Final Project Report EM1

How do peripheral and central vascular markers relate to cognitive decline?

- **Introduction**

Testing potential biomarkers of cognitive ability in late life is of interest for both theory and practice in dementia research. Not only might such biomarkers be informative about the causes of age-related cognitive decline, they may also be predictive of phenoconversion to dementia; they may thus be used in the prodromal phase of the disorder to distinguish those who will experience pathological cognitive ageing from those who will age more healthily. In this proposal, we examine one set of possible cognitive ability level and change biomarkers: lipidomics and lipoproteins.

Evidence suggests that diverse lipidomic profiles exist in dementia, and that these may predict phenoconversion (http://www.ncbi.nlm.nih.gov/pubmed/24608097 & http://www.ncbi.nlm.nih.gov/pubmed/24041970). Differential lipidomic profiles in diverse patient populations across brain white and gray matter have also been suggested (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4099521/; see http://www.ncbi.nlm.nih.gov/pubmed/24568356 for a recent review). Lipidomic profiles may therefore be highly relevant to profiles of change in brain and cognitive ageing, including conversion to dementia.

Brain White Matter Hyperintensities (WMH), detected on magnetic resonance imaging scans, may be linked to lipidomic profiles. WMH are indicative of cerebral small vessel disease, and are a common feature of ageing, but are also related to neurodegenerative diseases such as AD and VCI, poorer cognitive and functional outcomes (http://www.ncbi.nlm.nih.gov/pubmed/24190781). Their presence is associated with increased risk of stroke, dementia, and mortality. They are part of small vessel disease burden (including lacunes, perivascular space enlargement and microbleeds; http://www.ncbi.nlm.nih.gov/pubmed/25165388), and are a marker of diffuse damage and loss of integrity throughout 'normal appearing' white matter (http://www.ncbi.nlm.nih.gov/pubmed/25457555). Such relationships may be moderated by genetic variants such as *ApoE* e4, the presence of which has been linked to the extent of cerebrovascular disease as indicated by WMH (http://www.ncbi.nlm.nih.gov/pubmed/23858411).

Other measures of the structure of the brain's white matter are also related to cognitive and health outcomes. Measures derived from diffusion-tensor MRI (DT-MRI), such as the magnetization transfer ratio (MTR), longitudinal relaxation time (T1), fractional anisotropy (FA) and mean diffusivity (MD) have been found to associate with cognitive ability in later life (http://www.ncbi.nlm.nih.gov/pubmed/25309438, http://www.ncbi.nlm.nih.gov/pubmed/24561387, http://www.ncbi.nlm.nih.gov/pubmed/25247594). Such measures may therefore provide complementary information about links between lipidomic profiles, cognitive decline and phenoconversion.

Recent developments in technology allow hundreds to thousands of lipids to be analysed simultaneously. Mass spectrometry-based lipidomic platforms are increasingly popular. They may be targeted to measure specific well-defined metabolites or untargeted whereby they detect thousands of features, with those showing a positive association with the trait of interest potentially being annotated using databases post analysis. Ultra-performance liquid chromatography (UPLC) mass spectrometry is a highly sensitive method of quantifying a wide range of biologically relevant small molecules http://www.ncbi.nlm.nih.gov/pubmed/27479709. In nuclear magnetic resonance (NMR) spectroscopy, the area of a resonance is directly related to the number of nuclei generating the

signal. This provides a highly quantitative method for detecting small molecules in plasma and other biofluids (http://www.ncbi.nlm.nih.gov/pubmed/25691689).

Goal of the study: To investigate the potential links between plasma lipidomics and lipoproteins and cognitive and neurovascular imaging parameters that index variation in age-related decline. The project will test whether these lipidomic parameters could be used to stratify subjects relevant to diverse populations with varied risk of decline in cognitive performance, vascular health and lifestyle measures. The results would provide data in a pre-competitive framework that could support potential therapeutic strategies for vascular causes of cognitive impairment and dementia.

Scope of the study

To design and conduct a scientifically robust pilot study with new analysis of plasma samples and existing cognitive and imaging data derived from the Lothian Birth Cohort 1936 (LBC1936).

Cost to DPUK: £91,000

Additional funds from elsewhere: None.

RESULTS:

Lothian Birth Cohort 1936 (LBC1936) plasma samples were delivered to the National Phenome

Centre (NPC) in April 2016. A problem was identified with some of the samples and further samples were sent in July 2016. We received the first batch of data from the National Phenome Centre in November 2016. Final data sets were received from the National Phenome Centre in March 2017. Four data sets were received: 1) Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS) untargeted data set; 2) The Biocrates AbsoluteIDQ® p180 (Biocrates Life Sciences AG, Innsbruck, Austria) kit provided absolute quantification for 53 compounds, and semi-quantitative measurements for a further 135 compounds. Biocrates data were acquired on Waters TQ-S instruments; 3) Nuclear Magnetic Resonance (NMR) Spectroscopy untargeted data set; 4) Specific lipoproteins were measured using the Bruker B.I.-Lisa platform (Bruker IVDr Lipoprotein Subclass Analysis). The lipoproteins measured were, cholesterol, free cholesterol, phospholipids, triglycerides, apolipoproteins A1, A2, B and particle numbers for the primary plasma and serum lipoproteins and their subclasses.

Initial analyses to investigate the underlying structure of the Biocrates-derived sphingolipid markers was performed using exploratory factor analysis. One strong general factor explained ~72% of the variance across all 14 sphingolipids. A small correlation was identified between general cognitive ability and general sphingolipid level (r=0.12, p=0.008).

We decided not to test the 10 lipid panel identified by Mapstone et al., 2014 (http://www.ncbi.nlm.nih.gov/pubmed/24608097) as to whether it may represent fit to cognitive performance with evidence of cerebrovascular burden. Larger studies suggest that it is not a good predictor of Alzheimer's Disease (http://www.ncbi.nlm.nih.gov/pubmed/26617567 & http://www.ncbi.nlm.nih.gov/pubmed/26806385.

We have used penalized regression models (LASSO) to identify sets of metabolites in the Biocrates, B.I.-LISA, untargeted UPLC-MS and untargeted NMR spectroscopy data sets that can be used to predict general cognitive ability in LBC1936. Splitting the data into a training set and a test set, we predicted up ~ 9% of the variance in general cognitive ability using the UPLC-MS dataset, in the test

set. The other three data sets did not predict variance in cognitive ability in LBC1936. Models are currently running to identify the percentage of the variance in MRI brain variables that can be predicted by the four data sets. Elastic-net models are also being used to identify specific metabolites associated with general cognitive ability and MRI brain variables. These analyses will be completed shortly. Longitudinal analyses to investigate if plasmid lipid biomarkers predict cognitive decline in LBC1936 are also planned.

The analyses were performed by Drs Sarah Harris and Stuart Ritchie, who will prepare the manuscripts for peer-reviewed publication.

- **Conclusion**

Lipid biomarkers can be used to predict a small amount of the variance in general cognitive function in members of LBC1936 at age ~73 years.

- **Recommendations** None
- **Bibliography**

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