Depression and Risk of Alzheimer Dementia: A Longitudinal Analysis to Determine Predictors of Increased Risk among Older Adults with Depression

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Objective: *Older adults with depression are at increased risk of Alzheimer dementia, but predictors of increased risk remain incompletely understood. We aim to identify characteristics of older adults with depression most at risk of progressing to Alzheimer dementia. Identification of high-risk subgroups could facilitate future interventional strategies to reduce risk of Alzheimer dementia in older adults with depression.* **Methods:** *Using data from the National Alzheimer's Coordinating Center, 1,965 participants with clinically defined depression and mild cognitive impairment at baseline were followed until development of Alzheimer dementia or loss to follow-up.* **Results:** *Seven hundred and eighty (39.7%) developed Alzheimer dementia over a median follow-up duration of 27 months. In survival analyses, age (hazard ratio [HR] 1.04, 95% 1.03–1.05), baseline Mini-Mental State Exam (HR 0.85, 95% confidence interval 0.83–0.87), amnestic subtype of mild cognitive impairment (HR 1.66, 95% 1.30–2.12), presence of APOE4 allele (HR 1.99, 1.69–2.36), and presence of active depression within the last two years (HR 1.44, 95% confidence interval 1.16–1.79) were all independently associated with increased risk of Alzheimer dementia. Six hundred and fifty-six (41.7%) participants with mild cognitive impairment and active depression within the last two years developed Alzheimer dementia compared to 120 (31.6%) of those with a more remote history of depression.* **Conclusion:** *Older adults with depression and mild cognitive impairment demonstrated a high rate of progression to Alzheimer dementia over a relatively short duration of follow-up. Individuals with a combination of mild cognitive impairment and recently active depression are a particularly high-risk subgroup.* (Am J Geriatr Psychiatry 2018; 26:819–827)

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Highlights

- Older adults with depression are at increased risk of Alzheimer dementia (AD), but predictors of increased risk remain incompletely understood.
- We followed 1,965 older adults with depression and mild cognitive impairment (MCI) until development of AD or loss to follow-up.
- Age, baseline cognition, APOE4 genotype, amnestic subtype of MCI, and recency of depression (active depression within the last two years) were all independently associated with increased risk of AD.
- Individuals with a combination of MCI and recently active depression are at particularly high risk of AD and should be considered for preventive interventions.

INTRODUCTION

Depression in later life has been associated with an approximate two-fold increased risk of Alzheimer dementia (AD).[1] However, depression is a heterogeneous disorder, and it is not clear which clinical characteristics among older adults with depression are most closely associated with risk of AD.

Several mechanisms of association have been proposed to explain the excess risk observed among older adults with depression. It has long been proposed that chronic glucocorticoid exposure secondary to stress axis activation in depression may have direct neurotoxic effects. Some support for this proposition has been provided by studies documenting reductions in hippocampal volume among adults with persistent or recurrent depression.[2] Inflammatory activation and oxidative stress frequently occur as part of the depressive syndrome and have been associated with accelerated cognitive decline.[3,4] Depression is often associated with a greater burden of vascular risk factors, and bidirectional relationships between depression and vascular disease have been well described.[5] Alternately, it has been proposed that depression is not a true risk factor for AD but occurs as an early symptom of beta-amyloid deposition and neurodegenerative disease. In support of this, it has been observed that depression with first onset in later years is more likely to be associated with cognitive impairment, and increased depressive symptoms have been noted in individuals with normal cognition and increased cerebral beta-amyloid burden.[6,7] Conversely, several studies, including those with much longer durations of follow-up, have reported an increased risk of AD among those with early onset depression. In these studies, an incremental risk has been reported according to number of previous depressive episodes and severity of symptoms.[8–10]

In the general population, efforts to prevent or delay the onset of AD have largely focused upon individuals with mild cognitive impairment (MCI), and particularly those with amnestic MCI more frequently associated with early Alzheimer pathology. Depression has been reported to accelerate conversion from MCI to AD in a number of population studies, and therefore individuals with both depression and MCI potentially represent a high-risk group suitable for preventive interventions.[11] However, findings from population studies may not be readily generalized to those attending specialist services, as older adults referred to specialist clinics typically have more severe depression and greater comorbidity.[12] A relatively smaller number of studies in clinical samples have reported that between 8% and 85% of adults with depression and MCI may progress to AD.[13,14] The considerable variability observed in clinical studies likely reflects variations in patient samples and clinical processes between centers. To the best of our knowledge, no study to date has undertaken a large-scale analysis specifically focused on older adults with depression and MCI attending specialized memory services utilizing standardized clinical processes to describe the overall risk of progression to AD. If we are to successfully reduce the incidence of AD in this vulnerable population, it will be critical to determine the overall risk of progression to AD among patients with depression and MCI. It will also be important to characterize subgroups at greatest risk according to