Association of Midlife Inflammatory Markers With Cognitive Performance at 10-Year Follow-up

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Study Question
Does low-grade inflammation, measured in midlife, predict poorer performance and greater decline in cognitive tests after a 10-year follow-up?

What Is Known and What This Paper Adds
Low-grade inflammation has been associated with cognitive decline and dementia, but there is mixed evidence regarding the associations between elevated inflammatory markers and cognitive decline. Many of the previous studies have been cross-sectional or have focused on older populations and have used various methods to measure low-grade inflammation. This study’s results show in prospective cohort design that low-grade inflammation measured in midlife with tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) is associated with worse performance and bigger decline in cognitive tests after a 10-year follow-up.

Methods
This longitudinal prospective cohort study was based on the Finnish multidisciplinary Health 2000 examination survey, its supplemental examination on a subpopulation in 2001–2002, and its follow-up survey, Health 2011 study, conducted by the Finnish Institute for Health and Welfare. The present study included individuals who had attended all 3 investigations (n = 915). At baseline, data on participants’ risk factors for cognitive decline were obtained, and IL-6, TNF-α, and high sensitivity C reactive protein (hs-CRP) were measured. Cognitive performance at baseline and at the follow-up was assessed with categorical verbal fluency (VF), word-list learning (WLL), and word-list delayed recall from the Consortium to Establish a Registry for Alzheimer’s Disease cognitive test battery. Associations between low-grade inflammation and cognitive performance were analyzed with multivariable linear models adjusted for age, sex, education, APOEε4 genotype, type 2 diabetes, hypertension, hypercholesterolemia, body mass index, depressive symptoms, and smoking.

Results and Study Limitations
Nine hundred fifteen participants aged 45–74 years (median age 54 years, 55% women) were included in the analysis.

<table>
<thead>
<tr>
<th>Table</th>
<th>Association Between Inflammation and Cognition</th>
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<tr>
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<td>Verbal fluency (β) (95% CI)</td>
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<td>Fully adjusted model</td>
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<tr>
<td>IL-6</td>
<td>-1.14 (-1.90 to -0.37)**</td>
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<tr>
<td>TNF-α</td>
<td>-1.78 (-3.10 to -0.47)**</td>
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<td>hs-CRP</td>
<td>-0.24 (-0.79 to 0.31)</td>
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Abbreviations: IL = interleukin; TNF = tumor necrosis factor.
N = 915. Estimates (β) and CI are derived from linear regression analysis and are adjusted for a multivariate linear model.
*p < 0.05, **p < 0.01.

Both higher IL-6 and TNF-α at baseline were associated with worse performance in VF and WLL at the 10-year follow-up. Elevated IL-6 was also associated with a greater decline in VF and WLL after a 10-year follow-up (VF: β = -0.81, p = 0.01; WLL: β = -0.53, p = 0.008). Baseline TNF-α was not associated with cognitive decline, and hs-CRP was not associated with cognitive performance or decline after 10 years. The results suggest that low-grade inflammation in midlife is an independent risk factor of poorer cognitive performance later in life. Of the studied markers, IL-6 and TNF-α seem to be stronger predictors for cognitive performance and decline than hs-CRP. The present study’s limitations include that the inflammatory markers were measured only at baseline and that no data of biomarkers and other measures of Alzheimer disease pathology were collected.

Study Funding and Competing Interests
The authors received funding from Finnish Governmental Research Funding and nonprofit foundation. They report no additional competing interests. Go to Neurology.org/N for full disclosures.