Amyloid Discovery Cohort
Work Package 4

Dementias Platform UK
Medical Research Council

Objective(s):

To establish a cohort of 500 men and women from the MRC National Survey of Health and Development (the UK1946 birth cohort 'Insight 46') characterised for amyloid status using amyloid PET imaging with concurrently acquired structural MRI and blood and urine testing. Work Package 4 (WP4) supported the third DPUK strategic objective of re-purposing existing cohorts for discovery studies.

1. Establish a biomarker resource of blood and urine samples with paired T1-volume scans and known brain amyloid status for biomarker discovery and validation, which will feed into WP6 (Biomarkers) and experimental medicine WPs.
2. Provide paired amyloid PET and MRI imaging for imputation and correlative analyses with other platform cohorts collecting volumetric MRI and blood samples.
3. Determine the relationships between PET Aβ load and blood measures of Aβ-42/tau, and brain atrophy in a cohort of identical age, of direct relevance to WP14 (risk stratification and biostatistics), allowing other cohorts (e.g. Prevent) to cross-validate results.
4. Provide a well-characterised cohort in which novel imaging markers (e.g. of tau or microglial activation/inflammation) can be tested in the future.

Data uploaded to DPUK portal

Overview Summary:

Insight 46 is a neuroimaging sub-study of the MRC National Survey of Health and Development (also known as the British 1946 birth cohort). For this sub-study, 502 participants were recruited to participate in two clinic visits in London. Data collection included cognitive, physical, and sensory assessments; blood, urine and cerebrospinal sample collections; and a positron emission tomography (PET)/magnetic resonance imaging (MRI) brain scan to assess amyloid (a brain

protein linked with dementia) and brain structure. Study data are available through the DPUK data portal and the MRC Unit for Lifelong Health and Ageing with approval from the cohort owners.

Executive Summary:

The MRC National Survey of Health and Development (NSHD) is a cohort of 5,362 individuals born in England, Scotland and Wales during the first week of March 1946. These individuals have participated in 24 waves of data collection throughout their lives. The waves of data collection have incorporated a wide range of health and functional measures, including repeat measures of cognitive function.

Insight 46 is a neuroimaging sub-study of the NSHD. In total, 502 individuals from the NSHD were recruited to participate in Insight 46—a prospective two time-point (0, 24 month) data collection covering clinical, neuropsychological, β-amyloid positron emission tomography (PET) and magnetic resonance imaging (MRI), biomarker and genetic information. All Insight 46 participants met the following minimum criteria: (1) attended a clinical visit at 60-64 years, and (2) relevant lifecourse data are available. Data collection started in 2015 (age 69), and cross-sectional data collection was completed in January 2018. Of the 502 participants who were recruited to participate in Insight 46, ~1/3 of individuals in this age group may be in the preclinical stages of Alzheimer's Disease.

To date, data analyses models and optimised statistical methodologies have been applied to the full cross-sectional data set. Imaging pipelines for amyloid PET and multi-modal MR imaging have been optimised. As a result of additional funding from the Weston foundation, SIMOA-based assays of β-amyloid, tau, p-tau and neurofilament light polypeptide (also known as neurofilament light chain) have been completed on the cross-sectional Insight 46 samples.

The study team continue to analyse the cross-sectional data, and early findings have been presented at the Alzheimer's Association International Conference—the world's largest dementia research gathering—in 2017, 2018 and 2019. A number of papers utilising cross-sectional data have been accepted for submission or are under review or in preparation. Longitudinal data collection is underway and will be completed in 2020.

Summary of Outputs: (as per Researchfish categories)

Key publications

1) Lane, C, Parker TD, Cash DM, Macpherson K, Donnachie E, et al. 2017. Study protocol: Insight 46 – a neuroscience sub-study of the MRC National Survey of Health and Development. BMC Neurology. 17(1):75**.** DOI: 10.1186/s12883-017-0846-x.

This is a detailed protocol paper outlining the Insight 46 study. This provides the overall rationale, details of each of the test administered, and the duty of care procedures — which will be of value to other researchers setting up studies or looking to access data.

