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Research paper

# Depression with melancholic features is associated with higher long-term risk for dementia

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ABSTRACT

*Background:* Depression has been reported to increase the risk of subsequently developing dementia, but the nature of this relation remains to be elucidated. Depression can be a prodrome/manifestation of dementia or an early risk factor, and the effect may differ according to depression subtypes. Our aim was to study the association between early-onset depression and different depression subtypes, and the later occurrence of dementia.

*Methods:* We conducted a cohort study including 322 subjects with depression, recruited between 1977 and 1984. A comparison cohort (non-exposed) was recruited retrospectively, to include 322 subjects admitted at the same hospital for routine surgery (appendicectomy or cholecystectomy), at the same period as the depressed cohort. Subjects were contacted again between 2009 and 2014, to assess their dementia status. We computed the risk for dementia in subjects with early onset depression and quantified the association between different depression subtypes (namely melancholic, anxious, and psychotic) and dementia.

*Results:* The odds of dementia were increased by 2.90 times (95% C.I. 1.61–5.21; $p < 0.0001$) for the depressed cohort when compared to the surgical cohort. When the analysis was restricted to patients younger than 45 years old at baseline, the odds for dementia in the depressed cohort were also significantly higher when compared to the surgical cohort (8.53; 95% C.I. 2.40–30.16). In the multivariate Cox analysis, subjects having depression with melancholic features had an increased risk for developing dementia compared to those without melancholic features (HR=3.64; 95% C.I. 1.78–11.26; $p=0.025$).

*Limitations:* About 59% of the participants with depression and 53% of those non-exposed were lost during follow up. The inclusion of biological biomarkers would strengthen the results. The sample included a low number of bipolar patients.

*Conclusions:* These results support depression as an early risk factor for dementia. Depression with melancholic features was found as an important risk factor for dementia, playing a main role in the relation between these disorders.



## 1. Introduction

As most dementing conditions are irreversible, and the available therapies have limited beneficial effects, primary prevention of cognitive decline is of paramount importance (Ritchie et al., 2010; Norton et al., 2014). Among the several risk factors so far identified, depression emerges as a potentially important target (Reitz et al., 2011), because is amenable to prevention, has a high prevalence, and can be diagnosed inexpensively and treated effectively (Kupfer et al., 2012; Malhi et al., 2015).

Depression has been found to be a risk factor for dementia or Alzheimer's dementia (AD) in several case-control (Cooper and Holmes, 1998; Green et al., 2003) and cohort studies (DalForno et al., 2005; Kessing and Nilsson, 2003; Saczynski et al., 2010; Irie et al., 2008; Dotson et al., 2010; Byers and Yaffe, 2011), but not all (Chen et al., 1999, 2008; Gatz et al., 2005; Brommelhoff et al., 2009). The meta-analyses and reviews performed have confirmed this association in general, finding that depression approximately doubles the risk for dementia (Jorm, 2001; Ownby et al., 2006;

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Silva et al., 2013).

However, the nature of this relation remains poorly understood. Two unsolved issues have been repeatedly raised (Byers and Yaffe, 2011; Kessing, 2012). The first is that depression, especially if occurring after 60 years old (called late onset depression) or next to the diagnosis of dementia, can be a prodrome/manifestation of a dementing disorder, instead of an early risk factor. Depressive symptoms are quite common in dementia, and depressive symptoms may arise from the anatomic lesions that are part of the neuropathological changes of dementing disorders (Boland, 2000). Case-control studies that do not take in account the time between dementia and depression diagnosis, and cohort studies with a short follow up, may not be able to distinguish between these two situations. The few studies that specifically compared late-onset depression with early-onset depression found discrepant results (Green et al., 2003; Geerlings et al., 2008; Brommelhoff et al., 2009; Lenoir et al., 2011; Almeida et al., 2016).

The second issue is the subtype of depression. The heterogeneity of depression has seldom been taken into account. A more severe disorder (expressed by higher frequency, duration, and severity of the depressive episodes) has been inconsistently associated with a higher risk for dementia (Kessing and Andersen, 2004; Geerlings et al., 2008; Kessing, 2012; Silva et al., 2013). Bipolar disorder has also been associated with a higher risk of dementia. In the review and meta-analysis by Silva et al. (2013) the majority of studies confirmed the association in accordance with subsequent published studies. Brodaty et al. (2003) explored the role of comorbid anxiety in depression on the risk for dementia and found no influence. On the other hand, the use of benzodiazepines has been reported to carry a higher risk (Billioti de Gage et al., 2012). Psychotic symptoms have been associated with a higher risk for cognitive deficits only in bipolar patients (Martínez-Arán et al., 2004). Few studies looked at the risk for dementia in DSM5 or ICD10 defined depression subtypes. DalForno et al. (2005), in a community based study, performed an additional risk analysis finding that a Center for Epidemiologic Study–Depression (CES-D) sub-scale based on a cluster of negative affective symptoms, related to melancholic features, did not influence the global risk for dementia. Different biological mechanisms underlying these different depressive conditions can carry different risks for dementia. Melancholic features, and to a lesser extent psychotic symptoms, have been associated with more consistent biological abnormalities and response to treatment (Brown, 2007; Parker et al., 2013) when compared to their absence.

