

The Disconnected Mind

Unlocking secrets of healthy mental ageing

The Disconnected Mind aims to understand how changes in the brain's white matter – its connectivity – contribute to age-related cognitive decline in humans.

Newsletter 57: March 2022

Welcome to the Spring 2022 Disconnected Mind newsletter. This issue includes news about the Disconnected Mind/Lothian Birth Cohorts (LBC) team, our latest publications, and recent events.

For further information or to contribute to a future issue, please contact us using the details on page 8.

Lothian Birth Cohorts News

LBC1936 Wave 6: An update

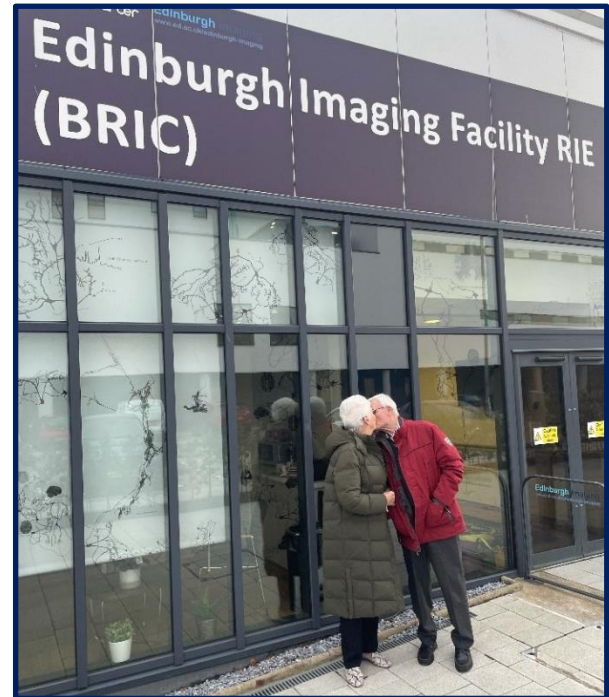
We are delighted to report that Wave 6 of the LBC1936 study has been progressing very well so far in 2022, and the team continue to be blown away by the enthusiasm and dedication of our participants. At the time of publication, we have reached two key milestones: we have had 100 participants return to the Wellcome Trust Clinical Research Facility (WTCRF) for cognitive testing appointments, and 50 have attended the new scanning facility at Edinburgh Imaging Facility (EIF), Royal Infirmary of Edinburgh, for an MRI brain scan. We are looking forward to seeing many more LBC1936 participants throughout 2022 and beyond, and continuing with this great progress.

In February, the testing team also celebrated Valentine's Day with an unusual coincidence. At the first wave of the LBC1936 study in 2004, a few of our 1091 participants were couples, some of whom still attend their LBC appointments together at every



LBC1936 couple Alistair and Margaret at the WTCRF

wave. By chance, on Monday 14th February 2022, all of our available appointments were booked by our couples! Alistair and Margaret spent Valentine's Day at the WTCRF completing cognitive and physical tests, and John and Helen spent that afternoon at the EIF each having an MRI brain scan. How romantic!

