

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 64: December 2023

Welcome to the December edition of the Disconnected Mind Newsletter! Each issue brings news about the Lothian Birth Cohorts team, our latest research and publications, and scientific and public engagement events.



LBC participants at the 2023 reunion

The year at a glance

As always, it has been a very busy year, with the LBC team making great progress with the study. Here we highlight some of the key events and achievements.

Updates from the Cognitive Testing Team

An important accomplishment of the last year was **the completion of Wave 6** of the LBC1936 study. The team saw a total of 293 participants at the Wellcome Trust Clinical Research Facility (WTCRF) for cognitive testing appointments, and 192 at the Edinburgh Imaging Facility (EIF) in the Royal Infirmary of Edinburgh for brain Magnetic Resonance Imaging (MRI) scans. Needless to say, this new data becomes more valuable every time we see them, and we are extremely grateful for their ongoing support and dedication to the LBCs! Similarly, we cannot fail to mention the contributions of the staff at the WTCRF and EIF as well as our local, national and international collaborators who have made this study and related discoveries possible, thank you all for your continuous support!

While the data from Wave 6 are being processed, the cognitive testing team look forward to welcoming the participants back for **Wave 7** of the LBC1936 Study in the new year!

Looking back at the past year, we cannot fail to mention **the LBC reunion** in May at the beautiful space of the National Museum of Scotland! It was a great opportunity for the team and collaborators to meet and engage with the participants, and to tell them how we have been holding up our end of the bargain, and also ask their views and suggestions for future studies.

Staff and students' achievements

Amongst this year's highlights are successes of our colleagues. We celebrated the promotional successes of three of the LBC Co-Investigators: Professor **Mark Bastin** has been appointed Personal Chair of Brain Imaging; Professor **Michelle Luciano** has been appointed Personal Chair of Behavioural Genetics; and Professor **Susan Shenkin** has been appointed Personal Chair of Healthcare for Older People. We also celebrated **Dr Gail Davies**, the LBC Statistical Geneticist, who was promoted to the post of Senior Research Fellow. We were delighted to hear the news that **Dr Hon Wah Yeung**, who joined the LBC as Research Associate, launched a new job at the Royal Observatory and the Department of Astronomy at the University of Edinburgh. In addition, two of our PhD students successfully completed their degree and now continue working with the team as Research Associates: **Dr Jure Mur** successfully completed his degree, which resulted in a series of high-profile publications on anticholinergic burden and different aspects of health in later life and continues to work with close LBC collaborator Professor Riccardo Marioni; and **Dr Eleanor Conole**, who completed her PhD in Translational Neuroscience with a thesis on the impact of chronic inflammation on brain structure and function across the life course, resulting in high-impact publications in *Neurology* and *Brain, Behaviour and Immunity*. We are also delighted with the achievements of **Arish Mudra Rakshasa-Loots**, a PhD candidate in Translational Neuroscience who has been awarded a BNA scholarship and became the winner of the University of Edinburgh's Three Minute Thesis Competition with his presentation '*When HIV meets Depression*'. Congratulations to everyone for a very successful year!

A big thank you to the LBC1936 research assistants!

This year has seen some changes in the cognitive testing team. We were sad to say goodbye to three of our valued team members: **Alison Pattie** has been a core member of the LBC studies since their inception in 1998. After her retirement in Spring 2019, Alison came back in October 2021 to help the LBC1936 team to complete Wave 6 in good time after the COVID-19 delay. **Beth Jones** joined the LBC in July 2022 to support the testing team during Wave 6 while completing her MSc in Neuroscience. Last but not least, **Danielle Page**, who was a member of the LBC1936 testing team for many years, has left the post to join a PhD programme in Clinical Psychology at the University of Edinburgh. You can read more about Danielle's journey in the next section. We will miss our colleagues and thank them for their hard work, wishing them the best of luck!

Welcome to new staff!

As sad as it is to see our colleagues leaving, we were delighted to welcome two new members of the team: **Sabela Mendez** who joined us in September as a new Research Assistant to support the cognitive testing team and **Dr Anna Fürtjes** who joined the team in June as a new Research Associate in Statistical Genetics. By now they are both an integral part of the team and we are thrilled to have them on board!