2) James SN, Lane CA, Parter TD, Lu K, Collins JD, Murray-Smith H, Byford M, Wong A, Keshavan A, Buchanan S, Keuss SE, Kuh D, Fox NC, Schott JM, Richards M. 2018. Using a birth cohort to study brain health and preclinical dementia: Recruitment and participation rates in Insight 46. *BMC Research Reports. doi.org/10.1186/s13104-018-3995-0*

Reports the recruitment and participation patterns from "Insight 46" a neuroscience sub-study supported by DPUK as work package 4, is similar to the parent cohort, the MRC National Survey of Health and Development. The results confirm that participants in the DPUK study are broadly aligned with the parent cohort in terms of socio-economic class.

3) Keuss SE, Parker TD, Lane CA, Hoskote C, Shah S, Cash DM, Keshavan A, Buchanan SM, Murray-Smith H, Beasley DJ, Malone IA, Thomas DL, Barnes A, Wong A, Barker S, Richards M, Fox NC, Schott JM. 2019. Incidental findings on blood tests and brain imaging: results from the first phase of Insight 46, a longitudinal prospective sub-study of the 1946 British birth cohort. *BMJ Open*. https://bmjopen.bmj.com/content/9/7/e029502

A summary of the incidental findings detected on brain imaging and blood tests during the first wave of data collection for the Insight 46 study. In this cohort, tested between the ages of 69-71 years, around 5% of participants showed potentially serious brain MRI findings. Clinical blood test anomalies were detected in a third of the participants but very few required urgent action and findings were mainly previously known to the participants' GPs and already acted on. These findings have implications for studies involving older adults, including clinical trials of secondary prevention drugs for Alzheimer's disease which often involve MRI-based outcome measures and blood testing.

4) Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, Malone IB, Lu K, James S-N, Keshavan A, Murray-Smith H, Wong A, Buchanan SM, Keuss SE, Gordon E, Coath W, Barnes A, Dickson J, Modat M, Thomas D, Crutch SJ, Hardy R, Richards M, Fox N, Schott HM. 2019. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurology*.
doi: https://doi.org/10.1016/S1474-4422(19)30228-5

It is known that midlife hypertension confers increased risk for cognitive impairment in later life. Utilising the Insight 46 cohort (all dementia free) this group aimed to identify if, and when, blood pressure or changes in blood pressure during adulthood contributed to this impairment. The study concluded that raised blood pressure does not appear to affect risk for AD through amyloidogenic pathways at 69-71 years. Instead, it suggests that the fourth to sixth decades of life are the sensitive period when blood pressure changes are particularly damaging to the brain. The implication of this work is that routine, and serial blood pressure measurement needs to start around 40 years of age, earlier than currently, and that any treatments should take account of longitudinal blood pressure changes.

5) Parker TD, Cash DM, Lane CA, Macpherson K, Malone I, Nicholas JM, James SN, Keshavan A, Murray-Smith H, Wong A, Buchanan S, Keuss, S, Sudre C, Barnes J, Barnes A, Dickson J, Modat M, Thomas D, Crutch SJ, Richards M, Fox NC, Schott JM. Hippocampal subfield volumes and pre-clinical Alzheimer's disease in 408 cognitively normal adults born in 1946. 2019 PLOS ONE
doi: https://doi.org/10.1371/journal.pone.0224030

Using PET and structural MRI imaging of a sub-set of the Insight 1946 cohort, this paper provides evidence of differential associations in cognitively normal older adults between hippocampal subfield volumes and β-amyloid deposition and, increasing age at time of scan. The relatively selective effect of lower presubiculum volume in the β-amyloid positive group potentially suggest that the presubiculum may be an area of early and relatively specific volume loss in the pathophysiological continuum of Alzheimer's disease. The work suggests that future studies using higher resolution imaging will be key to exploring these findings further.

