# Investigating the role of blood metabolites as biomarkers of cognitive function and dementia in the MRC 1946 British Birth Cohort

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## INTRODUCTION

- Decline in cognitive function in late midlife is indicative of dementia. With a long prodromal period, identifying early biomarkers of pathology is a priority [1].
- Known risk factors of dementia occur across the life course. Exploring biomarkers in the context of these influences could allow for complex relationships to be unpicked and interventions highlighted [2].
- Metabolites are influenced by both genetics and the environment, providing a snapshot into the physiological status of an individual. Thus, they may show utility as biomarkers of pathology, as well as allowing insight into underlying mechanisms [3].
- Participants of the 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 investigate early changes.
- As metabolites commonly act in concert, integrating single metabolite and systems-level analyses could reveal key pathways and drivers of pathology.

## AIMS

This study aimed to:

1. **Identify biological systems associated with late midlife cognitive function and decline in the NSHD cohort, exploring the influence of lifecourse factors.**
2. **Identify key, functionally important, metabolites that may present as promising biomarkers or candidates for intervention.**

## STUDY INFORMATION

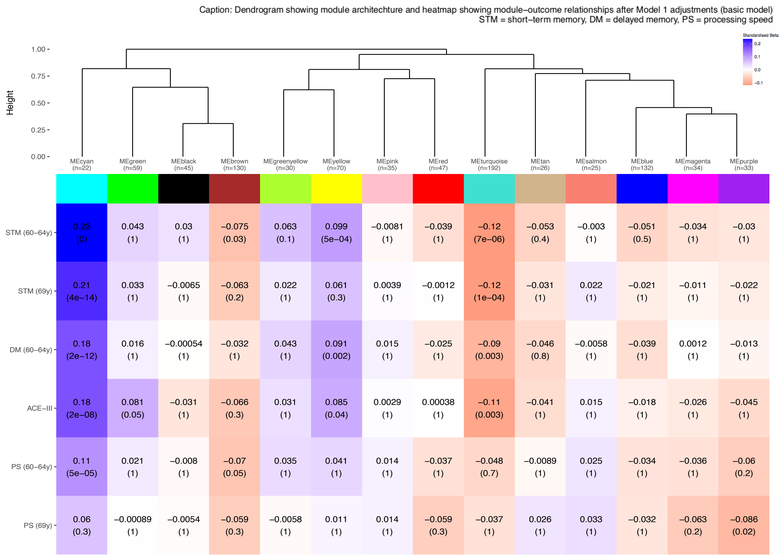
- **Participants**
  The MRC NSHD initially consisted of 5362 individuals born in March 1946. Metabolite data and complete cognitive function measures at age 60-64 were available for 1740 participants.
- **Metabolomics:**
  Levels of 1402 metabolites were quantified at age 60-64 using liquid chromatography-mass spectrometry. Metabolites with >20% missing data were excluded, leaving 1019 metabolites. Remaining missing data were imputed.
- **Cognition measures:**
  **Ages 60-64** – short-term verbal memory, delayed verbal memory, visual processing speed.

  **Age 69** - short-term verbal memory, visual processing speed, Addenbrooke's Cognitive Examination-III (ACE-III) (clinically used to screen for cognitive impairment).

## RESULTS

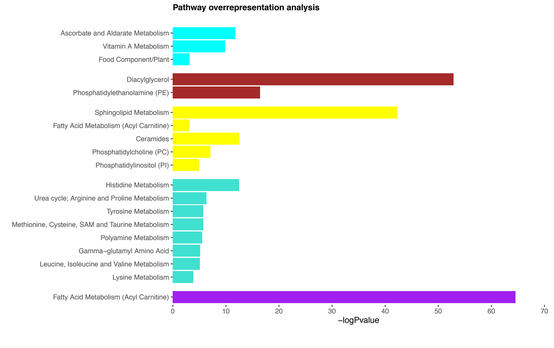
### 1 FIVE MODULES WERE ASSOCIATED WITH COGNITIVE OUTCOMES IN MODEL 1: CYAN, YELLOW, TURQUOISE, BROWN & PURPLE.

Caption: Dendrogram showing module architechture and heatmap showing module–outcome relationships after Model 1 adjustments (basic model)
STM = short–term memory, DM = delayed memory, PS = processing speed



