

# 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 56: December 2021

Welcome to the Winter 2021 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

### Wave 6 of the LBC1936 study begins

We are very glad to report that in October, following an 18 month delay due to the COVID-19 pandemic, we began the 6<sup>th</sup> wave of data collection with the LBC1936 cohort at the Wellcome Trust Clinical Research Facility (WTCRF). We hope to welcome 350 LBC1936 participants in total at mean age 86, and will again be collecting a huge range of cognitive, physical, health, lifestyle and MRI brain data, much of which has also been collected at previous waves. New to this wave, we are working closely with colleagues in the Alzheimer Scotland Dementia Research Centre (ASDRC), directed by Dr Tom Russ, one of the medics for the LBC studies. Tom's team are examining health records to determine important health outcomes in LBC1936 participants, including dementia diagnoses. This will be an invaluable resource for researchers trying to determine factors related to the development of dementia and other ageing-related outcomes.



An image of the first LBC1936 participant, Mrs Morrison, taking part in cognitive tests at wave 6; October 2021



LBC1936 participant Mrs Morrison with radiographers Maddy and Isla, taking part in the first MRI brain scan in October 2021

At the time this newsletter was published, 46 participants have attended a cognitive appointment at the WTCRF, and 16 have returned for an MRI brain scan at the new scanning facility at Edinburgh Imaging Facility (EIF), Royal Infirmary of Edinburgh. The team have been blown away by how keen participants have been thus far to return for Wave 6. The value of their generous contributions to the study only continues to grow each time we see them, and the data we collect holds tremendous promise for making many important scientific discoveries in the coming years. We look forward to continuing the wave into 2022 and beyond, and to the many discoveries which await following data collection.

### Breaking News: LBC team awarded new core funding from BBSRC

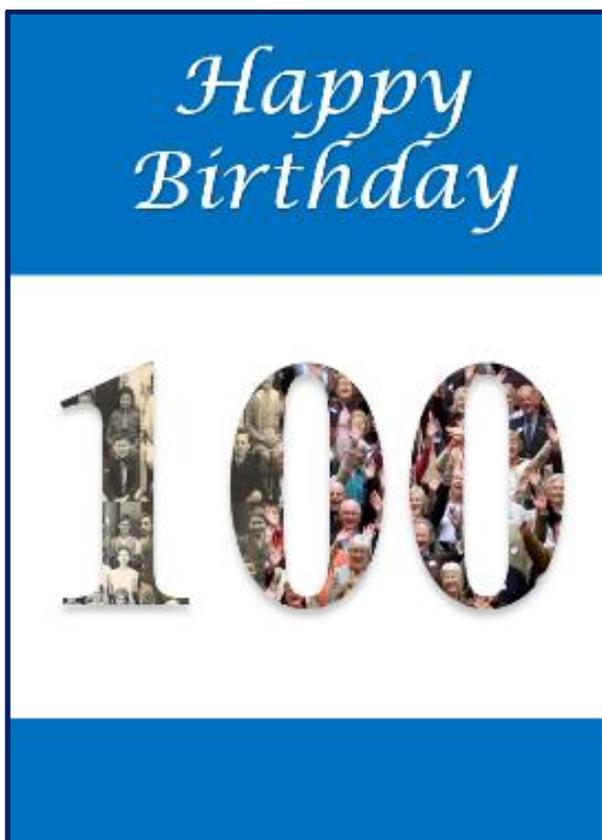
Christmas has come early for the team this year! In early December, we were informed that the Biotechnology and Biological Sciences Research Council has awarded core funding to the Lothian Birth Cohort studies. The £2 million award, which was led by Study Director Dr Simon Cox, will fund staff and data collection for LBC1936 Waves 6 and 7, taking the study up to 2025. More in the next newsletter!

