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Risk factors for late-life depression: A prospective cohort study among older women

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ABSTRACT

Depression prevention requires identifying key risk contributors. Prior studies have identified several factors related to late-life depression but have seldom addressed factors jointly or in dose-response fashion. This study aimed to examine a wide range of potential predisposing factors and to estimate individual and joint contributions to risk of late-life depression in women. A total of 21,728 women aged ≥65 years, without prior depression, in the Nurses' Health Study conducted in the United States were followed from 2000 to 2010. Demographic, social, lifestyle/behavioral and health variables were selected a priori from the literature or previous findings in this cohort. Depression was defined as physician/clinician-diagnosed depression, regular antidepressant use, or the presence of severe depressive symptoms. During 10-year follow-up, 3945 incident cases were identified. After simultaneous multivariable-adjustment, multiple factors in the domains of social stress (lower self-rated societal position and high volume of caregiving to disabled/ill relatives), unfavorable lifestyle (smoking, physical inactivity, heavy or binge drinking), and poor physical health (multiple comorbidity burden, excessive sleep, difficulty falling/staying asleep, bodily pain, and physical/functional limitation or disability) were significantly associated with higher depression risk; many featured dose-response relationships. Sensitivity analyses that excluded outcomes within 2 years yielded similar estimates. The total population attributable fraction for all factors was 55.5%. Physical/functional limitation accounted for one-quarter of population attributable fraction, followed by problematic sleep, inadequate exercise, and pain (combining for one-third of population attributable fraction). Efforts to remediate or prevent these factors may contribute to an efficient strategy for late-life depression prevention in women.

1. Introduction

Incident late-life depression (LLD) is defined as depression occurring for the first time typically after age 60 or 65, and is a common and life-impairing mental health problem in older people. LLD can be distinguished from early-life depression in both etiology and phenomenology (Sheline et al., 2010). Even with appropriate treatment, residual symptoms and dysfunction are common, underscoring the priority for prevention. A critical step in developing a rational prevention strategy is to determine major contributors to disease. Although the exact etiology is not fully understood, prior evidence points to key factors as potentially high-impact in LLD risk (Lyness et al., 2009; Schoevers et al., 2006), such as medical comorbidity burden and physical/functional limitations or disability. However, other potentially modifiable factors have been examined less comprehensively. In the literature in investigating LLD risk, potential limitations include: (1) risk factor information is often available once at baseline (Park et al., 2014; Luijendijk et al., 2008a); (2) association patterns (threshold/dose-response/plateau effects) are unclear due to lack of data (Almeida et al., 2013); (3) since health and lifestyle behaviors are often correlated, studying one factor without adjustment for relevant confounders may bias results; and (4) although average daily alcohol intake has been examined in prospective studies (Park et al., 2014; Tait et al., 2012; Weyerer et al., 2013), the specific relation of heavy or binge drinking to LLD risk has been relatively understudied.

To address the above challenges, we conducted prospective analyses in the Nurses' Health Study (NHS), a well-characterized cohort of women. We related potential risk factors to incident LLD, defined as onset among those aged ≥65 years, and aimed to investigate a

Abbreviations: LLD, late-life depression; NHS, Nurses' Health Study; PAF, population attributable fraction; BMI, body mass index; MHI-5, 5-item Mental Health Index; CESD-10, 10-item version of the Center for Epidemiologic Studies Depression; GDS-15, 15-item version of the Geriatric Depression Scale; TCAs, tricyclic antidepressants; SD, standard deviation; HR, hazard ratio; CI, confidence interval; N/A, not applicable.

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comprehensive array of potential risk/protective factors simultaneously – with particular attention to potentially-modifiable factors. We applied the Institute of Medicine concept of *selective* prevention (addressing persons at heightened risk for a clinical outcome), by addressing demographic, social, lifestyle/behavioral and health/medical factors which may place older women at high risk for developing depression. With respect to health factors, we were specifically interested in addressing sleep issues because emerging evidence supports sleep difficulty as an independent risk factor for depression (Almeida et al., 2011; Baglioni et al., 2011) – rather than merely a manifestation of it.

2. Methods

2.1. The Nurses' Health Study

The NHS began in 1976 when 121,700 U.S. female nurses, aged 30–55 years, returned a mailed questionnaire regarding lifestyle and medical history. Participants have received questionnaires biennially since then, with >90% follow-up rate in each 2-year cycle.

2.2. Risk and protective factors

All of the potential risk/protective factors examined in this study were self-reported from NHS questionnaires. They were selected *a priori* from the literature or prior NHS findings (Lyness et al., 2009; Schoevers et al., 2006; Brown et al., 2005) and were grouped into 4 categories:

