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Research paper

Exploring the excess mortality due to depressive symptoms in a community-based sample: The role of Alzheimer's Disease

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ABSTRACT

Background: Depression has been associated with increased risk of death. However, there is lack of studies exploring such relationship in the context of dementia. Given the high prevalence of both depression and Alzheimer's Disease (AD), investigating their temporal association with mortality is of public health relevance.
Methods: Longitudinal data from the WHICAP study were analyzed (1958 individuals aged ≥65 years). Depressive symptoms were assessed with the 10-item Center for Epidemiologic Studies Depression Scale (CES-D). Respondents were identified as having AD if they satisfied the criteria of the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Cox regressions analyses were performed to determine the association between depressive symptoms and risk of all-cause mortality using the overall sample, and by AD status.
Results: Depressive symptoms were significantly associated with higher mortality risk after adjusting for all potential covariates in the overall sample (HR=1.22; 95% CI=1.02, 1.46) and in individuals with incident AD (HR=1.88; 95% CI=1.12, 3.18).
Limitations: The CES-D does not measure clinical depression but depressive symptomatology. Since those who were exposed to known risk factors for mortality are likely to die prematurely, our results may have been skewed to the individuals with longer survival.
Conclusions: Strategies focusing on prevention and early treatment of depression in the elderly may have a beneficial effect not only on patient quality of life and disability, but may also increase survival in the context of AD.

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1. Introduction

Depression is a common mental condition among elderly individuals (Byers et al., 2010), with estimates ranging from 4.6% to 9.3% for a major depression episode and from 4.5% to 37.4% for any form of depressive disorders (Luppa et al., 2012). Depression has been consistently associated with physical and mental comorbidities, disability and increased risk of death both in clinical and epidemiological studies (Cuijpers et al., 2014; Ferrari et al., 2013; Prince et al., 2007; Saz and Dewey, 2001; Walker et al., 2015). Byers et al. (2012) found in a retrospective cohort study of male veterans that depression increased the risk of death over 40%, and Ganguli et al. (2002) showed a similar pattern in a community-based study of 1064 elder individuals. Nevertheless, there are other studies that have failed to find such association (Blazer et al., 2001; Everson-Rose et al., 2004). The inconsistency of findings may be explained by several factors, including the method for the assessment of depression, sample size, study design, follow-up period, or the control for potential confounding variables in adjusted models. That is the case for dementia, which has been rarely

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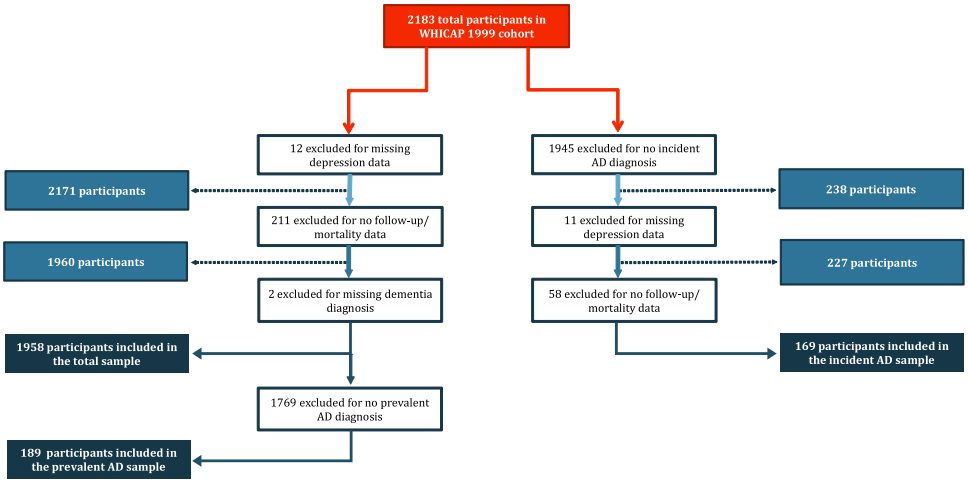

Fig. 1. Flowchart describing selection of study sample. AD=Alzheimer's Disease.

examined as a covariate in population or community-based studies, despite strong evidence suggesting the role of dementia as an independent risk factor for survival time and its relationship with depression (Todd et al., 2013).