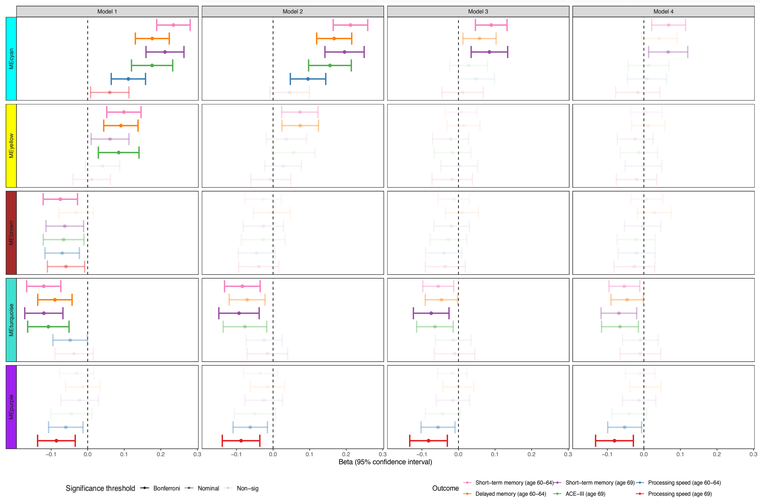

### 2 MODULES WERE ENRICHED FOR VARIOUS BIOLOGICAL PATHWAYS RELATED TO VITAMIN CONSUMPTION, LIPID METABOLISM AND AMINO ACID METABOLISM.

Caption: Bar chart showing the key biological pathways represented by Model 1 significant modules



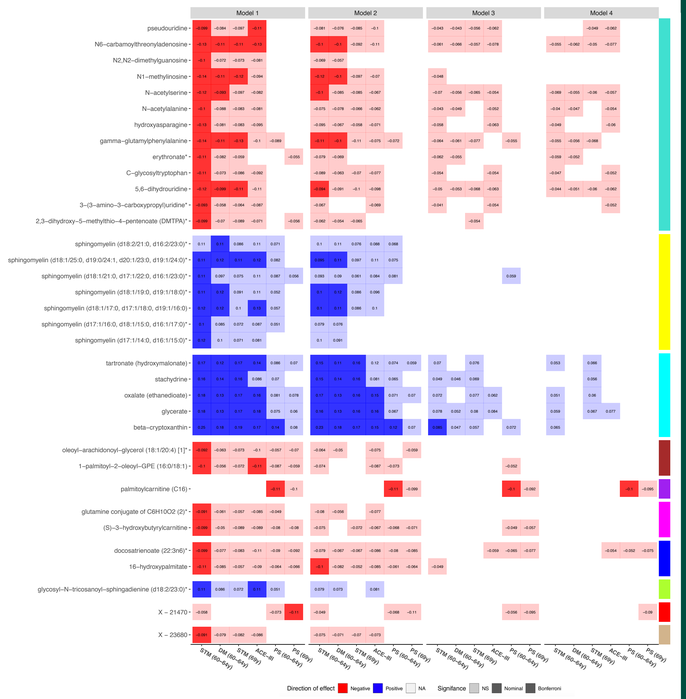

### 3 THE PURPLE MODULE SHOWED NEGATIVE ASSOCIATIONS WITH PROCESSING SPEED 5-9 YEARS LATER, INDEPENDENTLY OF LIFE COURSE FACTORS. Most other associations were lost when adjusting for life course factors.

Caption: Forest plot showing associations between modules and cognitive outcomes following sequential adjustment for life course influences



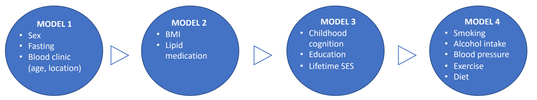

### 4 35 METABOLITES WERE ASSOCIATED WITH COGNITIVE OUTCOMES AND WERE KEY DRIVERS FOR THEIR MODULE. Associations for palmitoylcarnitine (C16) were independent of life course factors.

Caption: Heatmap showing relationships between hub metabolites and cognitive outcomes following sequential adjustment for life course influences
Colours of the right–hand bars refer to the module metabolites belong to, values inside tiles represent effect sizes
STM = short–term memory, DM = delayed memory, PS = processing speed




## STATISTICAL ANALYSIS

1. **Weighted metabolite coexpression network analysis (WGCNA)** - employed to group densely connected metabolites into modules [4].
2. **Pathway analysis -** for each module, hypergeometric tests were performed to identify key pathways.
3. **Linear regression models -** regression models were performed between cognitive outcomes and the following predictors:
   a) Single metabolites
   b) WGCNA modules
   Life course influences were included sequentially over four statistical models presented below.




4. **Hub metabolites** - metabolites showing a high intramodular connectivity (>0.65) were identified. Subsequently, these were filtered for those showing associations with the cognitive outcomes.

All statistical tests were subject to Bonferroni adjustment.

## CONCLUSIONS

- Five modules were identified to be associated with cognitive function and decline in late midlife. These modules were enriched in various pathways, providing insight into underlying biology.
- Most associations were lost after adjusting for childhood cognition, educational attainment and socioeconomic status, suggesting potential mechanisms of biological embedding and demonstrating the importance of adopting a combined systems biology and life course approach.
- One module, enriched in metabolites contained in the fatty acid (acyl carnitine) metabolism pathway, was negatively associated with processing speed 5-9 years later; this relationship was independent of life course influences.
- Palmitoylcarnitine (C16) was revealed to be a key driver for this module, presenting as a possible biological marker of decline and candidate for further study.

## FURTHER INFORMATION

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