## A century of the LBC1921

This year has marked an amazing milestone for our LBC1921 cohort, as they celebrated their 100<sup>th</sup> birthdays. Living to the age of 100 is a remarkable and rare achievement, and during 2021, study director Dr Simon Cox has been sending hand-written birthday messages to all of those in the cohort who are celebrating this marvellous milestone. We hope that all of our cohort members enjoyed a very happy birthday.

The LBC1921 study was established by Professor Ian Deary and the late Professor John Starr in 1998. At the time, 550 members of the cohort underwent cognitive and physical testing at mean age 79 years. Participants returned at up to four further occasions, with 59 participants tested at age 92 in the fifth and final wave of LBC1921 testing. Although data collection was completed in 2013, like their younger sister-cohort LBC1936, the LBC1921 have provided a lasting treasure-trove of data, which continues to contribute to scientific discoveries, particularly those focused on the genetics and epigenetics of ageing, up to the current day.

Many of these discoveries were explained in our recent podcast, 'Who gets to be 100?' which we told you about in our Autumn edition. During the podcast, we also spoke to two of our LBC1921 cohort about their childhood, memories of taking the famous Scottish Mental Survey of 1932, and their experience of being involved in research with the cohort. You can still listen to the podcast online.



## Staff news

### Welcome back, Mrs Alison Pattie!



In September, we were thrilled to welcome back Mrs Alison Pattie to the LBC study team. Alison started her retirement in March 2019, having worked continuously with the LBC studies since they began in 1999. Given her vast expertise on the study, having tested

LBC1921 and LBC1936 participants throughout all waves, she kindly agreed to come out of retirement in order to help the LBC1936 testing team with wave 6 data collection. Alison is an absolute asset to the team and we are thrilled to welcome her back. Some of you will see her at the WTCRF soon!

### RCPsych Awards 2021: Nominations for Dr Tom Russ and Dr Lucy Stirland

We are always delighted to share news of our researchers' and collaborators' amazing work being recognised by the scientific community. In October, Director of the Alzheimer Scotland Dementia Research Centre and Lothian Birth Cohorts co-investigator, Dr Tom Russ, was nominated for a prestigious Royal College of Psychiatrist Award 2021: the Saraswati Devi Jajoo Memorial Academic Researcher of the Year award. Our collaborator Dr Lucy Stirland, Postdoctoral Clinical Lecturer in Old Age Psychiatry, was also nominated for Higher Psychiatric Trainee of the Year. Congratulations, Tom and Lucy!

