Sex Differences in the Relationship between Depressive Symptoms and Risk of Amnestic Mild Cognitive Impairment

Erin E. Sundermann, Ph.D., Mindy J. Katz, M.P.H., Richard B. Lipton, M.D.

Objective: *The relationship between depressive symptoms and subsequent cognitive impairment in older adults is controversial. Sex differences and the differences in the method of categorizing depressive symptoms may contribute to the inconsistencies. The authors examined the effect of severity of baseline depressive symptoms on risk of incident amnestic mild cognitive impairment (aMCI) separately in men and women.* **Methods:** *Community-dwelling and cognitively healthy older adults (aged ≥ 70 years) from the Einstein Aging Study completed the 15-item Geriatric Depression Scale (GDS-15) at their baseline visit. Participants were categorized into "no/low symptoms" (GDS-15 score = 0–2), "mild symptoms" (GDS-15 score = 3–5), and "moderate/severe symptoms" (GDS-15 score > 6) groups. Sex-stratified Cox proportional hazards models, adjusted for age, education, and antidepressant medication, estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for incident aMCI as a function of depressive symptoms group.* **Results:** *We followed 572 women (mean age: 78) and 345 men (mean age: 77) for 4.2 years on average (range: 1.0–14.6 years). Ninety women and 64 men developed aMCI during follow-up. Cox models revealed that compared with no/low depressive symptoms, mild symptoms were associated with a two times greater risk of developing aMCI in men (HR: 2.22; 95% CI: 1.26–3.89) but not in women (HR: 1.26; 95% CI: 0.77–2.06). Conversely, moderate/severe depressive symptoms were associated with a two times greater risk of developing aMCI in women (HR: 1.99; 95% CI: 1.05–3.77) but not in men (HR: 0.28; 95% CI: 0.04–2.11), possibly because of low statistical power in this subgroup.* **Conclusion:** *Results indicate that mild depressive symptoms in men and moderate/severe symptoms in women may represent a marker for future cognitive impairment.* (Am J Geriatr Psychiatry 2017; 25:13–22)

Key Words: Amnestic mild cognitive impairment, sex differences, depressive symptoms, Geriatric Depression Scale

Received January 11, 2016; revised August 25, 2016; accepted August 29, 2016. From the Einstein Aging Study and the Department of Neurology, Albert Einstein College of Medicine, Bronx, NY. Send correspondence and reprint requests to Dr. Richard B. Lipton, Department of Neurology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Rousso 332, Bronx, NY. e-mail: richard.lipton@einstein.yu.edu

http://dx.doi.org/10.1016/j.jagp.2016.08.022

INTRODUCTION

Mild cognitive impairment (MCI) is the intermediate state between normal cognitive aging and dementia; 10%–12% of individuals transition from MCI to dementia annually but not everyone transitions.[1,2] Amnestic MCI (aMCI) is characterized by clinically evident memory impairment, subjective memory complaints, and an increased risk of progression to Alzheimer-type dementia.[1,2]

One approach to preventing aMCI and Alzheimer-type dementia is to reduce risk by modifying remediable risk factors (lifestyle and psychosocial factors). Late-life depression may be a remediable risk factor for aMCI because it affects 25% of older adults,[3] it is amenable to treatment,[4] and it is associated with cognitive decline and MCI risk.[5–17] However, some studies did not find a relationship between depressive symptoms and cognitive outcomes,[18,19] whereas in others the relationship varied by sex.[5,9,13–16] Some reported that the relationship between depressive symptoms and cognitive outcomes was male-specific or stronger in men,[9,13,14] whereas others reported a female-specific relationship.[5,15,16]

Sex differences and differences in the method of ascertaining and defining depressive symptomology may contribute to heterogeneity among studies. Women have higher rates of depression[20,21] and more severe depressive symptoms than men,[20] perhaps partly because men under-report symptoms.[13] Additionally, most studies have used a single cut-point to dichotomize depressive symptoms, and this cut-point varies across studies. Many studies applied a conservative cut-point that creates a depressive symptom group with moderate/severe symptoms only, otherwise referred to as "clinically significant."[5,8,9,12–16] Others applied a less conservative cut-point that combines mild or subclinical symptoms and moderate/severe symptoms in the depressive symptom group.[6,22]

We examined the effect of baseline depressive symptoms, assessed by the 15-item Geriatric Depression Scale (GDS-15), on risk of incident aMCI in a sample of community-dwelling, older adults with up to 15 years of follow-up and how this effect differs by sex. Because the optimal cut-point for predicting incident aMCI is unclear and because men and women differ in depressive symptom severity,[20] we determined whether there is a depressive symptom dose effect in relation to aMCI risk in men and women. Using two cut-points similar to those previously employed, depressive symptoms were trichotomized into the categories of "no/low" (GDS-15 ≤ 2), "mild" (GDS-15 = 3–5), and "moderate/severe" symptoms (GDS-15 > 5). Thus, we examined sex differences in the risk of aMCI associated with mild and moderate/severe symptoms compared with no/low symptoms in older adults.

METHODS

Participants

Data are from the Einstein Aging Study (EAS), a longitudinal, community-based, cohort study of older adults (≥70 years) who were systematically recruited from Bronx, New York, beginning in 1993. EAS study design and recruitment has been described previously.[23] EAS inclusion criteria include being ambulatory, noninstitutionalized, proficient in English, and no sensory loss that interferes with study assessments. EAS participants undergo clinical, neuropsychological, and psychosocial assessments. Participants with dementia, aMCI, or nonamnestic MCI (naMCI) at study enrollment were excluded from analyses. Informed consents were approved by the local institutional review board and obtained at clinic visits according to study protocol.

Procedure

MCI and Dementia Diagnosis

Participants' cognitive status was evaluated annually, and clinical diagnoses were made at diagnostic case conferences attended by a study neurologist and neuropsychologist. An aMCI diagnosis required objective memory impairment on the Free Recall portion of the Free and Cued Selective Reminding Test[24] and/or the Logical Memory Subtest of the Wechsler Memory Scale-Revised[25] and subjective memory complaints with no functional impairment.[2] Objective memory impairment was defined using a previously established cut-score of ≤24 on the Free Recall portion of the Free and Cued Selective Reminding Test (range: 0–48)[24] and/or an age-adjusted score of ≤5 on the Logical Memory Test (range: 0–50).[25] Subjective memory complaints were determined according to self or informant