EM 1 – Complete

How do peripheral and central vascular markers relate to cognitive decline? **Start date: 1 Aug 2015**	**Completion date: 1 Jul 2018**
Team members John Starr*, Ian Deary, Joanna Wardlaw, Derek Hill, Paul Wren *We are saddened to report that John Starr died in early December 2018. **ECR's:**	
Overall work package objectives: An exploratory study which will investigate statistical relations between measures of plasma lipidomics and lipoproteins and cognitive and neurovascular imaging parameters. The main hypothesis is that the lipidomic/lipoprotein markers will correlate with, and allow the stratification of, declines in the cognitive and neurovascular parameters. Contingent on its results, this pilot may permit the consideration of larger strategic bids to complete plasma assessments from the full range of ages at which data have been collected on the LBC1936. It may also encourage further assessments in other DPUK cohorts to qualify findings at scale. 1. Determine the individual Lipidomic/Lipoprotein/Biocrates profiles that may represent fit to cognitive performance. 2. Determine the individual Lipidomic/Lipoprotein/Biocrates profiles that may directly associate with intermediary imaging markers of vascular disease burden including MRI variables: visible markers as individual (WMH, lacunes, PVS, global and regional atrophy) and combined SVD features (SVD burden score); and subvisible markers (MD, FA, T1, MTR in normal appearing white and deep grey matter). 3. Determine the individual Lipidomic/Lipoprotein/Biocrates profiles that may represent fit to cognitive performance in presence or absence of markers of cerebrovascular burden. 4. To specifically test the 10 lipid panel identified by Mapstone et al, 2014 as to whether it may represent fit to cognitive performance with evidence of cerebrovascular burden. 5. To specifically test whether PC 16:0/20.4(5), PC16:0/22:6 & PC18:0/22:6 profiles may represent fit to cognitive performance with evidence of cerebrovascular burden to further enhance the King's Group established findings.	**Dependencies to and from other work packages, networks and themes**
Lessons Learnt (what went well, what did you have to change) • The assays were all performed successfully although there was a delay to us receiving the data for the Lipoprotein profiling using NMR spectroscopy, because the National Phenome Centre had to optimise the assay to work on a low volume of plasma. • Writing scripts to analyse such large data sets took longer than expected, therefore the initial publication will include only cross-sectional data. Longitudinal analyses will be included in a follow-up paper. • We decided not to proceed with initial plans to analyse the 10 lipid panel identified by Mapstone et al, 2014 as other studies failed to replicate results from this paper whilst we were acquiring our data.	
Were all Milestones completed- No Please see report below	

Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1:				
D1.1The individual Lipidomic/Lipoprotein/Biocrates profiles that may represent fit to cognitive performance.	None	M1.1 Complete	None	John Starr/ Ian Deary

Objective 2:				
D1.2 The individual Lipidomic/Lipoprotein/Biocrates profiles that may directly associate with intermediary imaging markers of vascular disease burden including MRI variables: visible markers as individual (WMH, lacunes, PVS, global and regional atrophy) and combined SVD features (SVD burden score); and subvisible markers (MD, FA, T1, MTR in normal appearing white and deep grey matter).	None	M1.2 Complete	None	John Starr/ Ian Deary
Objective 3:				
D1.3 The individual Lipidomic/Lipoprotein/Biocrates profiles that may represent fit to cognitive performance in presence or absence of markers of cerebrovascular burden	None	M1.3 Ongoing	None	John Starr/ Ian Deary
Objective 4:				
D1.4 To specifically test the 10 lipid panel identified by Mapstone et al, 2014 as to whether it may represent fit to cognitive performance with evidence of cerebrovascular burden	None	M1.4.1 Closed No longer appropriate.	None	John Starr/ Ian Deary
Objective 5:				
D1.5 To specifically test whether PC 16:0/20.4(5), PC16:0/22:6 & PC18:0/22:6 profiles may represent fit to cognitive performance with evidence of cerebrovascular burden to further enhance the King's Group established findings	None	M1.5.1 Ongoing	None	John Starr/ Ian Deary
D1.6 Aim to replicate the finding that sphingolipids (Biocrates) are associated with white matter microstructure in older adults (Gonzalez et al., Neurobiol Aging 2016 43, 156-163) and will investigate their association with cognitive change in later life.	None	M1.6.1 Complete		
D1.7 We will investigate the dimensionality of the NMR Bi-LISA data set and associations between individual and combined lipoproteins and cognitive function, cognitive decline and MRI variables.	None	M1.7.1 Complete		

Outcomes

EM 1 have some final analyses to perform before submitting the first paper. The working title is: "Plasma lipid biomarkers in LBC1936: Do they predict general cognitive function and brain structure?"

1) Stuart J Ritchie, Sarah E Harris, Chloe Fawns-Ritchie, John M Starr, Derek Hill, Paul Wren, Joanna M Wardlaw and Ian J Deary. Plasma sphingolipid biomarkers in the Lothian Birth Cohort 1936: Towards associations with lifetime cognitive function, Alzheimer's Association International Conference, July 2017, poster presentation.

2) Sarah E Harris. The Lothian Birth Cohorts: OMICS, Medical Genetics Section Talk, IGMM, University of Edinburgh, 7th February 2018.

3) A first paper is current being drafted. Its working title is "Plasma lipid biomarkers in LBC1936: Do they predict general cognitive function and brain structure?", the authors will be Sarah E Harris, Stuart J Ritchie, Chloe Fawns-Ritchie, John M Starr, Derek Hill, Paul Wren, Joanna M Wardlaw and Ian J Deary and it is anticipated to be submitted by March 2019 to Molecular Psychiatry.

We have used penalized regression models (LASSO) to identify sets of metabolites in lipidomic data sets that can be used to predict up to 9% of the variance in general cognitive ability in relatively healthy 73 year olds.

We anticipate publications in the following areas.

(Provide journal of choice if known etc.)

1) Further investigation of the function of specific metabolites that are associated with general cognitive function and the structure of the brain.

2) Longitudinal analyses to investigate if plasmid lipid biomarkers predict cognitive decline and structural brain changes in LBC1936.

Executive Summary of Project

This pilot exploratory study aimed to investigate statistical relations between measures of plasma lipidomics and lipoproteins and cognitive and neurovascular imaging parameters. The main hypothesis being addressed was that the lipidomic/lipoprotein markers will correlate with, and allow the stratification of, declines in the cognitive and neurovascular parameters.

The work progressed satisfactorily although there was there was the need to alter the experimental plan to deal with updates to the literature. The work is likely to yield to 2 to 3 initial publications and data sets that will be available for other researchers to analyse.

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 to 9% of the variance in general cognitive ability, in the test set. Results for the MRI brain variables will be available in January. 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.

DPUK enabled many thousands of metabolites to be measured in the Plasma of LBC1936 participants, which is allowing us to investigate their association with cognitive function, cognitive decline and MRI brain variables.

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