2022 Best Research Poster Award

Barwon Health

DEAKIN UNIVERSITY

Investigating the combined impact of blood protein markers and Alzheimer's disease risk factors on cognitive function in a population-based cohort of men

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INTRODUCTION

There is a substantial rise in the number of people living with Alzheimer's disease (AD), which is one of the leading causes of mortality worldwide. Despite its long preclinical phase, there is a paucity of studies aimed at elucidating biomarkers associated with cognitive function among cognitively unimpaired individuals.

Furthermore, given the multifactorial nature of AD pathology, biomarkers studies may also benefit by including AD risk factors such as genetic variants, mood disorders and poor bone health, an area that remains largely unexplored.

OBJECTIVES

a) To identify blood protein markers associated with cognitive function among cognitively unimpaired participants.

b) To investigate whether an interaction exists between biomarkers and AD risk factors (genetic, physical and mental).

METHOD

Participants: Four hundred and forty-eight male participants were drawn from the Geelong Osteoporosis Study.

Exposure: The blood samples were collected after overnight fasting and analysed for a panel of 269 proteins using a mass spectrometric-based platform.

Blood samples were also genotyped for 11 genetic polymorphisms, which have been linked with AD risk. The history of mood disorders and bone mineral density was determined using a semi-structured clinical interview and dual-energy x-ray absorptiometry, respectively.

Outcome: Cognitive function was assessed via the CogState Brief Battery.

Statistical analyses: Linear regression analyses were conducted to investigate cross-sectional associations between overall cognitive function and protein concentrations, adjusted for age and *APOE* ε4 carrier status. This was followed by interaction analyses to investigate whether genetic variants and health conditions modify the relationship observed between cognition and biomarkers.

RESULTS

Ten plasma proteins showed associations with cognitive function. Interestingly, this association was modified by genetic variants. As shown in Fig. 1, among non-carriers of the *ABCA7* risk allele, increasing plasma apolipoprotein C-I levels were associated with better cognitive function. However, for risk allele carriers, increasing apolipoprotein C-I levels were associated with poorer cognitive function.

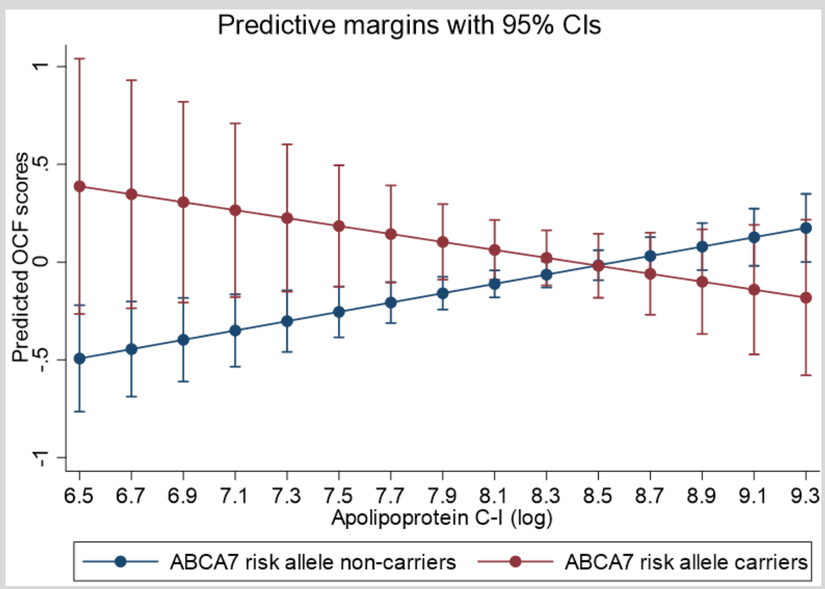

Fig 1. A predictive margins plot displaying interaction between apolipoprotein C-I and *ABCA7* risk allele in relation to cognitive function.

Modifiable health conditions such as mood disorders and poor bone health, which are postulated to be risk factors for AD, also impacted the relationship observed between biomarkers and cognition.

DISCUSSION

Plasma protein candidates may contribute to developing blood-based screening tests for identifying early cognitive changes. This has several advantages over current approaches; PET imaging is expensive and offers limited availability and CSF measurements involve an invasive lumbar puncture. However, future prospective studies are required to see whether these protein markers can predict any long-term cognitive change.

In addition, an altered biomarker profile was observed for individuals carrying the AD risk alleles or those with a mood disorder history and poor bone health.

CONCLUSION

Overall, this study suggests a relationship between plasma protein levels and cognitive function, and a blood-based proteomic signature can be exploited to enrich participants for more comprehensive AD testing.

The study also underscores the importance of including risk factors associated with AD in order to establish reproducible biomarkers.

ACKNOWLEDGEMENTS

We acknowledge the men who participated in the study and the staff who contributed to the data collection. The Geelong Osteoporosis Study was funded by the National Health and Medical Research Council Australia [Grant Nos. 299831, 628582].