6) Lu K, Nicholas JM, Collins JD, James SN, Parker TD, Lane, CAS, Keshavan A, Keuss SE, Buchanan SM, Murray-Smith H, Cash DM, Sudre CH, Malone IB, Coath W, Modat M, Barker S, Wong A, Kuh D, Henley SMD, Crutch SJ, Fox NC, Richards M, Schott JM. Cognition at age 70: life course

predictors and associations with Alzheimer's disease pathology. Neurology 2019 https://n.neurology.org/content/93/23/e2144 (see also section on Engagement Activities)

Insight 46 cohort members underwent cognitive assessment at 69-71 years to investigate the effects of sex, childhood cognitive ability, education and adult socioeconomic position. Childhood cognitive ability was strongly associated with cognitive scores almost 60 years later and there were independent effects of education and socioeconomic position. Participants with amyloid-beta plaques also scored lower on cognitive testing indicating that subtle cognitive differences are detectable in older adults even when dementia prevalence is very low. Continued follow-up studies of this cohort is needed to determine how best to use these findings to accurately predict how a person's thinking and memory will change as they age.

7) Parker T , Cash DM, Lane C, Lu K, Malone IB, Nicholas JM, James S, Keshavan A, Murray-Smith H, Wong A, Buchannan S, Keuss S, le H Sudro C, Thomas D, Crutch S, Bamiou, CE, Warren JD, Fox NC, Richards M, Schott JM. Pure tone audiometry and cerebral pathology in healthy older adults. Journal of Neurology, Neurosurgery, and Psychiatry (2020) https://jnnp.bmj.com/content/91/2/172

Pure tone audiometry performance did not predict concurrent β-amyloid deposition, small vessel disease or Alzheimer's disease-pattern neurodegeneration, and had limited impact on cognitive function, in healthy adults aged approximately 70 years.

8) Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Malone IB, Parker TD, Keshavan A, Buchanan SM, Keuss SE, James S-N, Lu K, Murray-Smith H, Wong A, Gordon E, Coath W, Modat M, Thomas D, Richards M, Fox NC, Schott JM. Associations between vascular risk across adulthood and brain pathology in late life. JAMA Neurology (2019) doi: 10.1001/jamaneurol.2019.3774

Midlife vascular risk burden is associated with late-life dementia. Less is known about if and how risk exposure in early adulthood influences late-life brain health. The objective of this analyses was to determine the associations between vascular risk in early adulthood, midlife, and late life with late-life brain structure and pathology using measures of white matter-hyperintensity volume, β-amyloid load, and whole-brain and hippocampal volumes. The results indicated higher vascular risk is associated with smaller whole-brain volume and greater white matter-hyperintensity volume at age 69 to 71 years, with the strongest association seen with early adulthood vascular risk. There was no evidence that higher vascular risk influences amyloid

deposition, at least up to age 71 years. Reducing vascular risk with appropriate interventions should be considered from early adulthood to maximize late-life brain health.

Collaborations & Partnerships

None

Further Funding

Additional funding from the Weston foundation (£328,663) allowed SIMOA-based assays of β-amyloid, tau, p-tau and NFL to be run on the cross-sectional Insight 46 samples. Assays will be run on the longitudinal samples upon completion of data collection in 2020.

Funding has been received from the Alzheimer's Association ($10,559,333) to support an additional wave of data collection (~2020 – 2023) for the neuroimaging sub-study. This additional wave of data collection will include assessments of an additional 500 participants from the MRC NSHD 1946 birth cohort, plus 250 members of the current cohort, and is currently being set-up. It will incorporate deep phenotyping, including tau PET.

Next Destinations

The following PhDs have been awarded or will be submitted as a result of this project.

- Lane C. 2018. The influence of life course vascular risk on brain pathologies and cognition in later life — a neuroimaging study of the British 1946 birth cohort. *Dr Lane is now working for industry (Roche).*
- Parker T. 2019. The consequences of, and relationship between, amyloid, grey matter microstructural change and atrophy in the MRC NSHD 1946 birth cohort. *Dr Parker is now completing clinical training with a view to becoming a clinical academic.*
- Keshavan A. 2019. Blood and cerebrospinal fluid-based biomarkers for neurodegenerative disease: from clinical to pre-clinical cohort. *Dr Keshavan will shortly be returning as a clinical lecturer.*
- Lu K. 2019. Insight 46: Characterising early cognitive changes and possible associations between cognitive and other AD biomarkers. *Dr Lu is now a post-doc working on the project.*

Upgrades complete

- Buchanan S. Movement and neurodegeneration in the MRC National Survey of Health and Development (NSHD; 1946 birth cohort). Submission due in 2020

- Keuss S. Exploring cerebral atrophy in the 1946 British birth cohort: insights into preclinical Alzheimer's disease and clinical trial design. Submission due in 2020.