Discoveries

The LBC had another successful year in making important discoveries. Of particular note is a cornerstone paper led by Dr Janie Corley, which tests the performance of the top 15 candidate predictors based on 5 waves of cognitive ageing, with participants' ages between 70 and 82 ([Corley et al., 2023, *Molecular Psychiatry*](#)). The findings give further credence to the concept of 'marginal gains' when thinking about protective factors for healthy ageing: many only uniquely accounted for small differences in cognitive ageing, but together they explained up to 20%, with the *APOE* gene consistently showing the strongest associations across cognitive domains. A study led by Dr Una Clancy found that apathy – a state characterised by diminished interest, enthusiasm, and concern – was related to increasing brain white matter damage, whereas depression, anxiety, and subjective memory complaints did not ([Clancy et al., 2023, *International Journal of Geriatric Psychiatry*](#)).

A study by PhD student Tyler Saunders found that a protein called Neurogranin (a brain protein related to memory formation) was lower in Alzheimer's disease patients, but was also lower in those LBC1936 participants who showed poorer lifetime cognitive ageing, suggesting it may be an important marker of both clinical and 'healthy' cognitive ageing ([Saunders et al., 2023, *Neurobiological Disorders*](#)).

Staff news

Thank you, Danielle Page!



LBC1936 Research Assistant, Danielle Page

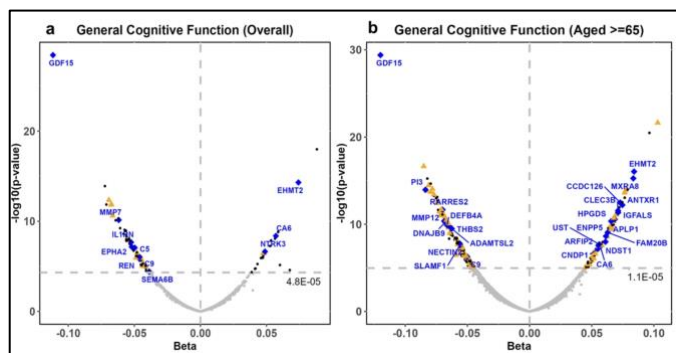
After many years with the LBC1936 team, Research Assistant Danielle Page has left the post for the highly competitive PhD programme in Clinical Psychology at the University of Edinburgh. Danielle joined the LBC in 2017 as a member of the cognitive testing team and was responsible for arranging LBC1936 participants' cognitive and MRI appointments and administering their cognitive tests at the Wellcome Trust Clinical Research Facility. She was also involved in many other tasks, including organisation of the most recent LBC Reunion and delivering school workshops as part of the University's widening participation scheme. Danielle – who has been assigned to the NHS Lothian 'Older Adult aligned' programme to begin her training – said: *"It was a genuine privilege to work with the LBC team, and to get to know so many of the LBC1936 participants over the last 6 years. Their dedication to the study always blew me away, and I am so grateful for the many fond memories with them in the clinic, and for the many opportunities which the LBC team has provided for me. I am also excited for this new opportunity: I hope to focus my research and clinical work around the neuropsychological assessment of dementia with the aim to support the mental health and independence of older adults when they receive a dementia diagnosis. I am excited to be able to*

continue to do research in a closely related field, and to directly help older people and their families, because of what I have learned during my time with the LBCs. I will miss the LBCs terribly, but I'm sure there will be opportunities for collaboration in future!"

The team are sad to see Danielle leave, but we are certain that she will thrive in her new role as much as she did with the LBCs. Congratulations, Danielle!

Scientific Highlights

LBC data contribute to a study identifying blood proteins associated with general cognitive function in middle-aged and older adults



Poor cognitive function in middle and later life is a risk factor for dementia. As dementia is expected to affect 153 million people worldwide by 2050 it is important to identify early biomarkers that can be used to identify individuals at risk of developing dementia. This could help us to understand the biological processes related to dementia and identify patients for early intervention. This study identified 246 proteins circulating in the blood that were associated with general cognitive function in middle-aged and older adults. Further analysis indicated that higher levels of NECTIN2, a protein that is involved in viruses entering brain cells, are associated with higher risk of developing Alzheimer's disease. Evidence suggests that levels of a further 14 proteins change as a consequence of Alzheimer's disease. This study provides new insights into the potential relationship between the immune system and Alzheimer's disease susceptibility as well as identifying potential therapeutic targets.

