DNA Methylation and Protein Markers of Chronic Inflammation and Their Associations With Brain and Cognitive Aging

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Cite as: Neurology® 2021;97:e2340-e2352. doi:10.1212/WNL.0000000000012997

Study Question
Does an epigenetic measure of inflammation, such as a DNA methylation (DNAm) signature of C-reactive protein (CRP), show stronger associations with brain structure and function than serum CRP?

What Is Known and What This Paper Adds
Low-level chronic inflammation increases with age and is associated with cognitive decline. Researchers have traditionally relied upon acute inflammatory proteins such as CRP to measure chronic inflammation, but these are highly variable and phasic, which can lead to misclassification of individuals’ baseline levels of inflammation in population cohorts. This investigation’s findings indicate that DNAm profiles of inflammation can serve as tools to index cumulative inflammatory exposure and that there may be more widespread consequences of chronic inflammation on brain health than previously thought.

Methods
For this cross-sectional study, structural and diffusion MRI and cognitive and inflammation data were obtained from 521 healthy older adults (mean 72.4 years, SD 0.716) from The Lothian Birth Cohort 1936. These participants were free from neurodegenerative diagnoses at baseline and were excluded if they had a self-reported history of neurologic disease, evidence of cognitive decline, or acute infection or illness at the time of blood draw. The primary outcome was variation in volumetric MRI measurements (adjusting for intracranial volume, age, and sex) explained by serum CRP or DNAm CRP. Linear models were used to examine the inflammation–brain health associations and mediation analyses were performed to interrogate the relationship among chronic inflammation, brain structure, and cognitive functioning.

Results and Study Limitations
Higher levels of DNAm CRP were linked with widespread neuroimaging markers of cognitive aging, including global and regional brain atrophy, alterations in white matter microstructure, and increased white matter hyperintensities. In contrast, serum CRP was not found to be associated with any MRI metrics. DNAm CRP scores were also associated with global and domain-specific cognitive functions (processing speed, visuospatial ability, and verbal memory). Variation in brain structure was found to partially mediate this association, supporting the hypothesis that chronic inflammation may contribute to neurodegenerative brain changes, which underlie differences in cognitive ability in later life. As this study was cross-sectional, it remains to be determined whether the link between chronic inflammation and brain structure is causal, consequential, or an epiphenomenon of cognitive aging. Other limitations include the homogeneity and relative health of the LBC1936 cohort, limiting the degree to which these findings can be extrapolated to other populations.

Study Funding and Competing Interests
This study was funded by the Wellcome Trust, UK Medical Research Council, and Age UK. The authors report no competing interests. Go to Neurology.org/N for full disclosures.
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Neurology 2021;97:e2340-e2352 Published Online before print November 17, 2021
DOI 10.1212/WNL.0000000000012997

This information is current as of November 17, 2021