Engagement Activities

AAIC – 2017, 2018, 2019

Cash DM, Burgos N, Modat M, Dickson J, Beasley D, Markiewicz P, Lane CA, Parker T, Barnes A, Thomas DL, Cardoso MJ, Malone IB, Veale T, Wallon D, Klimova J, Erlandsson K, Wong A, Richards M, Fox NC, Ourselin S and Schott JM. A comparison of techniques for quantifying amyloid burden on a combined PET/MR scanner. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):12.

James SN, Parker T, Lane CA, Cash DM, Wong A, Barnes A, Beasley D, Burgos N, Cardoso MJ, Dickson J, Klimova J, Malone IB, Modat M, Thomas DL, Kuh D, Ourselin S, Fox NC, Schott JM and Richards M. Midlife affective symptoms are associated with lower brain volumes in later life: evidence from a prospective UK birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):212.

Lane CA, Sudre CH, Barnes J, Nicholas JM, Parker T, Cash DM, Murray-Smith H, Wong A, Malone IB, Klimova J, Kuh D, Ourselin S, Cardoso MJ, Richards M, Fox NC and Schott JM. Vascular and early life influences on cerebrovascular disease in Insight 46: a sub-study of the MRC National Survey of Health and Development (NSHD) British birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):851.

Parker T, Cash DM, Lane CA, Murray-Smith H, Wong A, Malone IB, Burgos N, Modat M, Beasley D, Dickson J, Barnes A, Thomas DL, Cardoso MJ, Klimova J, Ourselin S, Frost C, Kuh D, Richards M, Fox NC and Schott JM. Brain volume, cerebral β-amyloid deposition, and ageing: a study of over 200 individuals born in the same week in 1946. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):1464.

Schott JM, Cash DM, Lane CA, Parker T, Burgos N, Modat M, Beasley D, Dickson J, Barnes A, Thomas DL, Murray-Smith H, Wong A, Macpherson K, James S-N, Cardoso MJ, Malone IB, Klimova J, Markiewicz P, Crutch SJ, Kuh D, Ourselin S, Richards M and Fox NC. Exploring the population prevalence of β-amyloid burden: an analysis of 250 individuals born in mainland britain in the

same week in 1946. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2017;13(7):1088.

James SN, Davis D, Rawle M, Wong A, Kuh D, Schott JM, Richards M and Fox NC. Head injury with loss of consciousness and subsequent cognitive decline: follow-up in the 1946 British birth cohort study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2018;14(7):278.

Lane CA, Sudre CH, Barnes J, Nicholas JM, Hardy R, Parker TD, Murray-Smith H, Keshavan A, Cash DM, Malone IB, Wong A, Kuh D, Ourselin S, Cardoso MJ, Fox NC, Richards M and Schott JM. Influences of blood pressure and blood pressure trajectories on cerebral pathology at age 70: results from a British birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2018;14(7): 626.

Schott JM, Keshavan A, Pannee J, Heslegrave A, Richards M, Fox NC, Zetterberg H, Blennow K. The 1946 birth cohort - relationships between cerebral amyloid pathology using two independent methods for plasma amyloid beta measurement. *AAIC* 2019; **featured research session**

James SN, Lane CA, Parker T, Nicholas JM, Sudre CH, Barnes J, Cash DM, Malone IB, Lu K, Keshavan A, Murray-Smith H, Wong A, Buchanan S, Keuss S, Coath W, Barnes A, Dickson J, Modat M, Thomas D, Crutch S, Kuh D, Fox NC, Schott JM, Richards M. Divergent associations between life course cognitive trajectories and brain pathologies: findings from the 1946 British birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2019:15(7): 883.