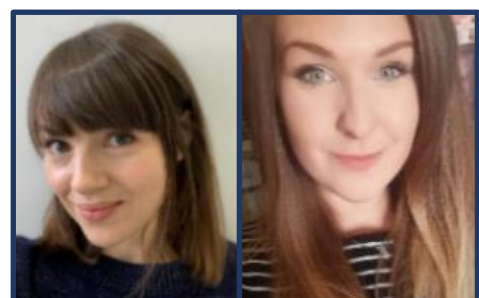


LBC1936 couple Helen and John share a romantic moment at the EIF

Staff news

MSc successes from the LBC1936 team

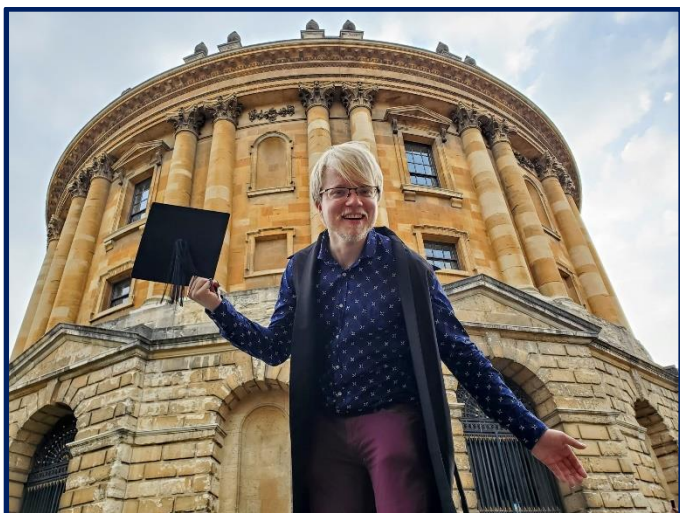
In our Autumn 2021 edition, we celebrated our young researchers, including two of our core LBC1936 team; Study Coordinator Adele Taylor and Research Assistant Danielle Page both completed MSc programmes part-time, using LBC data in their theses, while working full-time with the LBC team. We are delighted that they have now received their final degree awards: Adele received a distinction in her MSc by Research in Psychology, and Danielle received a distinction in her MSc in Human Cognitive Neuropsychology. Congratulations, both!



Congratulations to Adele Taylor (left) and Danielle Page (right)

Welcome PhD student: Otto-Emil Jutila

Otto-Emil Jutila joined the group as a Ph.D. student of Precision Medicine Doctoral Training Programme in collaboration with the University of Edinburgh and Karolinska Institute, funded by the Medical Research Council. His Ph.D. project will be supervised by LBC co-investigators Michelle Luciano and Tom Russ, as well as Postdoctoral researcher Ida Karlsson of the Karolinska Institutet, Sweden. Otto will investigate the relationship of air pollution with dementia and cognitive decline, the interaction of genetic predisposition on the relationship. He recently finished his MSc in Global health science and epidemiology from the University of Oxford, after completing his undergraduate degree in Biomedical Science at Robert Gordon University in Aberdeen. He is excited to be involved with Lothian Birth Cohort and to produce research to help clarify the relationship between air pollution and brain health.

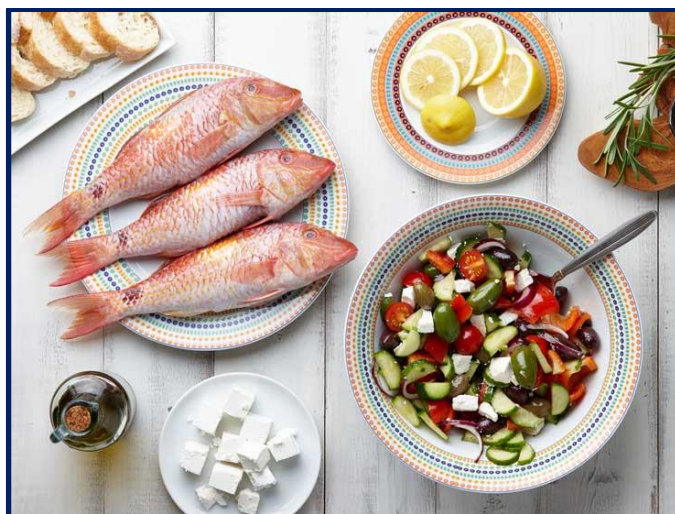


Scientific Highlights

Mediterranean diet is not associated with longitudinal change in MRI brain volume

Eating a Mediterranean diet, which contains a high volume of fruit, vegetables, legumes and cereals, and moderate consumption of fish, dairy products and wine, has been shown to have benefits on physical and mental health. In a recently accepted paper in *The Journal of Nutrition, Health & Aging*, LBC study co-investigator Dr Michelle Luciano and team tested whether Mediterranean-type Diet (MeDi) at age 70 in LBC1936 participants was associated with change in total brain MRI volume between ages 73 and 79. She found no association between MeDi adherence at age 70 and total brain volume change age at age 73-79 after controlling for other health confounding factors. This suggests that previous findings, which show associations between MeDi diet and brain volume, are potentially not long-lasting, or may become less important as ageing-

related conditions account for greater variation in brain volume change. She concluded that more frequent collection of dietary intake data may be required to confirm and clarify her findings.