The presence of depression in relation to dementia, particularly Alzheimer's Disease (AD onwards), has been extensively studied, and it has been reported that around 50% of AD patients may suffer from a depressive episode at least once during the disease course (Chi et al., 2014). Previous evidence suggests an association between depression and the risk of incident all-cause dementia (Diniz et al., 2013). It remains unknown, however, whether depression constitutes a prodrome of dementia or an independent risk factor. Few longitudinal investigations have explicitly examined the role of depression as a potential predictor of mortality in dementia or AD samples, and they have shown mixed results: while Andersen et al. (2010) and Pimouguet et al. (2015) reported an association between depressive symptomatology and mortality, Roehr et al. (2015) did not found such association. In general, examination of survival risk associated with depression in AD samples is infrequent, with most studies focusing on the analysis of well-established risk factors (i.e. age, cardiovascular factors, or functional limitations). Given the lack of studies that explore the relationship between depression and mortality considering all confounding factors and the high prevalence of both dementia and depression, investigation of their association to mortality is of public health relevance.

The present study examine the temporal association between depressive symptoms and mortality in a community-based cohort from northern Manhattan in New York City taking into account the presence of AD, and test the same relationship in a subsample of this cohort consisting of individuals with AD.

2. Methods

2.1. Study design

Longitudinal data from the Washington Heights-Inwood Community Aging Project (WHICAP) at Columbia University Medical Center were analyzed. Information about this project is briefly summarized here as it has been described in detail elsewhere (Tang et al., 2001). WHICAP is a community-based study of aging and dementia in Medicare-eligible northern Manhattan residents aged 65 or older. The population sample was composed by a multiethnic cohort that includes Caribbean Hispanic, African-American and Caucasian (non-Hispanic) individuals. The current study included participants from the 1999 cohort. They have been followed at intervals of approximately 1.5 years. Data were collected through face-to-face structured interviews performed in either English or Spanish. Physicians conducted a standardized physical and neurological examination, as well as a neuropsychological test battery assessment. Each assessment also included data on general health status and functional ability.

The 1999 cohort had an initial sample of 2183 participants. 12 individuals with missing depression information at baseline were excluded. Of the remaining 2171 participants, we excluded 211 individuals with no follow-up visits or mortality data and 2 with missing dementia diagnosis. Thus, the final analytical sample consisted of 1958 respondents. Each participant contributed up to 15 years of follow-up from the baseline examination to death or censoring at the last evaluation. Initial analyses utilized the entire cohort. We repeated the analyses limiting them to AD cases only, analyzing prevalent and incident cases separately. Respondents who were diagnosed with AD at baseline assessment were considered prevalent AD cases (N=189). Individuals who had not dementia upon entry into the study and developed AD during follow-up were selected for the incident AD analyses (N=169) (Fig. 1).

2.2. Ethic statement

The WHICAP study was reviewed and approved by the Institutional Review Boards of Columbia Presbyterian Medical Center and the New York State Psychiatric Institute. Written informed consent was obtained from all respondents.

2.3. Measurements

2.3.1. Outcome (Depressive symptoms)

The 10-item Center for Epidemiologic Studies Depression Scale (CES-D) (Irwin et al., 1999) was used to assess the presence and severity of depressive symptoms. Individuals were asked whether they had experienced each of 10 symptoms over the last week. Those questions answered with “yes” were endorsed with 1 point, leading to a total score that ranged from 0 to 10, with higher scores indicating greater depressive symptoms. We used two outcomes based on the CES-D: 1) The presence or absence of depressive symptoms was defined using a conventional cutoff score of ≥ 4 (CES-D depression); 2) Total CES-D score was treated as a continuous variable (CES-D severity).

Supplemental analyses were conducted by using additional questions included in the survey that evaluated the presence of

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