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Investigating the role of blood metabolites as biomarkers of cognitive function and dementia in the 1946 British birth cohort

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INTRODUCTION

- Cognitive function is a key predictor of dementia, one of the biggest healthcare challenges of the 21st century. With a long prodromal phase, the identification of early biomarkers that are easy to routinely measure is urgently required [1].
- Metabolites could present as a minimally invasive and modifiable solution to this problem [2]. Metabolic dysfunctions have been reported in dementia; however, the influence of lifecourse factors has rarely been explored [3,4,5,6].
- Participants of the longitudinal MRC 1946 National Survey of Health and Development (NSHD) are now at an age where dementia pathology is likely to be accumulating, providing an opportunity to identify early biomarkers.

This study aimed to evaluate the associations between circulating metabolites and cognitive function and decline at ages 60-64 and 69 in the NSHD cohort, exploring the influence of lifecourse factors.

METHODS

- **Participants:**
  The MRC NSHD consists of 5362 individuals born in March 1946. Metabolite data and complete cognitive function measures at age 60-64 were available for 1742 participants.
- **Metabolomics:**
  Levels of 1402 metabolites were quantified using liquid chromatography-mass spectrometry. Metabolites with >20% missing data were excluded, leaving 1019 metabolites. Remaining missing data was imputed.
- **Cognition measures:**
  Ages 60-64 – short-term verbal memory, delayed verbal memory, visual processing speed. **Age 69** - delayed verbal memory, visual processing speed, Addenbrook's Cognitive Examination-III (ACE-III) (clinically used to detect dementia).
- **Statistical analyses:**
  Missing covariate data was imputed and all outcomes and metabolites were standardised. Linear regressions models were performed to evaluate associations between metabolites and cognition measures, adjusting for the following covariates presented in Figure 1.

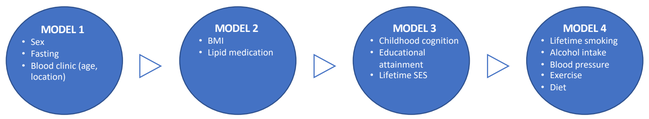


Figure 1. Summary of covariates used for each statistical model. *SES = socioeconomic status.*

- Sex and apolipoprotein E4 (APOE4) status were added as an interaction term.
  A metabolome-wide significance threshold was set to P<0.00011.