Circulating metabolome and white matter hyperintensities in females and males

White matter hyperintensities (WMH), signs of damaged brain tissue caused by diseased small vessels, are identified in MRI brain scan images as areas of enhanced brightness. WMH are a major risk factor for stroke, dementia, and mortality. However, there has not yet been a large-scale study to examine any relationship between WMH and circulating metabolites: substances found in the blood which are made or used when the body metabolises, or breaks down, food, drugs, chemicals, or tissue such as fat tissue. In a large study of 9290 individuals including members of the LBC1936, [published](#) in *Circulation*, collaborator Eeva Sliz of the University of Toronto and colleagues identified 30 metabolomic measures associated with WMH, which showed marked differences between the sexes. In total, 7 were still associated with WMH after adjustment for confounding factors, the most significant of which accounted for between 3-14% of variance in WMH. It would seem that metabolomic measures explain a sizable proportion of WMH variance in middle-aged and older adults, and show marked sex specificities.

Circulation

Circulating Metabolome and White Matter Hyperintensities in Females and Males

Eeva Sliz, Jean Shin, Shahzad Ahmad, Dylan M. Williams, Stefan Frenzel, Friederike Gauß, Sarah E. Harris, Ann-Kristin Henning, Maria del C. Valdes Hernandez, Yi-Han Hu, ... [See all authors](#) ✓
and for the NeuroCHARGE Working Group

Blood analysis identifies relationships between patterns of DNA modifications and the onset of age-related chronic diseases

Although our genetic code does not change throughout our lives, our genes can be turned on and off as a result of epigenetics. Epigenetics can track how the environment and even certain behaviours add or remove small chemical markers to the DNA that makes up the genome. The type and location of these markers may affect whether genes are active or silent, that is, whether the protein coded for by that gene is being produced or not. One common epigenetic marker is known as DNA methylation. DNA methylation has been linked to the levels of a range of proteins in our cells and the risk people have of developing chronic diseases. Blood samples can be used to determine the epigenetic markers a person has on their genome and to study the abundance of many proteins.

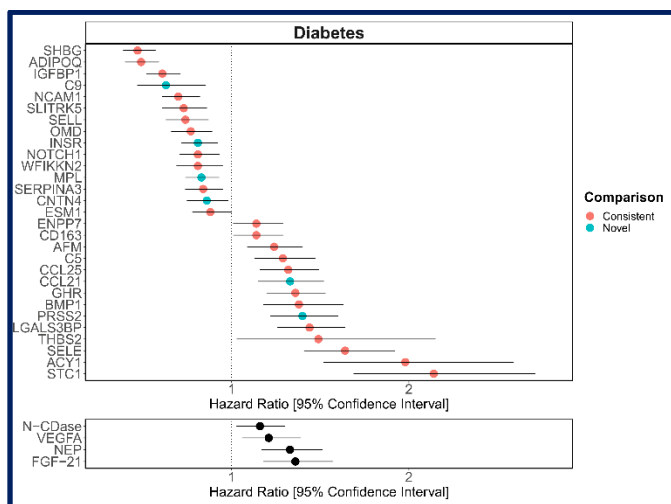


Figure from Gadd et al (2022) showing associations between 'EpiScores' and type 2 diabetes

In a [paper](#) accepted in *eLife*, PhD student Danni Gadd and colleagues studied relationships between DNA methylation and the abundance of 953 different proteins in blood samples from individuals in the LBC1936, as well as the German KORA cohort. They also used machine learning to analyse the relationship between epigenetic markers in people's blood and the abundance of proteins, obtaining epigenetic scores or 'EpiScores' for each protein. They found 109 proteins for which DNA methylation patterns explained between at least 1% and up to 58% of the variation in protein levels. Integrating the 'EpiScores' with medical records for over 9000 individuals from the Generation Scotland study revealed 137 associations between EpiScores and a future diagnosis of adverse health outcomes, including diabetes, stroke, depression, Alzheimer's dementia, various cancers, and inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease. Protein EpiScores

could therefore allow researchers to identify people with the highest risk of disease, making it possible to intervene early and prevent these people from developing chronic conditions as they age. The paper was selected for the eLife digest, and you can watch a summary [video](#) of the paper on YouTube.

