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 69: March 2025

Welcome to the March edition of the Disconnected Mind Newsletter. Catch up on the latest news from the Lothian Birth Cohorts team between December and February, including our recent research publications and scientific events, and public engagement and knowledge exchange activities.

Updates

Wave 7 of LBC1936

Since last March, our cognitive testing team – Sabela Mendez, Alison Pattie and Drs Janie Corley and Sarah McGrory have been making great progress with the 7th wave of data collection. They have seen 150 LBC1936 participants, who are 88 or 89 years old, for cognitive tests at the Wellcome Trust Clinical Research Facility. Eighty-one participants have now had an MRI brain scan at the Edinburgh Imaging Facility at the Royal Infirmary of Edinburgh. The team aims to complete their fieldwork in the next few months, in time for the participant reunion scheduled for June. The longitudinal dataset, spanning over 20 years, provides valuable insights into the participants' cognitive ability, brain health, medical history and other details about the participants' health. We would like to thank all participants for their continuous commitment, as well as to the staff at both facilities for their support!

Left to right: Barbora Skarabela, Janie Corley, Alison Pattie, Simon Cox, Sarah McGrory, Sabela Mendez, Ian Deary

Lothian Birth Cohorts prepare to join the Edinburgh Futures Institute

As our efforts to complete the fieldwork accelerate, the LBC team based in 7 George Square embarks on an exciting move to the Edinburgh Futures Institute this year. The award-winning refurbishment of the former Royal Infirmary of Edinburgh is designed to encourage cross-disciplinary dialogue and foster new collaborations, directly in keeping with the collaborative work of the studies. We are excited to join this stimulating and supportive research community. Equally, we can't wait to explore the new opportunities the Institute offers for sharing our research with the public.

We are thrilled that the LBC participants will soon be able to join us at the Institute for a reunion marking the completion of another wave of data collection. Scheduled for the 17th of June, the reunion will be a special occasion for the team and collaborators to meet with the participants, share our findings, and celebrate the participants' invaluable contributions that have driven our discoveries and advancements from our new home!

LBC participants at the 2017 reunion

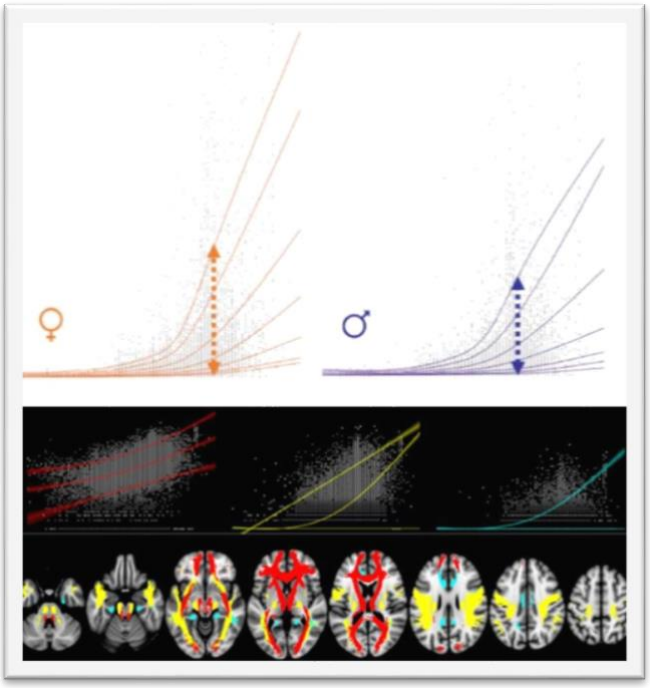
Scientific Highlights

Life-course exposure to air pollution and the risk of dementia in the Lothian Birth Cohort 1936

