Clinicians have long appreciated the links between depression, cognitive impairment, and development of Alzheimer’s disease (AD) and other dementias. More recently, investigators in the fields of epidemiology, genetics, neuroimaging, and neuropathology have sought to quantify the risk and to understand the underlying neurobiology of the relationship between depression and AD.

In this issue, Burke et al. (2016) used data from the National Alzheimer’s Coordinating Center (NACC) of the U.S. National Institute on Aging (NIA), a large database established nearly 20 years ago with information provided by 39 NIA-supported AD Centers, making it an important publicly available resource. The NACC was established in part to help investigators identify clinical and genetic risks associated with development of AD among cognitively normal individuals.

The authors accessed NACC data on 11,453 such participants, focusing on measures of depression, sleep, and apolipoprotein E (APOE) genotype. They found that cognitively normal patients with lifetime depression, especially those with current or recent depression, those with sleep disturbance and those with an APOE ε4 allele showed increased risk of developing AD. It is important to mention the definition of “depression” used in this study. As the authors note, the NACC database broadly defines depression as “depressive disorders for which a clinician was consulted, even if treatment or medication was not received.” Readers of the article should thus be aware that “depression” includes a wide variety of mood disorders.

This study’s findings have important clinical and scientific consequences. First, this paper provides confirmation in a large, well-characterized population of results from prior studies linking depression and incident AD. Second, the authors’ finding that lifetime risk of depression, but particularly presence of late life depression, confers increased AD risk, raises the same issues brought forth by Jorm 15 years ago (Jorm, 2001). Here, following a meta-analysis and qualitative review of studies of depression and AD risk, Jorm proposed three credible hypotheses to explain the relationship: (i) depression can be an early prodrome of dementia, (ii) depression brings forward the clinical manifestation of dementing diseases, and (iii) depression leads to damage to the hippocampus through a glucocorticoid cascade.

In the present study, the authors were able to control for important covariates, including demographic (sex, age, race), family history (parental dementia), and medical factors (presence of hypertension and hypercholesterolemia), along with APOE genotype. In these models, current (clinician-verified) and recent (past two years) depression demonstrated hazard ratios of greater than five for development of AD-related dementia. These results bolster the notion that for some individuals, onset of late life depression represents a prodrome of clinical AD, and as such is a harbinger of cognitive decline and dementia that will develop over the course of a few years. Consistent with the theory of depression as an AD prodrome, we previously reported an association between late-age onset depression and incident AD dementia, noting that risk ratios declined substantially with increasing time intervals between onset of depression and onset of dementia (Steffens et al., 1997).

It is noteworthy that Burke et al. also found that lifetime depression (which they defined as depression present 2 years or more prior to initial assessment) was associated with increased AD dementia risk, though the finding was stronger with more recent depression (hazard ratio of lifetime depression was 3.12 in the fully adjusted model). The finding of increased risk related to prior depression is consistent with the construct of depression as a neurobiological stressor, accompanied by hippocampal neurotoxic effects mediated through excess circulating glucocorticoids. This model was proposed by Sheline et al. (1999), who found that among middle aged to older women with a history of recurrent major depression, lifetime duration of depression was highly and inversely associated with hippocampal volume on magnetic resonance imaging (MRI). In a later prospective study, we found that older depressed patients showed greater hippocampal volume reduction on longitudinal MRI scans over 2 years compared with non-depressed older adults, and that among patients, two-year hippocampal change was associated with subsequent cognitive decline (Steffens et al., 2011).

Another key finding in the present study is the relationship between sleep disturbance and AD risk.
Given the high prevalence of sleep disturbance in depression, it is not clear to what extent sleep disturbance represents a risk separate from depression. Future studies are needed to better understand the role of sleep in development of AD, either as an independent risk factor or as a key depressive symptom that might further unlock the link between depression and AD.

Clinicians may rightly ask how they might best use this information when caring for older depressed adults. First, one should keep in mind the importance of modifiable factors in prevention of AD that include diabetes, mid-life hypertension, mid-life obesity, smoking, depression, low educational attainment, and physical inactivity (Barnes and Yaffe, 2011). In this study, the authors estimated that more than 10% of AD cases worldwide may be attributable to depression, such that a 10% reduction in depression prevalence could potentially result in more than 325,000 fewer AD cases. The notion of the large public health impact in preventing AD should provide further encouragement to clinicians to boldly detect, assess, and treat depression.

However, evidence that late life depression may represent a prodrome of Alzheimer’s dementia is a sobering notion for clinicians caring for older adults. Increased vigilance in screening for signs and symptoms of cognitive decline among depressed elderly now becomes an imperative. The question arises as to what additional screening measures might become standard of care. For example, should older depressed subjects routinely receive neuropsychological testing? Several studies help make a strong case that memory should be evaluated, as the combination of depression mild cognitive impairment, particularly in the memory domain, imparts a high risk of emergent dementia (Modrego and Ferrández, 2004; Steffens et al., 2014).

Another question that clinicians confront is whether to order APOE genotyping in older depressed patients. The finding by Burke et al. of a significant interactive effect of clinician-verified depression and APOE on incident AD risk supports the notion of genotyping older depressed patients; however, it is likely more study is needed. Perhaps future research can identify a population for whom genotyping would be most clinically useful, e.g. depressed patients with subjective or objective memory problems or those with a family history of AD.

In sum, this article adds important new insights into the complex relationship between depression, sleep, and development of AD. This paper on one hand helps firm up prior the literature, identifying a clear relationship between depression, especially late-age onset depression, and AD, while also raising new questions about the role of APOE genotype and sleep disturbance as putative and testable risk factors that could move the field forward in helping to unravel the knotty links between late-life depression and dementia.

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References


