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Alzheimer's Disease Polygenic Scores Predict Changes in Executive Function and Episodic Memory Across 12 years in Late Middle Age

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ABSTRACT:

Genome-wide association studies (GWAS) are instrumental in quantifying genetic influences underlying Alzheimer's disease (AD), and applications of *polygenic scores* (PRS) derived from GWAS have already shed light on early disease pathology. What remains unclear is how AD-PRS relate to objectively measured cognitive changes across midlife. We examined 1388 men in the Vietnam Era Twin Study of Aging (VETSA) who were cognitively normal at their first assessment and had up to 3 cognitive assessments across 10-12 years (mean ages 56, 62, and 68). Latent growth models of executive function were based on 6 tasks spanning inhibition, shifting, and working memory subdomains and growth models of episodic memory were based on 7 subtests from the Logical Memory, Visual Reproductions, and California Verbal Learning tests. The AD-PRS was based on Kunkle et al. (2019), $p<5x10^{-8}$ threshold. Results demonstrated that baseline executive function (r=.11) and memory (r=-.07) were not associated with AD-PRS. Importantly, individuals with higher AD-PRS had sharper declines in executive functioning (r= -.38, 95% CI [-.64, -.14]) and episodic memory (r= -.20, 95% CI [-.37, -.03]) from midlife to early old age. Associations were driven by ApoE and were nonsignificant after excluding the ApoE region from the AD-PRS. These findings highlight the importance of considering executive function changes in midlife, especially for predicting disease progression and AD-related biology. Executive functions are one of the first cognitive abilities to decline in midlife in normal aging. This study is among the first to demonstrate that this early decline also relates to AD genetic influences.

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