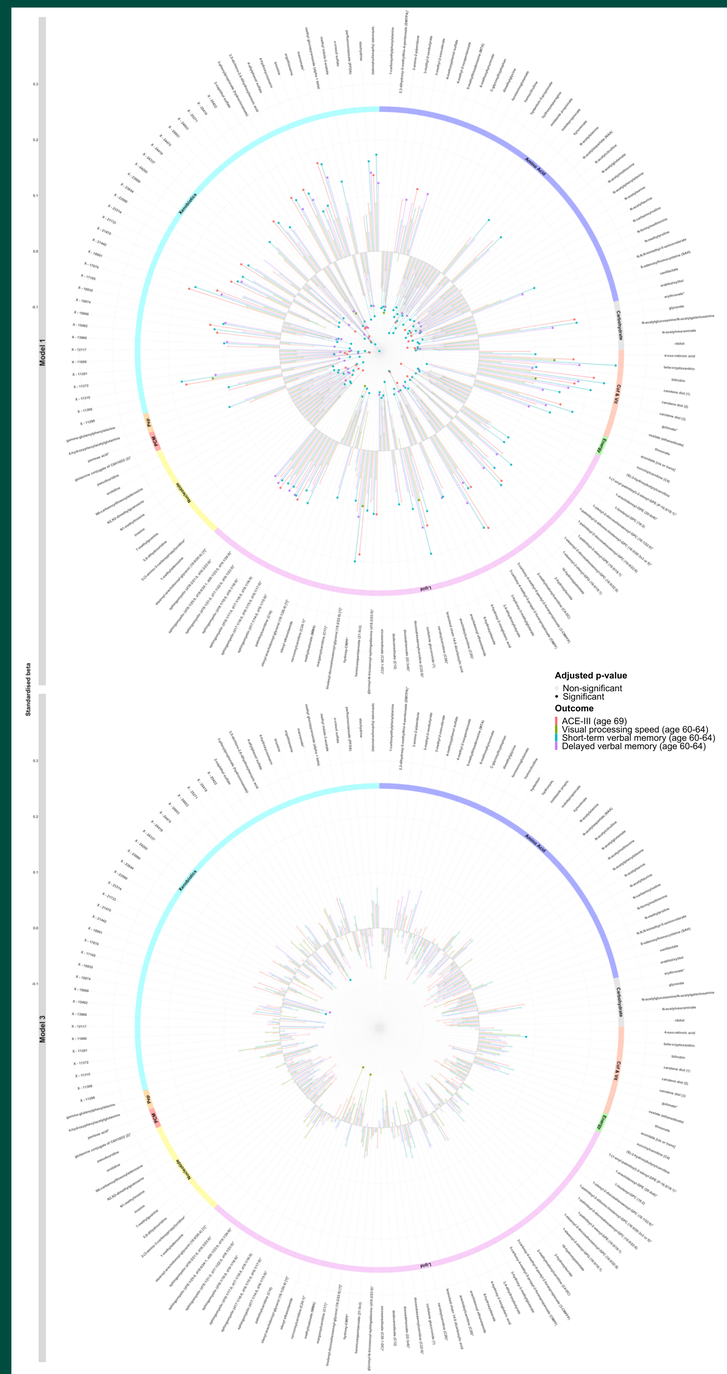
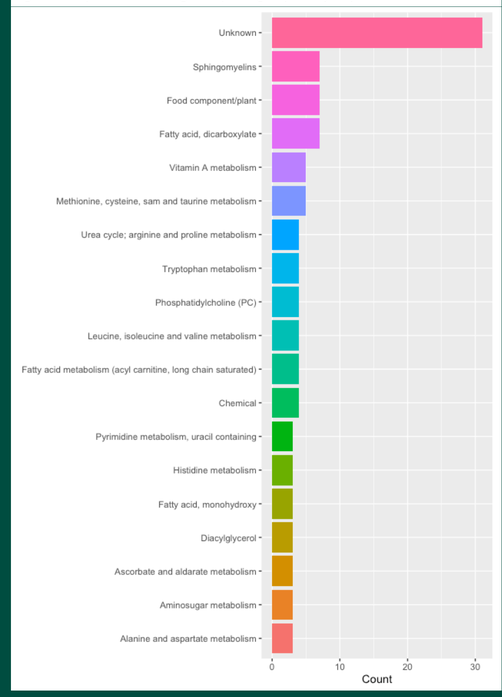


Figure 3. Bar plot demonstrating the top biological pathways implicated.



⭐ HIGHLIGHTS ⭐

- Similar metabolites and effect directions are seen across short-term and delayed memory and the ACE-III.
- Many associations attenuate when adjusting for early life influences.
- Key metabolite families – amino acids, lipids, nucleotides.
- Key pathways – fatty acids, sphingomyelins.

Figure 2 (LEFT). Polar plot of associations between the 154 metabolites and cognitive outcomes in model 1 and model 3. Bars represent standardised betas and associations passing the multiple testing threshold (p<0.0001) are represented by a hollow circle.
Pep = peptides, PCM = partially characterised molecules, Cof & Vit = cofactors & vitamins

RESULTS

- 154 metabolites were associated with cognitive outcomes in model 1 (p<0.00011) (Figure 2).
- Similar metabolites were associated with short-term and delayed verbal memory at ages 60-64 and 69, and the ACE-III.
- When mapped to their biological pathway, top known pathways included fatty acids and sphingomyelins (Figure 3).
- There is evidence for sex- and APOE- effect modification.
- Most associations attenuate when adjusting for childhood cognition, educational attainment and socioeconomic status (Figure 2).

CONCLUSION

- We identified 154 metabolites linked to cognitive function, including the clinical measure for dementia.
- These findings are in line with previous research, highlighting sphingomyelins, amino acids and fatty acids in cognitive function, and bringing new pathways to our attention [3,4,6]. This suggests new interventional targets and mechanistic insights for exploration.
- Most associations do not remain following adjustment for childhood cognition and educational attainment, demonstrating the importance of adopting a combined systems biology and lifecourse approach in biomarker discovery [1,6].
- Metabolites could present as promising biomarkers of cognitive decline/dementia, but replication is required to validate these findings.

FUTURE DIRECTIONS

1. Are there sex and APOE-specific associations between metabolites and cognitive function and decline?
2. Are these metabolites able to discriminate between individuals above or below the ACE-III threshold for clinical dementia?
3. Do associated metabolites lie in the causal pathway to cognitive function and dementia?

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