NIHR | Maudsley Biomedical Research Centre

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

Rebecca Green[ab], Jodie Lord[a], Jin Xu[ad], Jane Maddock[c], Min Kim[d], Richard Dobson[aef], Cristina Legido-Quigley[d], Andrew Wong[c], Marcus Richards[c*], Petra Proitsi[a*]
*equally contributing authors

[a] Institute of Psychology, Psychiatry & Neuroscience, King's College London.
[b] UK National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre, South London and Maudsley Hospital, London. [c] MRC Unit for Lifelong Health & Ageing, University College London.
[d] Institute of Pharmaceutical Science, King's College London.
[e] Farr Institute of Health Informatics Research, UCL Institute of Health Informatics, University College London.
[f] NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation Trust, London.

@becki_e_green
rebecca.e.green@kcl.ac.uk

MRC Medical Research Council | KING'S College LONDON

INTRODUCTION

- Cognitive function is a key predictor of dementia. With a long prodromal phase, the identification of early biomarkers that are easy to routinely measure is urgently required [1].
- Metabolites provide a snapshot into the physiological status of an individual and could present as a minimally invasive and modifiable solution to this problem [2].
- Metabolic dysfunctions have been reported in dementia, but life course influences and causality are rarely interrogated and replication has proved challenging [3:6].
- 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 initially consisted 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 at age 60-64 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, Addenbrooke's Cognitive Examination-III (ACE-III) (clinically used to screen for cognitive impairment).
- **Statistical analyses:**
  Linear regressions models were performed between metabolites and cognition measures, adjusting for the following covariates presented in Figure 1. A metabolome-wide significance threshold was set to P<0.00011.

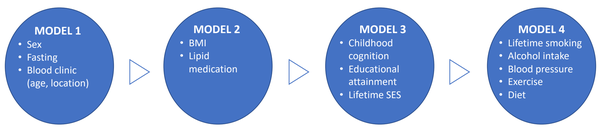


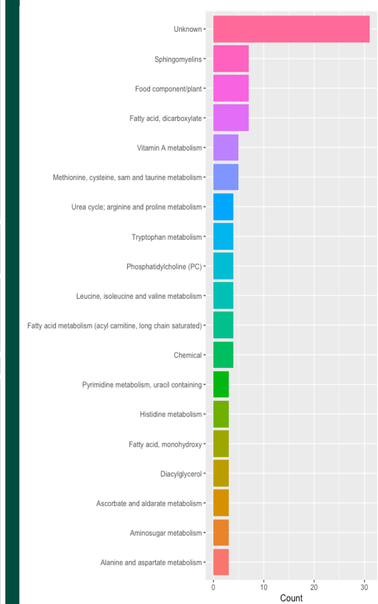
Figure 1. Summary of covariates used for each statistical model. *SES = socioeconomic status.*

- **Two-sample mendelian randomisation (MR):**
  Significant metabolites were taken forward for MR analysis using publicly available metabolite (exposure) [7] and cognition (outcome) [8] GWAS summary statistics.
  MR methods included inverse variance weighted and robust methods (MR egger, weighted median, weighted mode).

Figure 2 (LEFT). Heat map of associations between the 154 metabolites and cognitive outcomes in models 1-4. Panel colours represent the direction of effect and colour intensity represents p-value. Metabolites with an unadjusted p>.05 are displayed in white.

Carb = carbohydrates, Cof & Vit = cofactors & vitamins, En = energy, PCM = partially characterised molecules, Pep = peptides.
ACE-III = Addenbrooke's Cognitive Examination-III, DVM = delayed verbal memory, SVM = short-term verbal memory, VPS = visual processing speed

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



HIGHLIGHTS

- Similar metabolites and effect directions are seen across memory measures and clinically significant cognitive impairment 5-9 years later.
- Key metabolite families – amino acids, lipids, nucleotides.
- Many associations attenuate when adjusting for early life influences.
- No evidence of causal associations thus far.

RESULTS

- **OBSERVATIONAL:** 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.
- Many associations appear to be mediated by childhood cognition, educational attainment and socioeconomic status (Figure 2).
- **KEY PATHWAYS:** fatty acids, sphingomyelins, food/plant intake, unknown (Figure 3).
- **MR ANALYSIS:** analysis still in progress. Many metabolites identified have insufficient instrument strength for MR analyses.

	beta	se	pval
Erythronate	0.21	0.15	0.17
Succinylcarnitine	-0.06	0.14	0.65
X-11315	0.10	0.08	0.20

Table 1. Inverse variance weighted MR results.

- Initial results indicate no casual effect of erythronate, succinylcarnitine or X-11315 on cognitive function (Table 1).

CONCLUSION

- We identified 154 metabolites linked to cognitive function, including cognitive impairment 5-9 years later.
- 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 early cognitive changes relevant to 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 predict individuals that will be above or below the ACE-III threshold for clinically significant cognitive impairment?

Acknowledgements: We would like to thank participants of the NSHD for their incredible, continued support allowing this research to occur.
Rebecca Green is in receipt of a PhD studentship funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

References:
[1] Jack Jr, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., ... Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. The Lancet. Neurology, 12(2), 207–216.
[2] Beger, R., Dunn, W., Schmidt, M. A., Gross, S., Kirwan, J., & Cascante, M. (2016). Metabolomics enables precision medicine: "A white paper, community perspective. 12(10):149.
[3]Jiang, Y., Zhu, Z., Shi, J., An, Y., Zhang, K., Wang, Y., ... Chen, X. (2019). Metabolomics in the Development and Progression of Dementia: A Systematic Review. Frontiers in Neuroscience, 13, 343.
[4] van der Lee, S. J., Teunissen, C. E., Pool, R., Shipley, M. J., Teumer, A., Chouraki, V., ... van Duijn, C. M. (2018). Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies. Alzheimer's & Dementia, 14(6), 707–722.
[5] Varma, V. R., Oommen, A. M., Varma, S., Casanova, R., An, Y., Andrews, R. M., ... Thambisetty, M. (2018). Brain and blood metabolite signatures of pathology and progression in Alzheimer disease: A targeted metabolomics study. PLOS Medicine, 15(1), e1002482.
[6] Proitsi, P., Kuh, D., Wong, A., Maddock, J., Bendayan, R., Wulaningsih, W., ... Richards, M. (2018). Lifetime cognition and late midlife blood metabolites: findings from a British birth cohort. *Translational Psychiatry*, *8*(1), 203.
[7] Shin S-Y, Fauman EB, Petersen A-K, Krumsiek J, Santos R, Huang J, et al. An atlas of genetic influences on human blood metabolites. Nat Genet. 2014;46(6):543–50.
[8] Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet. 2018;50(8):1112–21.