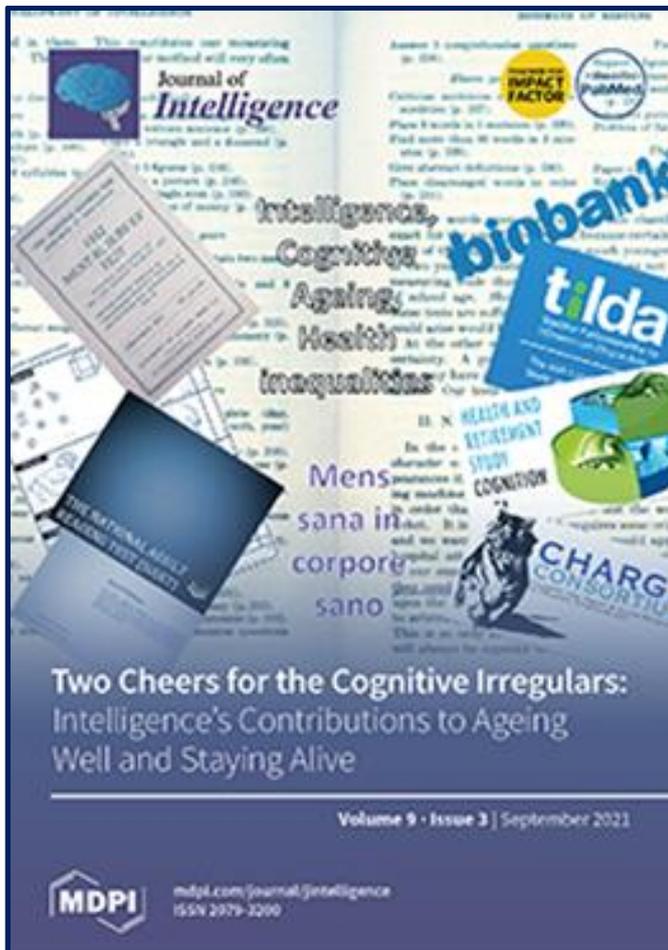


Dr Tom Russ and Dr Lucy Stirland

## Scientific Highlights

### Two cheers for the cognitive irregulars!

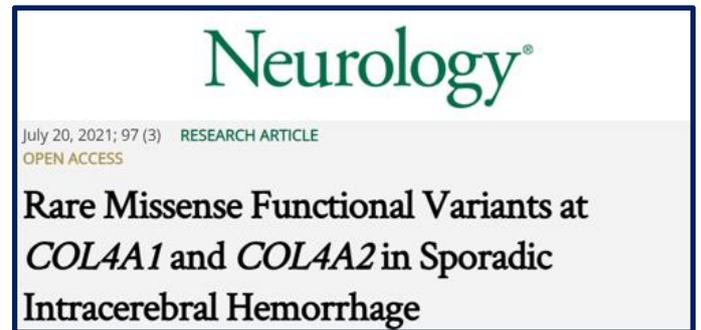
Former LBC study director, Professor Ian Deary, recently authored an [article](#) which was featured as the cover story in *Journal of Intelligence* in their autumn edition. In the article, Ian described how cognitive tests offer assessments of brain functioning, which is otherwise quite difficult to assess, and tests' value in the fields of medicine and health research. He also addressed how certain, often brief, cognitive tests might be used to address some current societal problems in the field, including our ageing society and subsequently increasing number of people with ageing-related cognitive problems and dementia, and inequalities in health outcomes including mortality. He also explained how these cognitive tests, including those taken by the LBC studies, are being used to contribute to research which helps people stay sharp, remain healthy, and live longer.



### Rare Missense Functional Variants at COL4A1 and COL4A2 in Sporadic Intracerebral Hemorrhage

Genome-wide association studies have previously identified common genetic loci associated with intracerebral haemorrhage (ICH) risk, particularly in the genes *COL4A1* and *COL4A2* (collagen IV  $\alpha$  chain 1 and 2). In this study by our collaborator

Jaeyoon Chung and colleagues, published in *Neurology*, LBC1921 and LBC1936 participant whole genome sequencing data were included as stroke-free controls in a study looking to examine associations between sporadic ICH and rare 'missense variants', genetic alterations in genes which cause them to produce slightly different amino acids than usual. They indeed identified some rare missense variants in *COL4A1/A2* which were associated with sporadic ICH, and subsequent simulation studies suggest these rare variants would be good targets for follow-up studies.



### Epigenetic scores for the circulating proteome as tools for disease prediction

In a paper now under review with *Biology* and available as a pre-print [online](#), PhD student Danni Gadd and colleagues used LBC1936 data along with four other cohorts to create scores for levels of 953 proteins in the blood, using epigenetic data. She then tested these scores in another large sample, Generation Scotland, and found 137 protein scores which predicted diseases, including the onset of Alzheimer's Dementia, as well as diabetes and stroke, over a follow-up of 14 years. The paper provides new insights into early markers of a range of diseases, including types of dementia.

