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Functional Medicine

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## CHRONIC LOW-GRADE INFLAMMATION, APOE4 AND ALZHEIMER RISK

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### Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers.

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**Abstract**

**IMPORTANCE:** The association between peripheral inflammatory biomarkers and Alzheimer disease (AD) is not consistent in the literature. It is possible that chronic inflammation, rather than 1 episode of inflammation, interacts with genetic vulnerability to increase the risk for AD.

**OBJECTIVE:** To study the interaction between the apolipoprotein E (ApoE) genotype and chronic low-grade inflammation and its association with the incidence of AD.

**DESIGN, SETTING, AND PARTICIPANTS:** In this cohort study, data from 2656 members of the Framingham Heart Study offspring cohort (Generation 2; August 13, 1971-November 27, 2017) were evaluated, including longitudinal measures of serum C-reactive protein (CRP), diagnoses of incident dementia including AD, and brain volume. Chronic low-grade inflammation was defined as having CRP at a high cutoff level at a minimum of 2 time points. Statistical analysis was performed from December 1, 1979, to December 31, 2015.

**MAIN OUTCOMES AND MEASURES:** Development of AD and brain volumes.

**RESULTS:** Of the 3130 eligible participants, 2656 (84.9%; 1227 men and 1429 women; mean [SD] age at last CRP measurement, 61.6 [9.5] years) with both ApoE status and longitudinal CRP measurements were included in this study analysis. Median (interquartile range) CRP levels increased with mean (SD) age (43.3 [9.6] years, 0.95 mg/L [0.40-2.35 mg/L] vs 59.1 [9.6] years, 2.04 mg/L [0.93-4.75 mg/L] vs 61.6 [9.5] years, 2.21 mg/L [1.05-5.12 mg/L]; P < .001), but less so among those with ApoE4 alleles, followed by ApoE3 then ApoE2 genotypes. During the 17 years of follow-up, 194 individuals (7.3%) developed dementia, 152 (78.4%) of whom had AD. ApoE4 coupled with chronic low-grade inflammation, defined as a CRP level of 8 mg/L or higher, was associated with an increased risk of AD, especially in the absence of cardiovascular diseases (hazard ratio, 6.63; 95% CI, 1.80-24.50; P = .005), as well as an increased risk of earlier disease onset compared with ApoE4 carriers without chronic inflammation (hazard ratio, 3.52; 95% CI, 1.27-9.75; P = .009). This phenomenon was not observed among ApoE3 and ApoE2 carriers with chronic low-grade inflammation. Finally, a subset of 1761 individuals (66.3%) underwent brain magnetic resonance imaging, and the interaction between ApoE4 and chronic low-grade inflammation was associated with brain atrophy in the temporal lobe (β = -0.88, SE = 0.22; P < .001) and hippocampus (β = -0.04, SE = 0.01; P = .005), after adjusting for confounders.

**CONCLUSIONS AND RELEVANCE:** In this study, peripheral chronic low-grade inflammation in participants with ApoE4 was associated with shortened latency for onset of AD. Rigorously treating chronic systemic inflammation based on genetic risk could be effective for the prevention and intervention of AD.

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"**Results**: *1227 men and 1429 women (mean age at last CRP measurement, 61.6 years) with both ApoE status and longitudinal CRP measurements were included in this study analysis. During the 17 years of follow-up, 194 individuals (7.3%) developed dementia, 152 (78.4%) of whom had Alzheimer's disease (AD). ApoE4 coupled with chronic low-grade inflammation, defined as a CRP level of 8 mg/L or higher, was associated with an increased risk of AD, especially in the absence of cardiovascular diseases (hazard ratio, 6.63), as well as an increased risk of earlier disease onset compared with ApoE4 carriers without chronic inflammation (hazard ratio, 3.52). This phenomenon was not observed among ApoE3 and ApoE2 carriers with chronic low-grade inflammation*.

**Conclusions and Relevance**: *In this study, peripheral chronic low-grade inflammation in participants with ApoE4 was associated with shortened latency for onset of AD. Rigorously treating chronic systemic inflammation based on genetic risk could be effective for the prevention and intervention of AD.*"