early onset depression from the late-onset cases. Moreover, in a cross-sectional study, the causal relationship between CVRFD and depression cannot be examined. Future longitudinal studies and randomized clinical

Table 3 Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) for depression, according to demographics and cardiovascular risk factors ($n = 1012$)

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)*
Female gender	1.81 (1.31–2.52)#	1.86 (1.28–2.71)#
Marital status		
Married	1	1
Single	1.32 (0.80–2.20)	1.05 (0.63–1.78)
Widower	1.88 (1.31–2.71)#	1.54 (1.03–2.32)#
Divorced	1.35 (0.67–2.72)	1.06 (0.51–2.19)
Dyslipidemia	0.58 (0.31–1.08)	0.63 (0.33–1.18)
Physical inactivity	1.61 (1.16–2.24)#	1.61 (1.15–2.26)#
Smoking	1.62 (1.15–2.29)#	2.03 (1.40–2.95)#

*Multivariate logistic regression analysis, adjusted for all other variable described in the table.
#$p < 0.05$.

trials are necessary to clarify if a causal relationship between depression and CVRFD actually exists.

This study replicates in a large postmortem sample previous epidemiological findings. We found that smoking and physical inactivity were related to higher odds of depression. Public health programs aimed to reducing the impact of these risk factors in the population may potentially decrease the incidence of not only cardiovascular diseases but also depression.

Conflict of interest

None declared.

Key points

- Depression was associated with physical inactivity and smoking in this large cross-sectional postmortem sample.
- Depression was more common among women and individuals that were widowed.
- The most common causes of death among depression group were heart failure, myocardial infarction, and aortic aneurysm. Individuals without depression died mostly from myocardial infarction, heart failure, and pneumonia.
- The index of cumulative vascular risk factors and diseases are similar between groups with and without depression.

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