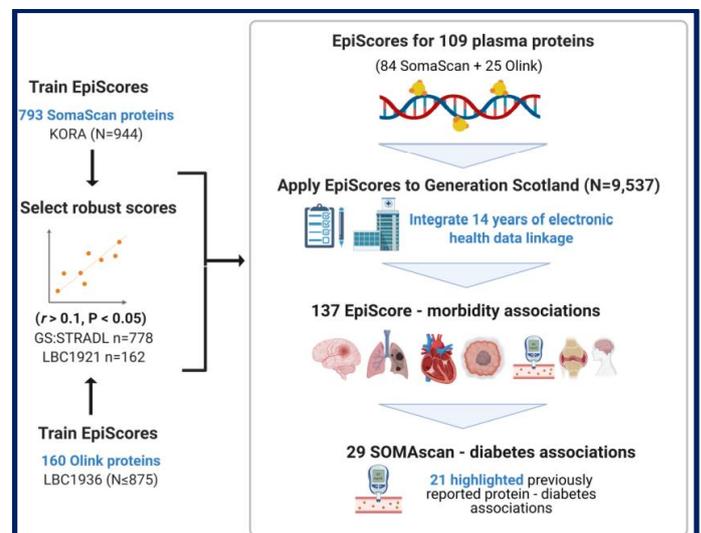
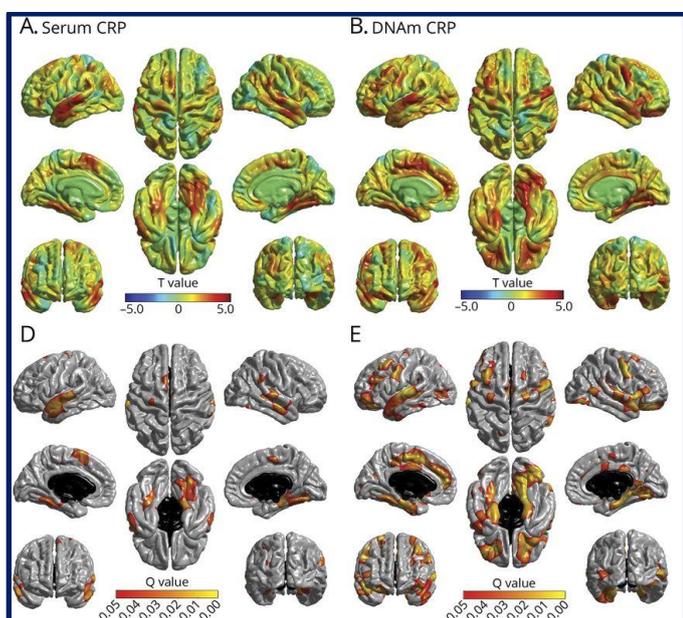


Figure from Gadd et al 2021 showing process of identifying and testing protein scores

## DNA Methylation and Protein Markers of Chronic Inflammation and their Associations with Brain and Cognitive Aging

Low-level chronic inflammation increases with age and is associated with brain ageing and cognitive decline. However, traditional measures of chronic inflammation that assess inflammatory proteins in the blood, such as C-reactive protein (CRP), provide unreliable estimates their concentration in the blood can change very rapidly. Epigenetic markers might provide a more accurate reflection of an individuals' chronic inflammation status. In a paper published in *Neurology*, by Disconnected Mind PhD student, Eleanor Conole, she examined whether a DNA methylation signature of CRP (DNAm CRP) was more strongly associated with brain structure and function than a blood-based measure of CRP, in 521 participants from the LBC1936 study.



Adapted figure from Conole et al (2021) showing associations between CRP measures and regional brain structure

Eleanor found that associations between DNAm CRP and brain imaging measures were consistently stronger than those with blood-based measures. Higher DNAm CRP levels were associated with global and regional brain atrophy, altered white matter microstructure and increased white matter hyperintensities, and global and domain-specific cognitive function. The partial mediation of associations between DNAm CRP scores and cognitive function by brain structural measures suggests that chronic inflammation may be related to neurodegenerative brain changes in older age, which in turn contribute to cognitive ability differences in later life. Overall, DNA methylation signatures of inflammation may act as promising proxies for tracking chronic inflammatory status in older age.