Adherence to the MIND diet is associated with 12-year all-cause mortality in older adults

The role of diet in extending life expectancy has been the focus of extensive scientific research. The MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet, was recently developed to address optimal nutrition for the ageing brain. It is unknown whether it might also be related to a reduced risk of mortality, given its emphasis on healthy, plant-based foods. In a [paper](#) just published in *Public Health Nutrition*, Dr Janie Corley showed that greater adherence to the MIND diet at age 70 was associated with a reduced risk of mortality over 12 years (age 70 to 82). Participants in the top compared with the bottom third of MIND diet score had a 37% lower risk of death to follow-up, even after controlling for demographic and other lifestyle variables. Greater adherence to the MIND diet may therefore be associated with prolonged survival in older people.

Association of low-frequency and rare coding variants with information processing speed

In a recently published [paper](#) in *Translational Psychiatry*, co-led by LBC team members Dr Gail Davies and Prof Ian Deary, and Dr Jan Bressler of the University of Texas Health Centre at Houston, for the CHARGE consortium, the team explored contributions of rare coding variants of genes to processing speed scores. Low scores on a psychometric test of processing speed have been associated with mild cognitive impairment and dementia, and are potentially an endophenotype for age-related neurological disorders and other psychiatric conditions. There is interest in genetic contributions due to previously found heritability estimates of up to 67% for inter-individual variation on tests of processing speed in twin studies. Nine population-based cohort studies, including both LBC1921 and LBC1936, contributed to a sample size of 36,334 individuals; 30,576 of European ancestry and 5758 African Americans. Variants in one gene, RNF19A, were found to be associated with processing speed in the European ancestry individuals. This is important as previous studies have focused on contributions of common genetic variation, and the availability of a genotyping array designed to capture rare variation allowed those previously missing rare variants to be explored for the first time in this study.

Sex Differences in Cerebral SVD

Cerebral small vessel disease (SVD) is a common cause of stroke, mild cognitive impairment, dementia and physical impairments, but there are no studies investigating sex differences in incidence of severity. In a recently published [paper](#) including LBC data in *Frontiers in Neurology*, Translational Neuroscience PhD candidate and LBC collaborator Lorena Jiménez-Sánchez conducted a meta-analysis to examine the male-to-female ratio of participants with evidence of SVD, and this was linked to male:female differences in SVD risk factors or severity. Across 123 relevant studies with a total of almost 37,000 participant, there was a greater incidence in males in hospital-based studies compared to community-based studies, more males had moderate to severe SVD, particularly those presenting with stroke. The results have important clinical implications and may suggest male:female differences in risk factor exposure, adherence to risk factor interventions, SVD susceptibility, or recruitment settings. The authors suggest future research should include demographic information, risk factors, and outcomes, separately for males and females.

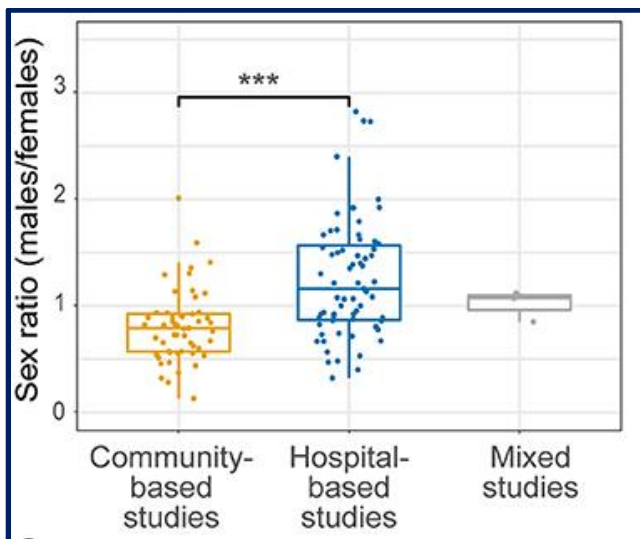


Figure from Jiménez-Sánchez et al (2022) showing significant differences between sex ratios in different study types