[Tin, A., et al. \(2023\). Identification of circulating proteins associated with general cognitive function among middle-aged and older adults. *Communication Biology*.](#)

Does childhood intelligence influence risk of depression in later-life?



Depression is predicted to be the leading cause of global disease burden by 2030 (WHO), which makes it of great importance to identify factors that may predict risk of depression, particularly those from early life when interventions for mental health problems may be most effective. A study conducted by Dr Emily Ball and LBC colleagues explored whether childhood intelligence (assessed at age 11) was associated with risk of depression in later-life (up to age ~85) as well as other factors, including whether childhood family structure (i.e., number of children in the family) and adulthood socio-economic status and geographical location influenced this association. To do this, the study followed up 53,037 people who took part in the Scottish Mental Survey in 1947. The cognitive test scores collected in 1947 were linked to the participants' electronic health records (collected between ~1980 to 2020). Using the electronic health records, the researchers looked at hospital admission records to identify whether participants had been diagnosed with depression whilst they were in hospital, and also looked at whether the participants had been prescribed antidepressants. This population-level data-linkage study found that higher childhood intelligence test scores were associated with a reduced risk of depression in later-life. However, this association was only present when depression diagnoses were identified in hospital admissions data. There was no association between childhood intelligence and being prescribed antidepressants in adulthood. Adjusting for childhood family structure and adult socio-economic and geographical factors did not greatly influence the association.

[Ball, E. L., et al. \(2024\). Childhood intelligence and risk of depression in later-life: A longitudinal data-linkage study. *SSM-Population Health*.](#)

A longitudinal impact of physical activity and personality on older people's wellbeing



Global life expectancy continues to increase. In Scotland, the number of residents who are 65 years and above is projected to rise from 19% of the total population in 2020 to 25% by 2040. However, a significant number of adults in their 70's is believed to experience a lower quality of life than their younger peers, and they report a significant decrease in positive affect and a decline in satisfaction with life. Understanding what drives self-reported satisfaction with life is a priority across many sectors of society. There is some evidence that the positive relationship between physical activity and subjective wellbeing is stronger among older adults with higher levels of extraversion and those with higher levels of openness to experience. A recent study with LBC data aimed to examine the interaction between physical activity and personality on subjective wellbeing longitudinally between two time points in older age. The study was based on 520 LBC participants with self-reported measures of physical activity and personality and who also had measures of subjective wellbeing at the average age 76 and then three years later. The study found that while the five personality traits were significant predictors of later subjective wellbeing, this was not the case for physical activity. It may be, the study suggests, that the combined effects of physical activity and personality on wellbeing that were reported in previous studies could be related to age differences between groups of older adults– the youngest-old, middle-old and oldest-old.

[Chan, B. C. L., et al. \(2023\). A longitudinal study of physical activity and personality in the wellbeing of older adults. *Journal of Aging and Health*.](#)

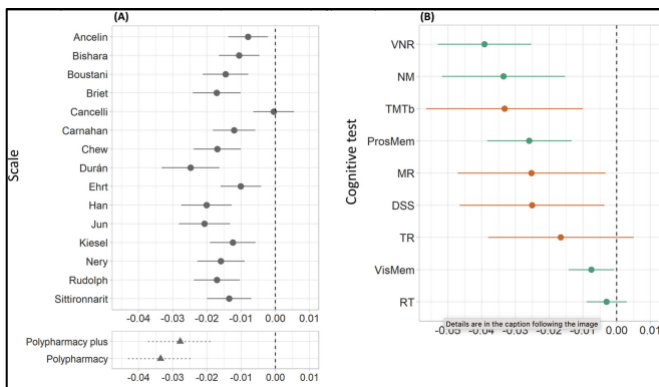
Air pollution exposure in early life associated with higher cancer-related mortality in late adulthood



The impact of environments on our physical and mental health across the lifecourse has been the focus of a recently completed ESRC-funded project led by our collaborators at the School of GeoSciences. Dr Gergö Baranyi has led several LBC-related studies exploring the relationship between neighbourhood features and their impact on cognitive function, frailty, and biological ageing. His research highlights the importance of our environment and its lasting effects on health and ageing. Using LBC1936 data, Gergö and team showed that living in disadvantaged areas of Edinburgh in mid- and late adulthood was associated with –on average– slightly lower levels of general cognitive ability at age 70, and faster cognitive decline in the following years. His most recent publication, which is separate from the ESRC-funded LBC collaboration, is based on data from the larger Scottish Longitudinal Study Birth Cohort of 1936, of which the LBC1936 is a sample. The study found that spending early childhood in areas with higher air pollution is linked with earlier mortality, including cancer-related deaths and specifically lung cancer among women. The study also found preliminary evidence for higher mortality from neurodegenerative disorders among men. Childhood cognitive ability mediated 25% of the total association between early life air pollution and mortality. Gergö presented this work at a recent Scottish Parliament Cross-Party Group meeting on Lung Health, attended by MSPs, clinicians, pharmacological and charity representatives and people living with lung conditions.