## KE & Impact

### Brain Matters: Explore your senses

We returned, virtually, to primary schools around Edinburgh this October at the Midlothian Science Festival Programme for Schools with our 'Brain Matters: Explore your Senses' workshop. Over two days, team members Judy Okely and Barbora Skarabela led over 180 Midlothian P4 children from four schools through activities designed to help them discover more about their senses and how the brain processes information from our sense organs, while supporting their development of scientific concepts and skills. The pupils participated in five hands-on activities that helped them investigate the reliability and limitations of the senses, using taste tests, limits of sound and optical illusions.



The workshop was a great success and received great feedback from children and teachers alike. One teacher said: *"Thank you so much for your stunning workshop - I really appreciate all the hard work that has gone into planning and resourcing it. Not to mention, the calm and knowledgeable presentation under very tricky technical difficulties. You couldn't see the excitement the children had at using the materials, testing the sandpaper and tasting the food. I loved the added details of the incredible senses of some animals. Thank you!"* Well done, Judy and Barbora!

### Stuart Ritchie's book 'Science Fictions' nominated for Royal Society Science Book Prize

Lothian Birth Cohorts co-investigator Dr Stuart Ritchie's book, *Science Fictions*, was recently shortlisted for the prestigious Royal Society Science Book Prize 2021. Stuart's book investigates flaws, biases and mistakes in today's science which can have disastrous consequences. Congrats, Stuart!



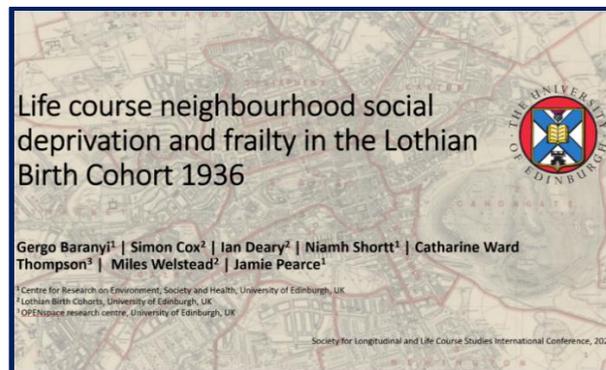
## Celebrating International Day of Older Persons

In 1990, the United Nations General Assembly designated 1<sup>st</sup> October as International Day of Older Persons. To mark the day, we celebrated all of the wonderful contributions our older people, in the LBC1921 and 1936 study, have made to science in a series of tweets. We shared facts about the cohort, scientific papers, and knowledge exchange resources, and reached 7680 unique twitter users. Our most successful tweet, which reached 2285 people, featured an LBC1936 [paper](#) published by team member Dr Drew Altschul and Professor Ian Deary, which found that playing analog games such as cards, chess, or doing crosswords is associated with less relative cognitive decline from age 11 to age 70, and less cognitive decline from age 70 to 79. We were excited that this was shared by two big names: Susan Polgar, chess grandmaster who made history as the first woman to win 'Grandmaster of the Year' from the United States Chess Federation, and Rob Jacques, crossword setter for papers including The Independent, The Financial Times, and The Telegraph!



### Gergo Baranyi presents LBC1936 findings at two conferences

In September, Research Associate at the Centre for Research on Environment, Society and Health, Gergo Baranyi, presented LBC1936 findings at two conferences: the Society for Longitudinal and Life Course Studies conference, and the Society for Social Medicine & Population Health 65th Annual Scientific meeting. His study explored how living in socially deprived neighbourhoods with more overcrowding and higher unemployment from childhood contributes to frailty. Frailty is an important topic of study: people who are frail tend to have greater vulnerability to stressors including injury and illness. Although frailty becomes more common generally as people age, there are individual differences with some people remaining less frail than others.



