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TITLE: Exploring the genetic overlap underlying Alzheimer's disease and hearing loss

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ABSTRACT:

Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by a progressive decline in neuronal function that leads to cognitive, behavioural and motor dysfunction over time. It is well established that several non-modifiable risk factors for AD, such as age and genetics, exist. However, as these cannot be targeted to reduce

disease progression, emphasis on identifying modifiable risk factors is paramount. Hearing loss has recently been identified as the potentially largest modifiable risk factor for AD (OR 1.94), estimated to account for a similar increase in AD risk to APOE  $\epsilon$ 4 (1). However, the mechanisms underlying this association are still poorly understood. In this study, we investigate whether the relationship between hearing loss and AD is due to shared genetic aetiology, and seek evidence for a causal relationship between the traits. We found a significant genetic correlation between hearing difficulty, the use of a hearing aid and AD and polygenic risk score for AD was able to significantly predict hearing loss in an independent cohort. Additionally, regions of the genome involved in inflammation and immune response were identified to be shared between hearing difficulty and AD using Pairwise-GWAS. However, causality tests found no significant evidence of a causal relationship between these traits in either direction. Overall, these results currently do not support the hypothesis that hearing difficulty is a modifiable risk factor for AD and that the simple management of hearing loss will likely not mitigate AD risk.

- 1) Livingston G *et al.* Dementia prevention, intervention, and care. *The Lancet*. 2017;390(10113):2673-734.

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