Lane CA, Barnes J, Nicholas, JM, Parker T, Keshavan A, Buchanan S, Keuss S, Sudre CH, Cash DM, Malone IB, James SN, Murray-Smith H, Wong A, Richards M, Fox NC, Schott JM. Early adulthood vascular risk strongly predicts brain volumes and white matter disease, but not amyloid status, at age 69-71 years – evidence from a British Birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2019:15(7): 1269-1270.

Parker TD, Cash DM, Lane CA, Lu K, Malone IB, Nicholas J, James SN, Keshavan A, Murray-Smith H, Buchanan S, Keuss SE, Sudre CH, Thomas DL, Wong A, Barnes A, Dickson J, Modat M, Crutch SJ, Richards M, Fox NC and Schott JM. Age, β-amyloid and cognition selectively influence

hippocampal subfield volume: a study of 408 healthy adults born in 1946. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2019:15(7): 906.

Cash DM, Modat M, Coath W, Cardoso J, Markiewicz P, Lane C, Parker T, Keuss S, Buchanan S, Burgos N, Dickson J, Barnes A, Thomas D, Beasley D, Malone I, Wong A, Erlandsson K, thomas B, Ourselin S, Fox N, Richards M, Schott J. Longitudinal rates of amyloid accumulation in a 70-year old British birth cohort. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2019:15(7): 16-17.

Coath W, Modat M, Cardoso MJ, Markiewicz P, Lane CA, Parker TD, Keuss SE, Buchanan S, Burgos N, Dickson J, Barnes A, Thomas DL, Beasley DG, Malone IB, Wong A, Thomas B, Ourselin S, Richards M, Fox NC, Schott JM and Cash DC. Centiloid scale transformation of Florbetapir data acquired on a PET/MT scanner. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2019:15(7): 17-18.

Kehsavan A, Lane CA, Parker TD, Lu K, Cash DM, Sudre CH, Nicholas JM, Heslegrave AM, James SN, Murray-Smith H, Buchanan SM, Keuss SE, Thomas D, Malone IB, Wong A, Richards M, Zetterberg H, Fox NC, Schott JM. Plasma amyloid, tau and serum neurofilament light chain in Insight 46, the neuroscience sub-study of the 1946: associations with cognition and brain imaging. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2019:15(7): 1023.

AAIC 2020 (status as March 2020)

James S-N, Lane CA, Parker TD, Lu K, Keshavan A, Buchanan SM, Keuss SE, Cash DM, Malone IB, Barnes J, Sudre CH, Coath W, Prosser L, Nicholas JM, Murray-Smith H, Wong A, Hughes AD, Chaturvedi N, Fox NC, Richards M, Schott JM. Lifetime cigarette smoking and later-life brain health: the population-based 1946 British Birth Cohort. *Accepted as poster.*

Keshavan AK, Karikari TK, Lane CA, Parker TD, Lu K, Cash DM, Sudre CH, Nicholas JM, Heslegrave AJ, Wellington H, James S-N, Murray-Smith H, Buchanan SM, Keuss SE, Thomas D, Malone IB, Wong A, Richards M, Zetterberg H, Blennow K, Fox NC, Schott JM. Plasma phosphor-tau in Insight 46 – associations with cerebral amyloid, structural imaging and cognition. *Accepted as oral.*

Keuss SE, Poole T, Cash DM, Lane CA, Parker TD, Buchanan SM, Keshavan A, Coath W, Malone IB, Thomas DL, Sudre CH, Barnes J, Lu K, James S-N, Wagen A, Storey M, Murray-Smith H, Wong A, Richards M, Fox NC, Schott HM. Cerebral amyloid and white matter hyperintensity volume are independently associated with rates of cerebral atrophy in Insight 46, a sub-study of the 1946 British birth cohort. *Accepted as poster.*

Lu K, Pavisic I, James S-N, Street R, Keuss SE, Buchanan SM, Wagen A, Storey M, Parker TD, Lane CA, Keshavan A, Murray-Smith H, Cash DM, Malone IB, Coath W, Wong A, Henley SMD, Crutch SJ, Fox NC, Ricahrds M, Schott HM. Accelerated forgetting is sensitive to β-amyloid pathology and cerebral atrophy in cognitively-normal 72-year-olds. *Accepted as poster.*