Gergo found that growing up and growing old in disadvantaged neighbourhoods leads to greater risk frailty in late adulthood among men, but for women, neighbourhood deprivation only showed an influence during the second half of life. This might be because, historically, in childhood boys tended to spend more time outside of the home in their wider neighbourhood than girls, and so would be exposed to more physical and social neighbourhood influences. Gergo also showed that growing old in less deprived areas was important for staying resilient to frailty. These areas likely provide better opportunities to support healthy ageing, with access to recreational, cultural and health facilities, higher quality green spaces, and lower rates of crime and violence. His presentations were very well-received at both conferences, and highlight the many ways the environment can influence physical and cognitive ageing over the lifespan.

### Alan Gow presents LBC findings

Alan Gow has been busy participating in a series of events using LBC findings as a solid foundation. These included four "How to Stay Sharp" sessions in libraries across West Lothian, as part of a new 'Borrow a Researcher' initiative between Heriot-Watt University and West Lothian Libraries. Alan explored various protective and risk factors for brain health, with specific findings from the LBC studies to help bring them to life. He also gave a presentation to another active and very engaged Probus group in Longniddry, as well as a discussion of physical activity and brain health for Sustrans, concluding with another outing for his 'Marginal Brain Gains' show, live at the Stand Comedy Club Edinburgh as part of the Cabaret of Dangerous Ideas.



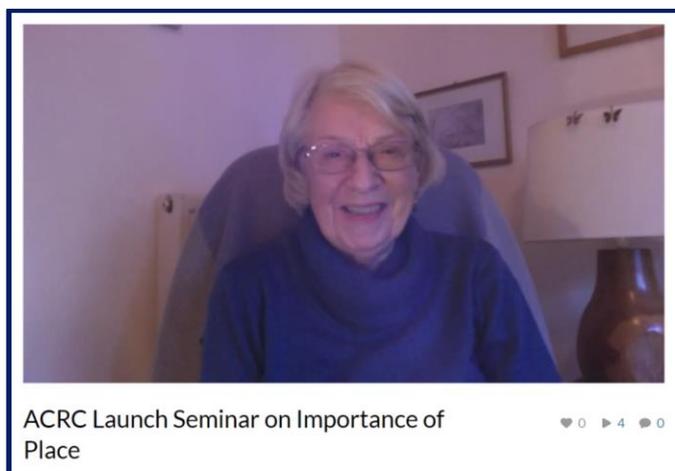
## LBC1936 participant at ACRC 'Importance of Place' seminar

The Advanced Care Research Centre (ACRC) is a multi-disciplinary research centre who are looking at care in later life. The centre has been up and running since the beginning of 2021, and they held an online launch event on Wednesday 3rd November, followed by six exciting seminars on some of their different research areas. At one of these seminars titled 'Importance of 'Place'', which is now available to view [online](#), one of our LBC1936 participants, Margaret Lawson, was invited to speak to give her perspective on the importance of 'place' to her.



The seminar also included interested talks from Prof. Catharine Ward Thompson, Professor of Landscape Architecture, Edinburgh College of Art; Dr. Alan Marshall, Senior Lecturer in Quantitative Methods, University of Edinburgh; Prof. Jamie Pearce, Personal Chair in Health Geography, University of Edinburgh; and Dr. Matthew Lowther, Head of Place and Equity, Public Health Scotland. The presentations and subsequent discussion with Margaret focused on the relationship between the quality, quantity and accessibility of green space and people's health and wellbeing, and the influence of 'place' during throughout life on ageing.

Margaret offered some very insightful comments in response to the presentations and participated in the panel discussion. She also reflected on the importance of place to her, and spoke about her own experiences of outdoor space as a child, how that might have changed over time in Edinburgh, and how this might differ for other people.



LBC1936 participant Margaret Lawson at the 'Importance of Place' seminar

## Why play the serpent?

The serpent is an unusual musical instrument, with history going back to the 16<sup>th</sup> century. It is one of many historic musical instruments included in St Cecilia's Hall's collections at the University of Edinburgh. The LBC team partnered with St Cecilia's for 'Being Human', the festival of humanities, to offer an online musical event with expert-led stories and activities, live performances, and facts about the benefits of playing musical instruments for our health.

