Association of Polygenic Risk Score for 5 Diseases with Alzheimer Disease Progression, Biomarkers, and Amyloid Deposition

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Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder influenced by both genetic and environmental factors. Conditions such as type 2 diabetes (T2D), cardiovascular disease, obesity, depression, and obstructive sleep apnea (OSA) have been associated with increased risk and progression of AD. To explore the role of genetic susceptibility to these comorbidities, a retrospective analysis was conducted using data from 752 non-Hispanic White participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with whole-genome sequencing data. Polygenic risk scores (PRSs) were generated for OSA, T2D, coronary artery disease (CAD), major depression, and body mass index (BMI). In a subset of 463 participants with mild cognitive impairment (MCI) at baseline, a higher OSA PRS—independent of BMI—was significantly associated with increased risk of progression to AD at both 3- and 5-year follow-ups. No significant associations were observed for PRSs related to T2D, CAD, depression, or BMI. Participants in the highest OSA PRS quartile showed greater PET amyloid burden, more rapid cognitive decline, and elevated levels of CSF amyloid-β42 (Aβ42), phosphorylated tau (p-tau), visinin-like protein 1 (VILIP-1), tumor necrosis factor receptor 1 (TNFR1), and plasma neurofilament light (NfL). These findings highlight a potential role for OSA-related genetic pathways in modifying AD pathophysiology and progression. However, the lack of objective OSA diagnoses and the modest sample size limit interpretation and call for further validation.

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