[Baranyi, G., et al. \(2023\). Early life PM_{2.5} exposure, childhood cognitive ability and mortality between age 11 and 86: A record-linkage life-course study from Scotland. *Environmental Research*.](#)

Anticholinergic use in the UK: Longitudinal anticholinergic burden in middle and older age healthy individuals



Anticholinergics are drugs that block the neurotransmitter *acetylcholine* from sending a signal between nerve cells in order to inhibit the parasympathetic nervous system. They are prescribed for a wide range of health conditions, including urinary incontinence or chronic obstructive pulmonary disorder (COPD), and are found among various classes of drugs, including antidepressants, painkillers, and cardiovascular drugs. Their prescribing increases with age and some studies have linked their long-term use in older people with a risk of dementia. How these drugs influence cognitive function and brain structure before the onset of advanced age and dementia is, however, not clear. This was the focus of a new study led by Dr Jure Mure, based on the UK Biobank data of healthy middle and older age adults. The study found that the use of specific classes of anticholinergics, namely opioid painkillers and a certain type of antibiotics, was associated with a slight decrease in general cognitive ability, but there were no differences in brain structure among individuals with varying levels of anticholinergic use. The authors conclude that while it is possible that anticholinergic use could contribute to reduced cognitive capacity and dementia over time, future studies should focus on a more specific, narrow class of anticholinergic drugs as well as polypharmacy as it may be those individuals who are prescribed anticholinergics in combination with other drugs over a longer term that may be particularly vulnerable and at risk of cognitive decline.

[Mur, J., et al. \(2023\). Anticholinergic burden in middle and older age is associated with lower cognitive function, but not with brain atrophy. *British Journal of Clinical Pharmacology*.](#)