Across two sessions, one of which was recorded and is available [online](#), LBC team member Dr Judy Okely shared how LBC1936 members are helping us discover some of the non-musical benefits of playing an instrument, including potential links between musical training and our physical abilities, listening skills, and thinking skills. There was also a live performance from Tony George of the Royal Conservatoire of Scotland, who performed with long-forgotten instruments and gave the history of their evolution.



In the private morning session, we were joined by 20 members from the East Lothians branch of Headway, the brain injury association which supports those impacted by traumatic brain injuries, during their in-person meeting. The event generated a great discussion in between attendees about the benefits of music in their lives. In the public evening session, there were a further 30 participants from different parts of the UK and Europe, many of whom were professional musicians, who also keenly contributed to the event with questions and comments. One said: *"the presentation was very informative and really well balanced, and the presenters came over as really nice, friendly, knowledgeable and approachable people."*

We plan to build on this partnership with St Cecilia's Hall in the future; watch this space!

## Contact

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



[lbc1936@ed.ac.uk](mailto:lbc1936@ed.ac.uk)



[@EdinUniLBC](https://twitter.com/EdinUniLBC)



[www.ed.ac.uk/lothian-birth-cohorts](http://www.ed.ac.uk/lothian-birth-cohorts)



## Some new publications

### Accepted/in press

Sliz, E., Shin, J., Ahmad, S., Williams, D. M., Frenzel, S., Gauß, F., ... Pausova, Z. (2021). Circulating metabolome and white matter hyperintensities in females and males. *Circulation*.

### Published

Backhouse, E., Shenkin, S. D., McIntosh, A. M., Bastin, M. E., Whalley, H., Hernandez, M. del V., ... Wardlaw, J. M. (2021). Early life predictors of late life cerebral small vessel disease in four prospective cohort studies. *Brain*.

Bressler, J., Davies, G., Smith, A. V., Saba, Y., Bis, J. C., Jian, X., ... Deary, I. J. (2021). Association of low-frequency and rare coding variants with information processing speed. *Translational Psychiatry*, 11(1), 613.

Conole, E. L. S., Stevenson, A. J., Maniega, S. M., Harris, S. E., Green, C., Valdés Hernández, M. D. C., ... Cox, S. R. (2021). DNA Methylation and Protein Markers of Chronic Inflammation and Their Associations With Brain and Cognitive Aging. *Neurology*, 10.1212/WNL.0000000000012997.

Corley, J., & Deary, I. (2021). Dietary patterns and trajectories of global and domain-specific cognitive decline in the Lothian Birth Cohort 1936. *British Journal of Nutrition*.

Hamilton, O., Cox, S., Ballerini, L., Bastin, M., Corley, J., Gow, A., ... Deary, I. (2021). Associations between total MRI-visible small vessel disease burden and domain-specific cognitive abilities in a community-dwelling older-age cohort. *Neurobiology of Aging*, 2021.02.02.21250986.

Min, J. L., Hemani, G., Hannon, E., Dekkers, K. F., Castillo-Fernandez, J., Luijk, R., ... Relton, C. L. (2021). Genomic and phenotypic insights from an atlas of genetic effects on DNA methylation. *Nature Genetics*, 53(9), 1311–1321.

Stevenson, A. J., Gadd, D. A., Hillary, R. F., McCartney, D. L., Campbell, A., Walker, R. M., ... Marioni, R. E. (2021). Creating and validating a DNA methylation-based proxy for interleukin-6. *The Journals of Gerontology: Series A*, glab046.

Yang, T., Jackson, V. E., Smith, A. V., Chen, H., Bartz, T. M., Sittlani, C. M., ... Morrison, A. C. (2021). Rare and low-frequency exonic variants and gene-by-smoking interactions in pulmonary function. *Scientific Reports*, 11(1), 19365.