Supplementary Online Content


**eAppendix 1.** Methods  
**eAppendix 2.** Results

This supplementary material has been provided by the authors to give readers additional information about their work.
**eAppendix 1. Methods**

**Clinical Assessments**

All participants were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer’s disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date in formation, see www.adni-info.org.
Each participant was formally evaluated using eligibility criteria that are described in detail elsewhere (http://www.adni-info.org/index.php?option=com_content&task=view&id=9&Itemid=43). The institutional review boards of all participating institutions approved the procedures for this study. Written informed consent was obtained from all participants or surrogates. Experienced clinicians conducted independent semi-structured interviews with the participant and a knowledgeable collateral source that included a health history, neurological examination, and a comprehensive neuropsychological battery. The current study was restricted to participants who were diagnosed at baseline as cognitively normal (n = 91) or as having amnestic mild cognitive impairment (MCI) (n = 150).

**MR Image Processing**

All ADNI MRI scans were acquired at multiple sites using either a GE, Siemens, or Philips 1.5T system. Parameter values vary depending on scanning site and can be found at http://www.loni.ucla.edu/ADNI/Research/Cores/. Multiple high-resolution T1-weighted volumetric MRI scans were collected for each subject and the raw DICOM images were downloaded from the public ADNI site (http://www.loni.ucla.edu/ADNI/Data/index.shtml).
Appendix 2. Results

Analysis of CSF p-tau_{181} and CSF Aβ_{1-42} as continuous variables

To ensure that our results were not due to a categorical treatment of variables, we examined CSF p-tau_{181p} and CSF Aβ_{1-42} as continuous variables. Using a mixed effects model, we concurrently examined interactive effects of CSF clusterin and CSF Aβ_{1-42} and CSF clusterin and CSF p-tau_{181p} on entorhinal cortex atrophy, co-varying for age, sex, carrier status for the ε4 allele of apolipoprotein E (APOE ε4), group status (MCI vs. HC), and disease severity (CDR-Sum of Boxes). Consistent with the results obtained from categorizing subjects on the basis of cutoff values, we found a significant interaction between CSF clusterin, CSF Aβ_{1-42} levels and time on entorhinal cortex volume loss (β-coefficient = 2.5 x 10^{-4}, SE = 1.0 x 10^{-4}, p = 0.01); the interaction between CSF clusterin, CSF p-tau_{181p} and time was not significant (β-coefficient = 5.5 x 10^{-4}, SE = 4.2 x 10^{-4}, p = 0.89).

Subgroup Analyses with the MCI and HC cohorts

When CSF p-tau_{181p} and CSF Aβ_{1-42} were treated as continuous variables, we found a significant interaction between CSF clusterin, CSF Aβ_{1-42} levels and time (MCI: β-coefficient = 3.9 x 10^{-4}, SE = 1.9 x 10^{-4}, p = 0.03; HC: β-coefficient = 3.5 x 10^{-4}, SE = 1.3 x 10^{-4}, p = 0.006) and a non-significant interaction between CSF clusterin, CSF p-tau_{181p} levels, and time (MCI: β-coefficient = -4.1 x 10^{-4}, SE = 6.1 x 10^{-4}, p = 0.95; HC: β-coefficient = -3.6 x 10^{-4}, SE = 5.6 x 10^{-4}, p = 0.52).