KE & Impact

Professor Joanna Wardlaw wins BNA prize



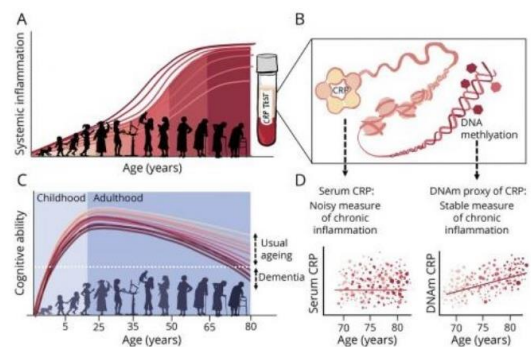
In December, LBC study Co-Investigator Professor Joanna Wardlaw won the prestigious British Neuroscience Association Award for Outstanding Contribution to Neuroscience. This is the most prestigious of the BNA's awards, reflecting excellence in the field of neuroscience. Congratulations, Joanna!

Eleanor Conole's 'Chronic Inflammation' paper appears in Neurology recommended section

In our December 2021 edition, we summarised a [paper](#) published in *Neurology* by LBC PhD student Eleanor Conole. In an exciting development, Eleanor's paper appeared in *Neurology*'s 'recommended' section of their website in December. In her paper, she examined associations between brain imaging measures and measures of low-level chronic inflammation, including traditional measures of inflammatory proteins in the blood such as C-reactive protein, and epigenetic markers which might more accurately reflect individuals' chronic inflammation status. Using data from 521 LBC1936 participants, she showed that a DNA methylation measure of C-reactive protein (DNAm CRP) was consistently more strongly related to brain imaging measures than traditional blood-based measures.

Notable This Week

Selected by José G. Merino, MD, MPhil, FAAN, Editor-in-Chief



RESEARCH ARTICLE | Brain Health

DNA Methylation and Protein Markers of Chronic Inflammation and Their Associations With Brain and Cognitive Aging

Dr Robert Hillary wins Sir Kenneth Mather Memorial Prize

Congratulations to Dr Robert Hillary who was awarded the Sir Kenneth Mather Memorial Prize for PhD work using LBC and Generation Scotland data. Robert completed his Wellcome-funded PhD programme in Translational Neuroscience with Dr Riccardo Marioni, of the Marioni Group, and LBC's founding Director Prof Ian Deary. His thesis, for which he was awarded this prestigious prize, aimed to determine whether blood-based molecular markers can predict dementia risk. Congratulations, Robert!



Primary school children 'meet the scientist' with Susana Muñoz Maniega

In February, team member Susana Muñoz Maniega was invited to speak to a class of 11 year olds at Whitehill Junior in Hitchin, Hertfordshire, for a 'Meet the Scientist' event as part of a Science and Computing week organised by local schools. Susana contributed with a presentation all about brain MRI. The children were fascinated to learn about how MRI works, and Susana challenged them with some fun quizzes, like MRI images of some fruit, veg and chocolate bars that the children had to guess! She also talked about the research on brain ageing we do with the MRI data of the LBC1936 participants. The children, age 11 themselves, were absorbed hearing about the Scottish Mental Surveys and asked great questions about how the brain changes as we grow older, particularly about how the brain's "wiring" is affected. Susana also presented videos illustrating some of the findings from LBC MRI data and gave them tips on how to keep their brains active and healthy.