(1) Demographic: Age (continuous, in years); education (registered nurse/bachelor/advanced degree); and race/ethnicity (non-Hispanic whites/blacks/others).
(2) Social: Social network, measured by the simplified Berkman-Syme Social Network Index (incorporating information of marital status, number of close contacts, church attendance, and participation in community organizations) (quintiles; higher quintile representing higher level of social network)(Berkman and Syme, 1979); low subjective social status (measured using a 10-point visual analog scale of subjective feeling about standing in U.S. society) (high/medium-high/medium-low/low standing)(Adler et al., 2000); hours of regular caregiving to children/grandchildren and to disabled/ill relatives (no/some(1–20 h/week)/a lot(>20 h/week)).
(3) Lifestyle/behavioral: Body mass index (BMI, in kg/m^2) (<18.5/18.5–24.9/25.0–29.9/30.0–34.9/≥35.0); alternate Mediterranean (aMed) diet score (quintiles; higher quintile representing better adherence to aMed diet)(Fung et al., 2009); cigarette smoking (never/past/current:1–14/15–24/≥25 cigarettes/day); physical activity (measured as average hours/week engaging in moderate to vigorous exercise) (0/0.1–0.9/1.0–2.4/2.5–4.9/≥5.0); largest number of alcoholic drinks in a single day of a typical month during the past year (none/1–2/≥3; having ≥3 drinks is considered as heavy/binge drinking). Of note, although individual nutrients have been related to depression (Lucas et al., 2011), we chose aMed diet to represent overall dietary pattern. Self-reported weight, physical activity, and dietary intake have been shown to be reliably and validly measured through NHS validation studies (Salvini et al., 1989; Willett et al., 1985; Rimm et al., 1990; Wolf et al., 1994; Colditz et al., 1986).
(4) Health/medical: Medical comorbidity burden (≤1/≥2)(Sun et al., 2011); daily hours of sleep (≤6/7–8/9/≥10); difficulty falling/staying asleep (none/little/some/most or all of the time); total bodily pain (none/very mild or mild/moderate/severe or very severe); physical/functional limitations, defined as having any limitations in milder activities or more than moderate limitations in demanding activities (yes/no)(Sun et al., 2011). Questions on pain and physical/functional limitations came from 36-item Short-Form Health Status Survey (SF-36)(Ware and MOS, 1992).

For each variable, the category with hypothesized lower/lowest risk was the referent. The category with most individuals was the referent if the category of putatively lower/lowest risk was uncertain. For the factors that did not have straightforward cutoffs, the cutoffs were determined by the distribution of response options, their plausible expected associations, and their conceptual degrees of intensity or severity. For caregiving intensity, because our data could not distinguish between people providing no care and those who did not have specific family members to be cared for, both groups jointly served as the referent.

2.3. Assessment and measures of depression

Depression information included self-reported depressive symptoms, regular use of antidepressants, and physician/clinician diagnosis. Symptoms were assessed using the Mental Health Index-5 (MHI-5) subscale of the SF-36 in 1992, 1996, and 2000, the Center for Epidemiologic Studies Depression-10 (CESD-10) in 2004 and the Geriatric Depression Scale-15 (GDS-15) in 2008, all of which have validated cutpoints for clinical depression (Yamazaki et al., 2005; Andresen et al., 1994; Friedman et al., 2005). Questions on antidepressant use and physician/clinician diagnosis of depression were assessed biennially since 1996 and 2000, respectively. For antidepressants, we included selective serotonin reuptake inhibitors but not tricyclic antidepressants (TCAs), as we found elsewhere that TCAs would be more likely to be prescribed for other indications (Okereke et al., 2015). Because 2000 was the earliest year in which we could classify women as ever having doctor-diagnosed depression, we designated this as the study baseline.

Because the NHS questionnaire was asked biennially, participants reported on their depressive symptoms, medications, or doctor diagnosis within each 2-year time window. We had no information on the number or duration of discrete depressive episodes within 2-year windows, so recurrent depression events could not be unambiguously determined; therefore, we only examined incidence in this study. The date of incident LLD onset was defined by the first occurrence of physician/clinician-diagnosed depression, regular antidepressant use, or severe depressive symptoms using published cutpoints during follow-up (Andresen et al., 1994; Friedman et al., 2005). This 'Boolean OR' definition was applied, as preliminary data from an ongoing validation study support its optimal sensitivity and specificity. Because we specifically aimed to examine the associations between sleep problems and depression risk, the item related to sleep in CESD-10 ("my sleep was restless") was removed for scoring. To be conservative, we did not alter the cutoff score of CESD-10 for probable depression after excluding the sleep item, so that a participant's CESD-10 score was not influenced by her sleep symptoms but by the severity of the remaining depressive symptoms. As expected, the observed LLD incidence was lower when using only 9 items compared to using 10 items (21.9 and 26.4 per 1000 person-years, respectively), although both estimates were in the range of LLD incidence estimates among women in prior studies that featured clinical evaluations of depression (Luijendijk et al., 2008b; Norton et al., 2006; Palsson et al., 2001).

2.4. Sample for analysis

After excluding women who died before 2000 or did not return the 2000 questionnaire (n = 26,908), whose history of depression could not be determined (n = 33,757), who had prior indication of depression assessed by MHI-5 score, physician/clinician diagnosis or antidepressant medication (n = 13,610), who aged under 65 years (n = 19,095), who did not provide information on all risk factors selected a priori (n = 5863), who stopped returning questionnaires after 2000 (n = 562) or had no health examination during follow-up (so there is no opportunity for depression detection) (n = 177), 21,728 women were included for analysis (Fig. 1). The institutional review board at Brigham and Women's Hospital approved the study protocol.