These unsolved issues – prodrome versus early risk factor and the heterogeneity of depression – regarding the risk for dementia in depressed patients, encouraged us to perform the current study. The objectives were to assess the association between early-onset depression and the long-term risk for dementia, and to analyze the risk for dementia of different depression subtypes, controlling for well known risk factors for dementia.

## 2. Methodology

### 2.1. Study design

This study is based on two cohorts followed in average 25 years for development of dementia. The exposed cohort (depression cohort) comprised 325 patients from the Hospital de Santa Maria, Lisbon, with the clinical diagnosis of depression, recruited between 1977 and 1984 in a taxonomic cluster analysis study of depression (Paes de Sousa et al., 1980).

A surgical comparison cohort (non-exposed) was recruited retrospectively, to include 325 subjects who were consecutively admitted to Hospital de Santa Maria, Lisbon, for routine surgery (appendicectomy or cholecystectomy) at the same period as the depressed cohort.

Participants were re-evaluated between 2009 and 2014, to establish the outcome - dementia status.

### 2.2. Baseline assessment

Data on demography, clinical history, and personal and family history as part of routine clinical files were collected for both cohorts. For the depressed cohort a comprehensive psychiatric and psychological evaluation was performed.

#### 2.2.1. Evaluations

*2.2.1.1. Association for methodology and documentation in psychiatry system (AMDP).* The AMDP-System was created in Nuremberg in 1960 and has been widely used in Europe in 1970–1980. The Psychopathology Scale contains 100 psychopathology items, including symptoms and other clinical features, derived from classic psychopathology studies from Jaspers, Bleuler, Schneider, and others. It renders a very detailed and standardized evaluation, including affective, behavioral, cognitive, psychotic, sensory, and social dimensions of psychopathology (Busch et al., 1980; Paes de Sousa et al., 1980).

Each symptom is scored for severity (0–3: absent, mild, moderate, severe).

This evaluation notably allowed the classification of depression by virtually any diagnostic system and has been used for diagnostic or reclassification purposes with other diagnostic systems, such as the DSM IV (Salvatore et al., 2007; Seemüller et al., 2008).

*2.2.1.2. Eysenck personality questionnaire (EPQ).* This questionnaire (Eysenck and Eysenck, 1975) includes 83 items (full version), allowing the evaluation of the three basic personality dimensions, according to Eysenck's personality theory: extroversion, neuroticism and psychoticism. Only the extroversion and neuroticism dimensions were analyzed in this study. The subject responds yes or no, and a positive answer is scored 1. The final result is the sum of the points in each scale (0–23 for extroversion and 0–23 for neuroticism).

The neuroticism dimension assesses emotional stability versus instability and identifies individuals prone to psychological distress. Low scores indicate a trend to more relaxed, unemotional, and self-satisfied subjects. The extraversion dimension measures interpersonal interaction, activity level, need for stimulation, and capacity for joy. The subjects with a low score tend to be more reserved, sober, task-oriented, and quiet.

A low extroversion (a score lower then median) and high neuroticism group (a score higher than median) of subjects was created, as these subjects were previously found to be at a higher risk for dementia (Wang et al., 2009).

*2.2.1.3. Clinical global impression (CGI)).* Clinical global impression – severity (CGI S; Guy, 1976) is 7-point scale to evaluate the current severity of the patient's illness, according to the clinician's total past experience, ranging from 1 (not at all ill) to 7 (extremely ill).

#### 2.2.2. Diagnosis of depression

Using AMDP symptoms at baseline, DSM 5 diagnostic criteria for Persistent Depressive Disorder (dysthymia), Major Depressive Disorder (MDD), melancholic and psychotic features were applied. Through baseline chart review, subjects were considered to have bipolar disorder if they met DSM 5 criteria for bipolar disorder.

The specifier of anxious distress could not be defined by AMDP as only two anxious symptoms (“psychic anxiety” and “somatic anxiety”) are present in the scale. A numerical variable “anxiety symptoms” was created adding both scores. Chronic disease was