Disputes & Debates: Editors' Choice

Editors' Note: Cognitive Activity and Onset Age of Incident Alzheimer Disease Dementia

In their prospective observational cohort study, Dr. Wilson et al. explored the relationship between cognitive activity and incident dementia among consecutive elderly patients from the Rush Memory and Aging Project. The investigators hypothesized that self-reported higher levels of cognitive activity such as reading would be associated with older age of dementia onset in patients with clinical Alzheimer disease (AD). Of the 1903 included patients, 457 (24%) developed possible or probable AD over a mean of 6.8 years (±4.6) of follow-up. In the primary analysis, higher cognitive activity was independently associated with later dementia onset in the accelerated failure time model (estimate 0.026, 95% CI 0.013–0.039). This relationship persisted in multiple other exploratory models, including a model that accounted for sex and educational level, a model which adjusted for early-life cognitive activity (which bore no independent association with dementia), and a model excluding patients with *possible* AD from outcome events. When the top 10th percentile of patients with high cognitive activity were compared with the bottom 10th percentile, patients in the top 10th percentile developed dementia at a mean of 5 years later (93.6 vs 88.6 years). Dr. Krauss suggests that the hypothesized direction of the association (more cognitive activity → delay in dementia diagnosis) may possibly be *reversed* and that the low level of cognitive activity in late life may be an early sign of dementia. In an attempt to disprove this alternative hypothesis, the investigators analyzed the relationship between cognitive activity with markers of AD at enrollment and found no association. The authors agree with Dr. Krauss that their study cannot fully disprove the reverse causality hypothesis; however, these data complement previous research that continues to build the argument for an important relationship between cognitive activity and the subsequent symptoms of dementia.

James E. Siegler III, MD, and Steven Galetta, MD
Neurology® 2022;98:170. doi:10.1212/WNL.0000000000013125

Reader Response: Cognitive Activity and Onset Age of Incident Alzheimer Disease Dementia

Howard Krauss (Santa Monica, CA)
Neurology® 2022;98:170–171. doi:10.1212/WNL.0000000000013131

The authors of this study note that postmortem markers of Alzheimer disease and other dementias may be distinct from the self-report measure of cognitive activity, which they state provides no support for the reverse-causality hypothesis.[1] The authors suggest that cognitive activities may lead to changes in brain structure and function that could enhance cognitive reserve. Is it not just as likely that there are features of brain structure or function that have not been discerned in postmortem evaluation, thus failing to fully disprove the reverse-causality hypothesis?

Author disclosures are available upon request (journal@neurology.org).

1. Wilson RS, Wang T, Yu L, Grodstein F, Bennett DA, Boyle PA. Cognitive activity and onset age of incident Alzheimer disease dementia. *Neurology*. 2021;97(9):e922-e929.

Author Response: Cognitive Activity and Onset Age of Incident Alzheimer Disease Dementia

Robert S. Wilson (Chicago)
Neurology® 2022;98:171. doi:10.1212/WNL.0000000000013133

We appreciate the interest in our research.[1] In the cohort study of older persons who developed incident Alzheimer disease (AD), we found that a lower level of cognitive activity was associated with earlier age of dementia onset.[1] According to the reverse-causality hypothesis, a low level of cognitive activity is not a risk factor for AD but an early sign of the disease. As a test of this hypothesis, we computed the correlations of cognitive activity at the time of study enrollment with markers of AD and related dementias from a postmortem neuropathologic examination. These correlations were not significant, which we concluded provided no support for the reverse-causality hypothesis.

Dr. Krauss notes in their comment that the study fails to fully disprove the reverse causality hypothesis because of possible changes in brain structure or function that are not captured on postmortem evaluation. We agree that our study does not disprove the reverse-causality hypothesis. However, observations in this research and previous studies that measurements of cognitive activity are related to risk of dementia but not to the neuropathologies thought to underlie dementia is certainly inconsistent with the reverse-causality hypothesis.[2,3] Furthermore, one may question the scientific value of a hypothesis if it depends on disease markers that cannot be specified and are apparently unrelated to neuropathologic markers traditionally associated with AD and related dementias.

1. Wilson RS, Wang T, Yu L, Grodstein F, Bennett DA, Boyle PA. Cognitive activity and onset age of incident Alzheimer disease dementia. *Neurology*. 2021;97(9):e922-e929.
2. Wilson RS, Scherr PA, Schneider JA, Tang Y, Bennett DA. Relation of cognitive activity to risk of developing Alzheimer disease. *Neurology*. 2007;69(20):1911-1920.
3. Wilson RS, Boyle PA, Yu L, Barnes LL, Schneider JA, Bennett DA. Life-span cognitive activity, neuropathologic burden, and cognitive aging. *Neurology*. 2013;81(4):314-321.

CORRECTION

Clinical Utility of Structural Connectomics in Predicting Memory in Temporal Lobe Epilepsy

Neurology® 2022;98:171. doi:10.1212/WNL.0000000000011076

In the article "Clinical Utility of Structural Connectomics in Predicting Memory in Temporal Lobe Epilepsy" by Balachandra et al.,[1] the fifth author's name should appear as "Sanam J. Lalani." The authors regret the previous omission of this author's middle initial.

Reference

1. Balachandra A, Kaestner E, Bahrami N, et al. Clinical utility of structural connectomics in predicting memory in temporal lobe epilepsy. *Neurology*. 2020;94(23):e2424-e2435.

Author disclosures are available upon request (journal@neurology.org).