Lu K, Nicholas JM, Pertzov Y, Grogan J, Husain M, Pavisic I, James S-N, Parker TD, Lane CA, Keshavan A, Keuss SE, Buchanan SM, Murray-Smith H, Cash DM, Malone IB, Coath W, Wong A, Henley SMD, Crutch SJ, Fox NC, Richards M, Schott JM. APOE-ε4 carriers have superior recall on the "What was where?" visual short-term memory binding test at age 70, despite a detrimental effect of β-amyloid. *Accepted as poster.*

Parker et al. Cerebral amyloid deposition predicts cortical neuritic microstructure, but not cortical thickness, in cognitively healthy adults aged approximately 70 years old. *Abstract submitted to AAIC 2020.*

Schott JM, Lane CA, Barnes J, Keuss SE, James SN, Lu K, Sudre CH, Cash DM, Parker TD, Malone IB, Keshavan A, Murray-Smith H, Wong A, Buchanan SM, Gordon E, Coath W, Barnes A, Dickson J, Modat M, Thomas D, Chaturvedi N, Hughes A, Crutch SJ, Richards M, Fox NC. Vascular risk factors and amyloid pathology: additive or interactive associations? *Accepted as featured research session.*

Street R, Lu K, Huckvale M, Brotherhood E, Pavisic I, James S-N, Keuss SE, Buchanan SM, Parker TD, Lane CA, Keshavan A, Murray-Smith H, Cash DM, Coath W, Wong A, Fox NC, Richards M, Schott JM, Crutch SJ. Performance on the Graded Naming Test in a population-based sample of 72-year-olds: associations with life-course predictors and β-amyloid pathology. *Accepted as poster.*

Wagen AZ, Coath W, Keuss SE, Buchanan SM, Storey M, Lu K, Pavisic I, James S-N, Carr H, Street R, Parker TD, Lane CA, Keshavan A, Murray-Smith H, Cash DM, Malone IB, Wong A, Henley SMD, Crutch SJ, Zetterberg H, Wellington H, Heslegrave A, Fox NC, Richards M, Cole J, Schott HM. Serum neurofilament light and whole brain volume associate with machine-learning derived brain-predicted age in the British 1946 Birth Cohort. *Accepted as poster.*

Other engagement activities

Schott JM. Determining the causes and consequences of brain amyloidosis, atrophy and cerebrovascular disease: a longitudinal amyloid-PET/MRI study of the MRC British 1946 birth cohort. *Presentation at the DPUK Collaboration Seminar. February 2015.*

Lane CA, Parker TD, Murray-Smith. A longitudinal amyloid-PET/MRI study of the MRC NSHD British 1946 birth cohort. *Poster presented at DPUK Symposium 2015.*

Murray-Smith H. A longitudinal amyloid-PET/MRI study of the MRC NSHD British 1946 birth cohort. *Poster presented at Leonard Wolfson Experimental Neurology Centre International Clinical Trials Day. Jaune 2015.*

Murray-Smith H. The MRC National Survey of Health and Development (NSHD) Neuroimaging Sub-study: INSIGHT 46. *Presentation at the Leonard Wolfson Experimental Neurology Centre Training Day. June 2015.*

Lane et al. Work Package 4: Amyloid Discovery Cohort. *Poster presented at DPUK Symposium 2016.*

Markiewicz PJ, Herholz K, Zaharchuk G, Schott J, Cash D, Schott JM, Button BP, Matthews JC, Fox NC, Barnkof F, Ourselin S. Unified infrastructure for harmonization of PET imaging across the Dementias Platform UK centres. *Poster presented at DPUK Annual Meeting 2017.*

Lu K. Visuomotor integration in Insight 46, a neuroscience sub-study of the MRC National Survey of Health and Development. *Presentation at UCL Queen Square Symposium 2017.*

James SN. Life-course incidence of head injury and subsequent later-life cognition. *Poster presented at DPUK conference 2018.*

Keshavan A. Exploring the role of blood-based biomarkers for Alzheimer's disease in a pre-clinical cohort: Insight 46 – The Neuroimaging Sub-study of the MRC National Survey of Health and Development. *Poster presented at the UCL Queen Square Symposium 2018.*

