Gene-environment interactions in Alzheimer's Disease (AD)

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Introduction:

AD is characterised by significant volume loss of cortex and hippocampal areas, with large-scale neuronal loss and dysfunction. This is attributed to high deposition rates of Aβ plaques extracellularly and hyperphosphorylated tau intracellularly in the brain. These result in greater neuroinflammation due to production of reactive oxygen species, mitochondrial dysfunction and oxidative stress.

Modifiable risk factors

These are factors (identified in The Lancet Commission on Dementia 2020) that could provide protection against AD onset, in which individuals may take action to help mitigate or prevent its pathogenesis. Those underlined are additional factors which were of interest.

1. Air pollution
2. Alcohol intake
3. Body Mass Index (BMI)
4. Hearing impairment
5. Depression
6. Diabetes
7. Diet
8. Education
9. Exercise
10. Hypertension
11. Sleep
12. Smoking
13. Social contact/support
14. Traumatic brain injury (TBI)/Head injury
15. Townsend Index

Objective of study

My study aims to explore the relationship between genetic risk, parameterised as polygenic risk score (PRS) and homozygote status for a major risk gene, Apolipoprotein E ε4 (APOE4), and the incidence of AD.

Methodology

My study population was from the UK Biobank, comprising a population-based cohort of 500,000 participants aged 40-69 years with data collected on their self-reported lifestyle and medical data. The final dataset filtered out neurological conditions, genetically related people, individuals lacking a PRS score, study withdrawals, individuals lost to follow up and any AD in the dataset who had prevalent dementia. Data analysis was performed on individuals with homozygous APOE4 status as well. As PRS was only valid for white ethnicity, I filtered out non-white and non-European ethnicities for data analysis (Figure 1)

Results

1. AD risk and risk factors

12/15 of the risk factors posed a significant risk to AD onset, namely high air pollution, hearing impairment, depression, diabetes, high meat intake. lack of secondary education, hypertensive,. below 6 hours of sleep and over 8 hours of sleep, smoking, social isolation, TBI and high Townsend Index (Figure 2)

2. Genetics and AD risk

4th and 5th quintiles had a significantly higher odds ratio (OR) for AD. Furthermore, individuals in the highest PRS quintiles were at an approximately **6x i**ncreased risk of AD compared to the lowest quintile (Figure 3)

3. Multiplicative interactions with AD PRS and risk factors

Analysis was done at false discovery rate (FDR) <0.10. There was evidence that diabetes, obesity, head injury and Townsend index are significant, but only the former three were significant at the FDR level. These suggest that diabetes, obesity, and head injury may be a more significant risk factor among individuals with low genetic risk of AD.

4. Multiplicative interactions with APOE4 homozygote status

Only hearing impairment showed significance at FDR level, however it is a negative interaction. There is nominal evidence that diabetes and head injury have negative interaction with APOE4. Again, these results suggest that diabetes and head injury may pose a significant risk factor among individuals with low genetic risk of AD, whilst hearing impairment could pose a more significant risk among those who are non-APOE4 homozygote. These results largely mirrored those exhibited by PRS, with diabetes and head injury showing negative interactions.



Figure 1: Filtering process to get final dataset

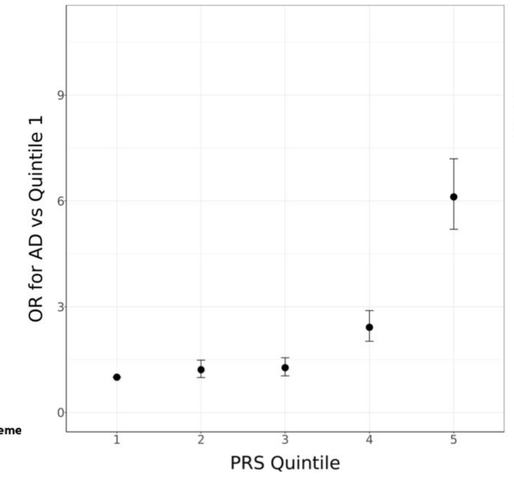


Figure 3: Odds ratio for AD by PRS quintile

Discussion

My results show that there are certain modifiable factors which play a vital role in contributing to AD onset risk, as well as the presence of APOE4 and PRS being significant. I investigated the interaction of modifiable factors and PRS and found that diabetes, obesity, head injury and high Townsend Index have a significant negative interaction with PRS, with increased risk among individuals with low genetic risk of AD.

An unusual trend I noticed in my results is how cardiovascular-related factors (e.g BMI) tend to have a negative interaction with AD risk, whilst social factors (e.g alcohol,) interact positively. This could be due to cardiovascular-related illnesses generally being harmful to anyone regardless of genetic risk, yet also presenting a further increased risk factor due to how it affects the vasculature and perfusion of the brain and influencing neuronal health. Meanwhile, social factors like smoking and alcohol intake might heighten the risk as they could play a substantive role in epigenetics interaction.

Furthermore,, I observed a significant negative interaction of APOE4 status and hearing impairment, with nominal evidence of negative interactions for both diabetes and head injury.

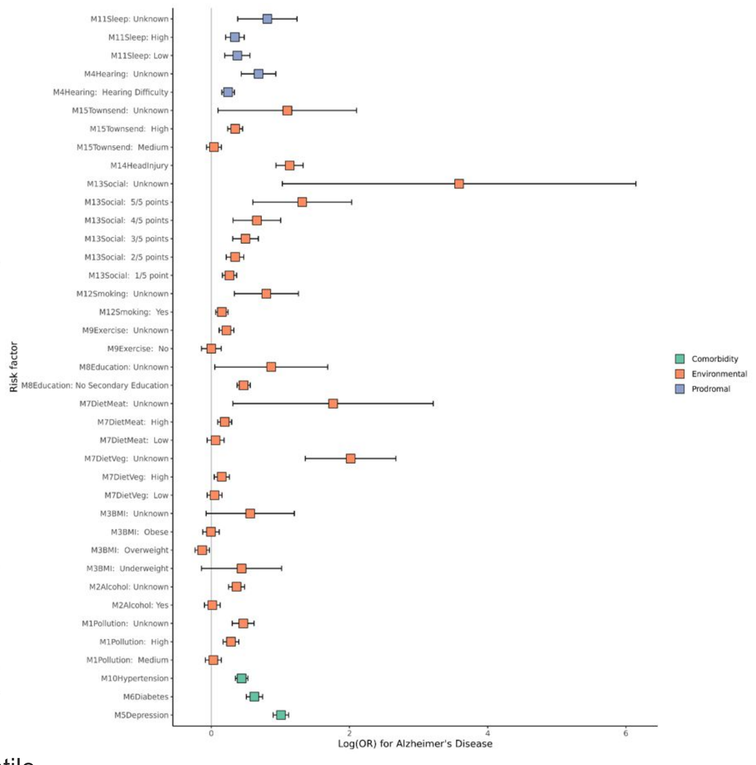


Figure 2: Associations of risk factors and incident cases of AD