Distinct APOE4-stratified modifiable risk profiles for Alzheimer's disease

Background

Alzheimer's disease (AD) results from interactions between age, genetic susceptibility and modifiable risk factors. APOE4 is established as the strongest common genetic risk factor for AD, but modifiable pathways contributing to risk may differ between carriers and non-carriers. We aimed to characterise and compare modifiable risk-factor profiles associated with AD across APOE4 strata within UK Biobank.

Methods

We conducted phenome-wide association analyses of approximately 15,000 modifiable exposures against AD status, stratified by APOE4 carrier status. False discovery rate correction was applied within each stratum. We extracted the most significant associations from carriers and non-carriers and compared clustering patterns across key modifiable domains, including cardiovascular, pulmonary, metabolic, lifestyle, and clinical phenotypes.

Results

Both strata showed large numbers of significant modifiable associations with AD and substantial overlap across lifestyle and metabolic factors. However, the distribution of risk-factor domains differed markedly between groups. APOE4 carriers demonstrated a concentration of cardiovascular and vascular-metabolic traits, including blood pressure measures, vascular disease codes and cardiometabolic medication exposures. In contrast, APOE4 non-carriers showed stronger representation of pulmonary and respiratory phenotypes, including spirometry-derived lung function measures and respiratory disease indicators. These differences were present despite broad shared lifestyle-related associations across both groups.

Conclusions

APOE4 carriers and non-carriers exhibit distinct modifiable risk-factor profiles associated with AD, with cardiovascular factors more prominent in carriers and pulmonary factors more prominent in non-carriers. These findings suggest that modifiable pathways to AD risk may vary by genetic background, highlighting the potential value of genotype-informed prevention strategies.