James SN, Lu K, Carr H, Popham M. Insight 46: Scanning people in the longest-running British Birth Cohort. *Information stall at the ARUK UCL network public engagement called Meet the Scientist. October 2018.*

James SN. Investigating risk factors for dementia: Over 65 years of follow-up in the 1946 Birth Cohort. *Presentation to the British Heart Foundation. October 2018.*

James SN. What have we learnt about longitudinal studies? *Invited presentation to the UK Sports Concussion Research Symposium*. *November 2018.*

Buchanan SM, Parker TD, Lane CA, Keshavan A, Keuss SE, Schrag AE, Fox NC, Richards M, Schott JM. Relationships between walking speed, cognition and brain pathologies: an imaging study of the 1946 birth cohort. *Oral presentation at ABN 2019.*

Buchanan SM et al. The cognitive profile associated with mild parkinsonian signs in a British Birth Cohort at age 69-71. *Poster presented at International Congress of Parkinson's Disease and Movement Disorders 2019.*

Keshavan A, Lane CA, Parker TD, Lu K, Cash DM, Sudre CH, Nicholas JM, Heslegrave AJ, James S-N, Murray-Smith H, Buchanan SE, Thomas D, Malone IB, Wong A, Richards M, Zetterberg H, Fox NC, Schott JM. Blood biomarkers of amyloid, tau and neurofilment light chain in the 1946 British birth cohort – relationships with cerebral amyloid and brain imaging. *Oral presentation at ARUK Student Day 2019.*

Keuss SE et al. Incidental findings on brain magnetic resonance imaging. *Abstract submitted to AAN 2020.*

Parker TD et al. Pure tone audiometry and cerebral pathology in healthy older adults. *Abstract submitted to ABN 2020.* Publication no 6 by Lu *et al*. was featured as a research story on the DPUK web-site. It showed that the performance of eight-year-olds on a test of thinking skills may predict how they will perform on tests of thinking and memory skills when they are 70. The study was covered by an article in The Times.
Influence of policy, practice, patients & the public
An important paper arising from this study examined changes in blood pressure and any implications for cognitive impairment was published in The Lancet Neurology (see Lane *et al*. 2019). This has public health implications suggesting that the monitoring of blood pressure, and any changes needs to be undertaken from age 40, earlier than current guidelines. https://doi.org/10.1016/S1474-4422(19)30228-5
Research Tools & Methods
None
Research Databases & Models
Processing is complete for the data on volumetric T1 and amyloid scans, date of scan, sex, month and year of birth, and MMSE score and all have been transferred to the central DPUK portal.
Intellectual property & licencing
None
Medical products, interventions & clinical trials
None
Artistic & creative products
None
Software & technical products
None
Spin outs
None
Awards & recognition

Other outputs & knowledge/future steps

None

Use of facilities & resources

Processing is complete for the data on volumetric T1 and amyloid scans, date of scan, sex, month and year of birth, and MMSE score and all have been transferred to the central DPUK portal.

Most successful outcome and what it means for future dementia research:

Given the breadth of the study and its outcomes it is difficult to identify one major outcome. Two particular highlights would be:

- The demonstration that midlife vascular risk influences late life brain health and that this may extend as far back as the 30s has significant implications for dementia prevention and public health policy.

- Our work – presented in abstract form and currently under review – demonstrating the utility of blood based biomarkers to pre-screen individuals for more invasive/expensive tests to predict β-amyloid load on a population basis is likely to have significant influence on pre-symptomatic clinical trial design

Lessons learned:

1) The Team optimised the processes for scheduling participants' visits and staffing and will use these in future data collection phases.
2) Tracer availability and production was problematic at times resulting in the need to reschedule scans. This could have been mitigated by using a tracer produced closer to London (limiting traffic delays) or a tracer than had more flexibility in it production time and QC processes.
3) There were technical hurdles to overcome in the analysis and transfer of data from the PET/MRI scanner to UCL and from UCL to the DPUK platform. Lessons learned will make similar activities more efficient in future.

Other:

None

Date of Report: 31 March 2020