

Depression and Risk of Dementia: Exploring the Interface

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Neuropsychiatric symptoms have not been part of the defining diagnostic criteria of dementia or mild cognitive impairment (MCI), but their characterization and importance in the preclinical stages of Alzheimer's disease and presentation of prodromal states such as MCI and potential conversion to dementia continue being established.¹ Subjects progressing to dementia have a higher prevalence of psychopathology than those who remain stable or improve, and thus neuropsychiatric symptoms appear to be a predictor of progression to dementia alongside established factors such as apolipoprotein E (*APOE*) $\epsilon 4$ carrier status, features of memory function, cerebrospinal fluid $A\beta$ /tau ratio, amyloid imaging, and magnetic resonance imaging volumetric measurements of the hippocampal formation.¹⁻³

Depression and cognitive disorders are the most common neuropsychiatric disorders in later life. Their co-occurrence most likely exceeds chance. On balance, data suggest that the presence of depressive symptoms confers higher risk of developing both MCI and dementia and that late-life depression, MCI, and dementia could represent a clinical continuum.⁴ The critical question is how the presence of depression modifies the risk of developing MCI or progressing from MCI to dementia. We struggle with multiple issues surrounding this interface. The exact mechanism of the interconnect between depression and cognitive impairment remains obscure. Proposed mechanisms include depression occurring as a psychological reaction to the awareness of gradual loss of abilities, similar to other function-limiting medical disorders; depression unmasking incipient cognitive impairment; depression causing pathophysiologic changes in brain tissue; and depression being a manifestation of a common neuropathologic condition that also results in cognitive decline.⁵ There is still more to do to fully explore the true nature of this relationship.

As the dementia epidemic is upon us, it will be extremely important to prevent even some of those cases. We do not yet fully know if treatment interventions or risk modifications are helpful in the short or long run—this question is a grand challenge, and one that urgently needs answers. As current pharmaceutical treatment of dementia provides only modest symptomatic improvement with limited impact on the underlying neuropathologic process, risk reduction or early intervention—including depression identification and treatment—may be the most promising approach until we have effective disease-modifying agents.⁶

In *JCP* this month, Locke and colleagues⁷ publish an article that advances our understanding in this important area. In a cleverly designed study, they address whether depressive symptomatology escalates preclinically concurrent with accelerated memory decline. Using the Arizona *APOE* Cohort, the investigators compared cognitively and functionally normal subjects who were free of major depression at study entry. All included participants remained cognitively and functionally normal at subsequent follow-up visits. Longitudinal changes in depression measures were assessed in *APOE* $\epsilon 4$ carriers as compared to noncarriers. Incident depression was estimated using accepted clinical cutoffs on depression measures and initiation of antidepressant medications.

The same group of investigators previously showed that age-related cognitive decline accelerates preclinically in heterozygote and homozygote *APOE* $\epsilon 4$ carriers who remain cognitively normal.⁸ Consequently, a similar accelerated increase in depressive symptoms would be anticipated if depression is intrinsic to the Alzheimer's disease syndrome.

The 2 study groups were well balanced for most baseline characteristics. There were more Hispanic/Latino participants in the noncarrier group and, as expected, a higher percentage of reported family history of Alzheimer's disease in the *APOE* $\epsilon 4$ carrier group. Adjusting the statistical models for those differences did not change the results.

Longitudinal analyses of depression scale scores did not differ between the *APOE* $\epsilon 4$ carriers and noncarriers. Slight increase in depressive scores was seen with age, regardless of genotype. There was also no significant difference between the groups in emergence of incident depression. These findings remained consistent using different statistical approaches and adjustments.

In conclusion, the investigators found no difference in measures of depression between *APOE* $\epsilon 4$ carriers and noncarriers who remained cognitively and functionally normal during the observation period. Previously, in the same cohort, the *APOE* $\epsilon 4$ carriers were shown to have accelerated age-related memory decline despite not crossing the boundary to abnormal cognitive function.⁸ If depression is intrinsic to Alzheimer's disease, we would expect a gradual increase in depressive symptoms and incident depression even at this preclinical stage and that this change would happen in tandem with the cognitive changes.

It remains possible that depressive symptomatology may accelerate later in the preclinical course or prodromal course when memory decline becomes symptomatic (MCI). Not enough participants in the Arizona *APOE* Cohort had

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progressed to symptomatic MCI at the time this analysis was conducted to address that question, but the cohort continues to be followed.

It is useful to characterize the interface between depression and risk of dementia further for both practical and theoretical purposes. Recognition of risk factors for late-life cognitive decline and early identification of clinical presentations that signal higher risk allow on the one hand for possible modulation of the risk factors and on the other hand for earlier treatment. Better understanding of the relationship of neuropsychiatric symptoms such as depression to the pathophysiology of cognitive decline has implications regarding critical nuances in studying and interpreting these transitional states and developing possible future treatment interventions.

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