Susana teaches the class about MRI brain scans and LBC findings

Michelle Luciano delivers talk on diet and the brain at New Town Cookery School event

LBC co-investigator Professor Michelle Luciano was invited in November 2021 to an event titled 'Good for you, Good for the Earth: the Mediterranean Diet', organised by Slow Food Organisation, Italian Consulate, Institute of Culture, and Chamber of Commerce and Industry at the New Town Cookery School, Edinburgh. Michelle delivered a talk about diet and brain MRI, drawing on findings from the LBC, to more than 30 attendees at the cookery school. The talk was very well received by all, and they had some great questions about the health benefits of a Mediterranean diet.



Michelle delivers talk at the New Town Cookery School, Edinburgh

Alan Gow at 'The Great British Brain Off'

In February, Alan Gow hosted two events exploring how lifestyles affect brain health including research findings from the Lothian Birth Cohort studies. As part of the RSE@Schools programme, Alan led an online session, "The Great British Brain Off", with two Higher Biology classes at St Matthew's Academy, Saltcoats. The students considered the 'recipe' for good brain health, including how things like smoking or physical activity might benefit brain health. Later that week, Alan was at a snowy Blackburn Partnership Centre continuing an outreach collaboration with West Lothian Libraries. His "How to Stay Sharp" session was part of a series of events for a Love Your Libraries Open Day being held across their libraries and centres, to encourage people back to those spaces as restrictions continue to ease across Scotland.



Resources at West Lothian Libraries event

Launch of the 'Unlock & Revive' Report: A key to wellbeing for people living with dementia through online heritage sessions

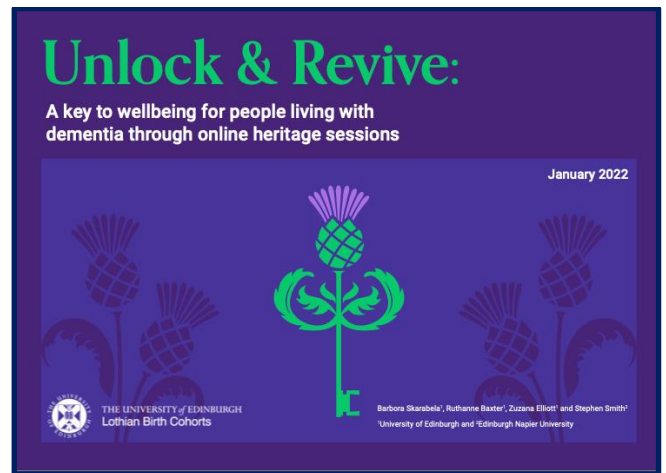
A year ago in Spring 2021, the LBC team participated in the 'Unlock & Revive' Programme, a cross-disciplinary [pilot project](#) aimed at supporting the wellbeing of people and communities living with dementia, through online heritage and cultural engagement activities. The programme was created as part of 'Prescribe Culture', the University of Edinburgh Museums' award-winning, heritage-based, non-clinical health, social care and wellbeing support initiative



The programme consisted of three series: 'Sing It Back', a series of online signing sessions, delivered by Heather Macleod in partnership with Lothian Birth Cohorts. Second, there were a series of online Historic Environment Scotland Archive Talks, which explored archive records. These aimed to engage participants in a journey through popular cultural and social events in recognisable destinations, as captured in photography recorded over the past 70 years. Third, there were the University of Edinburgh Museums' Heritage Share Conversations, a series of small-group conversational sessions inspired by archives from the University's heritage collections.

As well as being involved in these events, the LBC team led the evaluation of the project. We used a qualitative approach to explore findings from focus groups with people with dementia, their carers and community care leads, and semi-structured interviews with event facilitators. The aim was to capture the participants' experience and the events' impact on their wellbeing. This evaluation resulted in a report, launched in January 2022 and available as a [PDF](#), offering a set of practical recommendations for accessible and engaging online events, informed by the voices of the programme's participants. It highlights the challenges and benefits of delivering a programme of heritage-based online social prescribing for those living with dementia and related conditions, with useful tips for those interested in designing and delivering such

programme. The report was created as a resource primarily for heritage and cultural event organisers and Community Care professionals working with people and communities living with dementia and related conditions. It may also be of interest to health care professionals as well as carers and people with dementia.