PhD student Otto-Emil Jutila led a study that investigated the relationship between air pollution exposure and dementia risk over a lifetime. The study included data from 572 LBC1936 participants, who provided their lifetime residential history in 2014. Researchers modelled air pollution exposure for specific years (1935, 1950, 1970, 1980, 1990, 2001, and 2007) using an atmospheric chemistry transport model. The study found that higher cumulative exposure to fine particulate matter ($PM_{2.5}$) was associated with an increased risk of Alzheimer's disease (AD). Interestingly, there were no significant associations for specific periods of time for either all-cause dementia or AD. However, when considering cumulative exposure from *in utero (*1935), periods of cumulative exposure up to 1980 and beyond (45+ years of exposure) showed significant associations between $PM_{2.5}$ exposure and AD. Overall, the findings emphasise the importance of considering life-course exposure to air pollution when assessing dementia risk. The study has garnered attention in various media and academic circles. In the Guardian, Otto said: *"Air pollution exposure is a life-course problem with long-term detrimental effects on health."* The research has been well-received for shedding light on the cumulative effects of air pollution on cognitive health, highlighting the potential importance of environmental factors in dementia prevention. Additionally, the study adds to the literature supporting the need for policies aimed at reducing air pollution exposure throughout life to mitigate the risk of dementia and other neurodegenerative diseases.

Jutila, Otto-Emil I., et al. (2025). Life-course exposure to air pollution and the risk of dementia in the Lothian Birth Cohort 1936. *Environmental Epidemiology.*

LBC brain scans contribute to a large international study on white matter hyperintensities

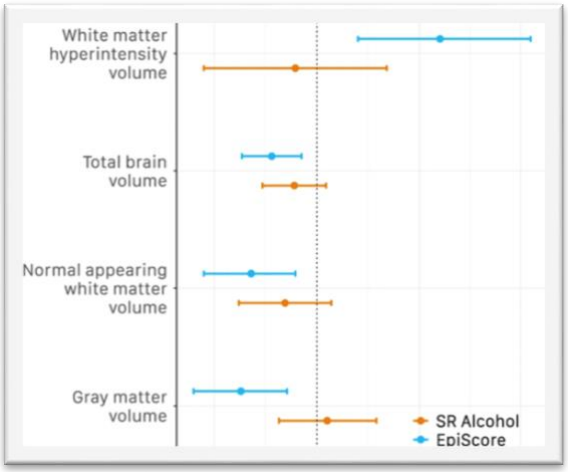


Top figure illustrates sex differences in WMHs across the lifespan. Bottom figure represents the lifespan trajectories of WMHs across three different brain regions.

White matter hyperintensities (WMHs) are lesions in the brain's connective tissue that appear on magnetic resonance imaging (MRI) scans. They are mostly absent in young adults, but become more prevalent with age, although the amount of WMHs can vary greatly even among older individuals. They are also a risk factor for cognitive decline and dementia. To better understand and assess WMHs, we joined a large international collaboration to chart age- and sex-specific normative data for WMH volumes across adulthood. The effort combined data from 15 cohorts across eight countries spanning four continents, with nearly 15,000 people aged 18 to 97 who did not have dementia, including those in LBC1921 and LBC1936. The study found that WMH volumes increased exponentially with age and double every 10 years for both sexes, but women generally had higher WMH volumes than men. The increase in WMHs was not the same across all areas of the brain and followed three different patterns depending on the brain region: *periventricular WMHs* located around the brain's ventricles; *deep WMHs*, found deeper within the brain's white matter; and *juxtacortical WMHs*, located near the brain's cortex. The study yielded detailed normative charts showing WMH volumes for different ages and sexes. These charts can be used to help doctors and researchers better understand and interpret WMH volumes in both clinical practice and research.

de Kort, F.A.S., et al. (2025). Cerebral white matter hyperintensity volumes: Normative age- and sex-specific values from 15 population-based cohorts comprising 14,876 individuals. *Neurobiology of Aging*.