Knowledge Exchange and Impact

CHARGE conference and projects in Texas

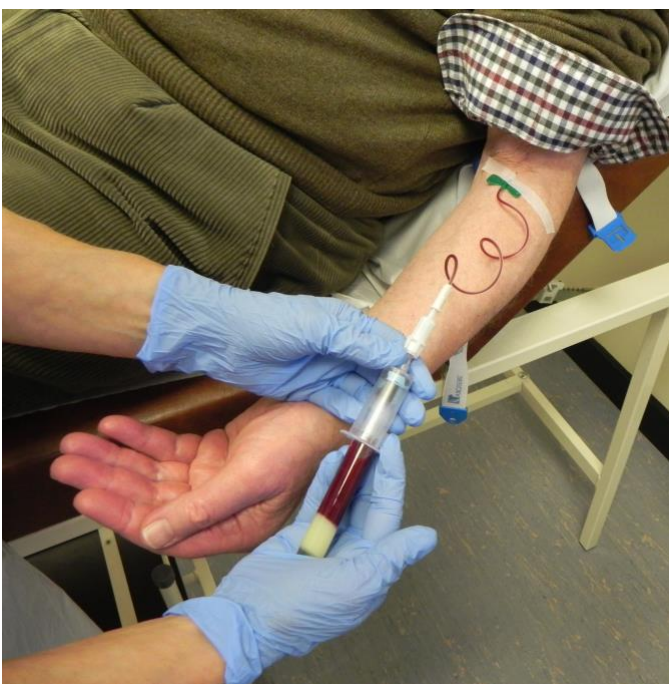


Drs Simon Cox and Elliott Tucker-Drob at the University of Texas

In October, Drs Simon Cox, Gail Davies, and Anna Fürtjes visited Texas to attend the Cohorts for Heart and Ageing Research in Genomic Epidemiology (CHARGE) conference. The LBCs have been an active member of the CHARGE consortium for many years. The LBC team continue to contribute to a wide variety of research projects investigating genetics, epigenetics and proteomics of aging, health and disease. As part of the CHARGE cognitive working group, Professor Ian Deary and Dr Gail Davies have previously led large genetic analyses of differences in the *level* of general cognitive function. In collaboration with Drs Elliot Tucker-Drob (University of Texas) and Andrew Grotzinger (University of Colorado), the LBC team now leads the largest genetic study of cognitive *decline* to date. This study will bring together data from more than 30 cohorts and could help better understand the genetic markers for cognitive decline prior to the onset of dementias. After the CHARGE meeting, the team were hosted by Dr Elliot Tucker-Drob at the Lifespan Development Lab, University of Texas in Austin. Dr Simon Cox gave a lecture which included many LBC brain imaging research findings, and the team enjoyed lively scientific discussions, planning for existing and future projects, and socialising with a 'cuppa' during 'Tea Time' – which had been specifically added to the busy schedule to make their UK visitors feel at home. Simon said: "It was excellent to have combined these two parts into one productive trip. Our longitudinal cognitive GWAS project was well-represented at the CHARGE meeting with talks and a poster. The exciting ideas and discussions further consolidated our Austin-Edinburgh-Boulder project links, with Elliot and team consummate and thoughtful hosts."

Dr Sarah Harris presents at the SomaLogic Roadshow

Dr Sarah Harris is a molecular and statistical biologist, and the LBC geneticist. She is interested in identifying molecular contributions to adult cognitive function, cognitive decline and other ageing-related traits. She has recently presented her research proposal *“Longitudinal multi-omic biomarkers for neurocognitive decline prior to dementia onset”* at the SomaLogic Roadshow, hosted by the University of Edinburgh’s Institute for Regeneration and Repair. SomaLogic is a protein biomarker discovery and clinical diagnostics company located in Boulder, Colorado. Sarah presented her plan to measure 7,000 proteins in plasma collected from LBC1936 participants at Waves 2, 3, 5 and 6 using SomaLogic’s SomaScan platform. She aims to lead a well-powered, consortium-based SomaScan proteomics association study of longitudinal changes in cognitive function and brain structure prior to clinical Alzheimer’s Disease (AD) diagnosis. The goal of this ambitious ~\$5M project is to identify novel blood proteomic biomarkers for the critical changes in cognitive function and brain structure that occur during early phases of disease progression prior to clinical AD diagnosis. Sarah has now submitted a revised application to fund the proposal to the US National Institutes of Health (NIH), and has just received excellent scores on the grant – more updates in 2024! We keep our fingers crossed and wish her success!



Blood samples are collected from LBC1936 participants at each wave

Dr Janie Corley talking to the BrainSTEMs



Dr Janie Corley was invited to give an online talk to members of the BrainSTEM group, formerly the Tayside branch of the British Science Association. Janie talked about the work of the Lothian Birth Cohorts to date, and presented some research findings on the factors that help to keep our brains sharp as we get older, including lifestyle, health, genetics and psychosocial factors. The key message with regard to predictors was much like the conclusion of Janie’s paper, namely ‘marginal gains, not magic bullet’; brain health is affected in small but significant ways based on a great number of small changes one can make to their lifestyle. As a group of mostly retired teachers, clinicians, and academics, they were a very engaged audience and had many interesting and insightful questions about the study. Sue Allen, who is the group convenor, wrote: *“Thank you very much for such an interesting (and entertaining) talk last night. Everyone found the content very absorbing and the presentation thoroughly professional - you must have given a number of talks to have developed such fluency!”*

Janie was also recently interviewed about her work on garden use during the pandemic by an undergraduate psychology student at Vanderbilt University in Nashville, Tennessee, Zoe Shacham. Zoe will use the interview for a podcast exploring environmental psychology and how connecting with nature’s green spaces can uplift our mental well-being. Zoe said: *“Recently, while diving into this topic, I came across Dr Janie Corley’s enlightening article discussing how gardens positively influenced the mental health of the Lothian Birth Cohort during the COVID-19 pandemic. The impact of green spaces during such a challenging time truly fascinated me, sparking my curiosity to reach out and learn more about this incredible study!”*