The launch of the report was celebrated with an event delivered by Ruthanne Baxter of the University of Edinburgh Museums' Services and Barbora Skarabela. They shared their findings, and reviewed the recommended practices for planning, co-designing, training, marketing, programme access, session content and event facilitation. Event attendees also heard from the participants, including Community Care Partner, Joyce Cavanagh of Headway East Lothian, Session Facilitator Jackie Sangster of Historic Environment Scotland, and two participants diagnosed with dementia and brain injury who had attended events. The event was very well attended, and the report has been well received with great feedback.

The Unlock & Revive pilot project evaluation was funded by the College of Arts, Humanities and Social Sciences (CAHSS) Knowledge Exchange and Impact Fund. LBC team member Barbora also recently attended the CAHSS Knowledge Exchange Network Meeting to share her insights and review KE practices based on the evaluation of the Unlock & Revive pilot project.



Contact

You can contact the LBC team by email, and keep up with our latest news on our website and Twitter.



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National Institutes of Health



THE ROYAL
SOCIETY



New publications

Accepted/in press

Luciano, M., Corley, J., Valdés Hernández, M. C., Craig, L. C. A., McNeill, G., ... Wardlaw, J. M. (2022). Mediterranean-type diet and brain structural change from 73 to 79 years in the Lothian Birth Cohort 1936. *Journal of Nutrition, Health and Aging*.

Brouwer, R. M., Klein, M., Grasby, K. L., Schnack, H. G., Jahanshad, N., Teeuw, J., ... Hulshoff Pol, H. E. (2022). Age-dependent genetic variants associated with longitudinal changes in brain structure across the lifespan. *Nature Neuroscience*.

Published

Bressler, J., Smith, A. V., Saba, Y., Bis, J. C., Jian, X., Hayward, C., ... Deary, I. J. (2021). Association of low-frequency and rare coding variants with information processing speed. *Translational Psychiatry*, 11(1), 613. <https://doi.org/10.1038/s41398-021-01736-6>

Corley, J. (2022). Adherence to the MIND diet is associated with 12-year all-cause mortality in older adults. *Public Health Nutrition*, 1–10. <https://doi.org/10.1017/S1368980020002979>

Gadd, D. A., Hillary, R. F., McCartney, D. L., Zaghlool, S. B., Stevenson, A. J., Cheng, Y., ... Marioni, R. E. (2022). Epigenetic scores for the circulating proteome as tools for disease prediction. *ELIFE*, 11. <https://doi.org/10.7554/eLife.71802>

McCartney, D. L., Hillary, R. F., Conole, E. L. S., Banos, D. T., Gadd, D. A., Walker, R. M., ... Marioni, R. E. (2022). Blood-based epigenome-wide analyses of cognitive abilities. *Genome Biology*, 23(1). <https://doi.org/10.1186/s13059-021-02596-5>

Schlosser, P., Tin, A., Matias-garcia, P. R., Thio, C. H. L., Joehanes, R., Liu, H., ... Teumer, A. (2021). Meta-analyses identify DNA methylation associated with kidney function and damage. *Nature Communications*, 12(1). <https://doi.org/10.1038/s41467-021-27234-3>

Sliz, E., Shin, J., Ahmad, S., Williams, D. M., Frenzel, S., Gauß, F., ... Pausova, Z. (2022). Circulating Metabolome and White Matter Hyperintensities in Females and Males. *Circulation*. <https://doi.org/10.1161/CIRCULATIONAHA.121.056892>

Tin, A., Schlosser, P., Matias-garcia, P. R., Thio, C. H. L., Joehanes, R., Liu, H., ... Köttgen, A. (2021). Epigenome-wide association study of serum urate reveals insights into urate co-regulation and the SLC2A9 locus. *Nature Communications*, 12(1). <https://doi.org/10.1038/s41467-021-27198-4>