Lothian Birth Cohorts at Trinity Academy for Being Human Festival



For the past three years our team has participated in the *Being Human Festival* taking place in November across the UK. The festival celebrates and demonstrates the ways in which the humanities inspire and enrich our everyday lives, help us to understand ourselves as well as the challenges we face in a changing world. This year Sabela Mendez and Dr Barbora Skarabela visited Trinity Academy and met with two groups of 30 Secondary 5 and 6 pupils on the Psychology Higher and Advanced Higher courses for a session about Lothian Birth Cohorts. The pupils learned about the historical and scientific significance of the study and joined in live polling about genetic and lifestyle factors that contribute to healthy brain ageing. The students were able to compare healthy and less healthy 3D-printed brains and brain scans of older individuals of the same age, and discussed why some brains age better than others and what we can do to keep our brain sharp into older age. The students were excellent – engaged and interested – and enjoyed testing their cognitive ability with verbal fluency tests and volunteered one of their peers with an impressive memory ability for the backward digit span test! The students were surprised when they learned that the brain changes and shrinks across the life-course, and that this is largely determined by our lifestyle rather than our genes. The teacher, who is the head of the Psychology unit, said: *“My classes really enjoyed it, thank you! I’ve only heard positive feedback and they liked how interactive it was. [...] They enjoyed trying out cognitive tests and seeing the brain models.”* We too enjoyed the event and meeting these young people, and look forward to another visit next year!

The LBC team at Edinburgh Doors Open Day



Dr Colin Buchanan at the Doors Open Day with an eight-year-old with the AR headset illustrating brain changes in later years

Doors Open Days are Scotland's largest free festival that celebrates places and stories. The University of Edinburgh regularly participates in the event, opening doors of many of its buildings to the public. This year, the Lothian Birth Cohorts joined colleagues from the Edinburgh Neuroscience network at the magnificent Playfair Library on Saturday 23 September to welcome visitors and invite them to learn about our research on healthy brain ageing. Drs Colin Buchanan and Barbora Skarabela drew the visitors' attention with a history of Lothian Birth Cohorts and our hands-on materials that illustrate our research and findings. The visitors were able to view brain ageing with the Augmented Reality glasses, and were keen to explore and comment on a pair of the 3D-printed models of healthy and less healthy ageing brains, and discuss the role of lifestyle in the process and what we can do to protect our brains throughout the lifecourse. It was an exciting event with over 140 visitors who came to talk to us at the Edinburgh Neuroscience table. One of them said: *“It was a great opportunity to see and learn about the brain and research connected to ageing, subjects which I knew little about. Amazing!”*

The LBC team also organised a new guided tour that was launched during the Doors Open Day. The *‘Bridge your mind’* walk was created and delivered by a third year Psychology student, Jana Tomastikova who took the audience on a walk around the historic university, drawing on clever parallels between buildings and the inner workings of the mind. One of the participants said: *“[We] thought the tour was outstanding! It was perfect for pace, interest and clarity. I hope you will be doing more of this tour in the future. We were blown away.”* Congratulations, Jana!

Publication update

Akshay, J., et al. (accepted). A structural heart-brain axis mediates the association between cardiovascular risk and cognitive function. *Imaging Neuroscience*.

Ball, E. L., et al. (2024). Childhood intelligence and risk of depression in later-life: A longitudinal data-linkage study. *SSM - Population Health*.
<https://doi.org/10.1016/j.ssmph.2023.101560>

Baranyi, G., et al. (2023). Early life PM_{2.5} exposure, childhood cognitive ability and mortality between age 11 and 86: A record-linkage life-course study from Scotland. *Environmental Research*.
<https://doi.org/10.1016/j.envres.2023.117021>

Chan, B. C. L., et al. (2023). A longitudinal study of physical activity and personality in the wellbeing of older adults. *Journal of Aging and Health*.
<https://doi.org/10.1177/08982643231206222>

Higbee, D., et al. (accepted). Genome Wide Association Study of Preserved Ratio Impaired Spirometry (PRISm). *European Respiratory Journal*.

Mur, J., et al. (2023). Anticholinergic burden in middle and older age is associated with lower cognitive function, but not with brain atrophy. *British Journal of Clinical Pharmacology*.
<https://doi.org/10.1111/bcp.15698>

Tin, A., et al. (2023). Identification of circulating proteins associated with general cognitive function among middle-aged and older adults. *Communications Biology*.
<https://doi.org/10.1038/s42003-023-05454-1>



Lothian Birth Cohorts



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Contact

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<https://lothian-birth-cohorts.ed.ac.uk/>



The LBC team in front of the McEwan Hall, April 2023