LBC1936 blood samples used to predict alcohol consumption

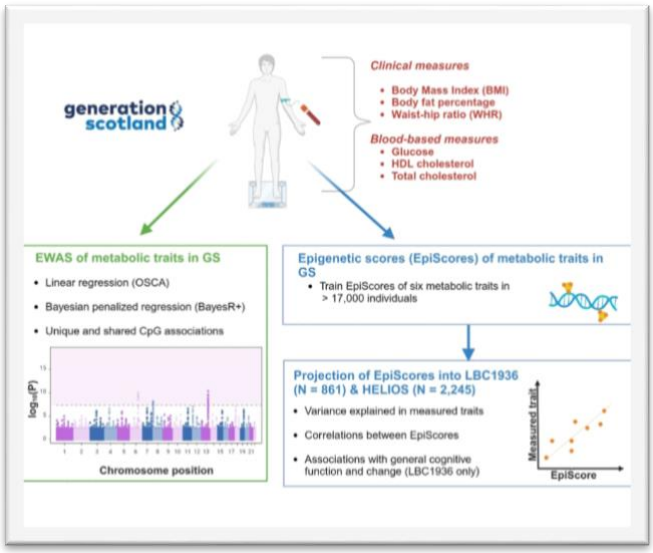


Self-reported (SR) alcohol consumption and alcohol EpiScore associations with LBC1936 global brain imaging

A new epigenome-wide association study (EWAS) aimed to find a way to objectively measure alcohol consumption from blood-based DNA, rather than relying on self-reported drinking habits. Researchers created an *epigenetic score* (EpiScore), which uses specific chemical markers on DNA to predict alcohol consumption. The team first build the EpiScore by looking at chemical changes in the DNA (known as methylation), which are affected by lifestyle factors like alcohol consumption. They trained a computer model on data from over 16,000 people, using self-reported alcohol consumption from the week before their blood was tested. This training enabled the model to learn where DNA methylation sites were linked to drinking levels. Then, they tested whether narrowing down the analysis to DNA sites previously linked to alcohol would make predictions more accurate. This turned out to improve performance. Additionally, they examined if focusing only on people whose drinking that week was typical for them would enhance the model's performance, but it did not add much benefit. Once the EpiScore was built, they tested it on over 10,000 people from four other studies to evaluate its ability to predict alcohol consumption in new groups, purely using their DNA methylation. The EpiScore was moderately accurate, showing a correlation with actual drinking habits. The EpiScore outperformed self-reported drinking levels in identifying links between alcohol consumption and brain health in older adults: individuals with higher EpiScores (indicating heavier drinking) showed signs of poorer brain health on scans, even when their self-reported drinking did not suggest this. The authors also identified two new DNA sites strongly linked to alcohol consumption. Unlike self-reports, the EpiScore provides a more objective method for studying alcohol's effects on health, helping researchers understand how alcohol consumption affects long-term health, including brain health.

Bernabeu, E., et al. (2025). Blood-based epigenome-wide association study and prediction of alcohol consumption. *Clinical Epigenetics*.

LBC1936 DNA methylation data used to study metabolic health in diverse populations



Metabolic health is crucial for overall well-being and longevity. It refers to the body's ability to efficiently process and convert food into energy, maintain stable blood sugar levels, and regulate various biochemical processes. Good metabolic health helps prevent chronic conditions such as type 2 diabetes, heart disease, and stroke. Hannah Smith, a PhD student working with the Lothian Birth Cohorts, led an Epigenome-Wide Association Study (EWAS) examining the relationship between changes in the DNA and metabolic traits. The authors used DNA data from over 17,000 participants from the Generation Scotland (GS) cohort, to develop EpiScores based on DNA methylation patterns. These scores were then used to estimate the likelihood of six metabolic traits: body mass index (BMI), body fat percentage, waist-hip ratio, and blood-based measures of glucose, high-density lipoprotein cholesterol, and total cholesterol. The EpiScores were then validated in two other datasets – Scottish (Lothian Birth Cohort 1936) and Singaporean (Health for Life in Singapore) cohorts, showing strong predictive performance. In the Singaporean cohort, the EpiScores for BMI and total cholesterol explained 20.8% and 7.1% of the variance, respectively, while in the Scottish Cohort, the scores explained 14.4% and 3.2%, respectively. Interestingly, the study found differences in the predictive power of EpiScores across ethnic subgroups in Singapore: the EpiScore for body fat explained around 9% of the variance in Chinese and Malay subgroups but only about 3% in the Indian subgroup. Additionally, the EpiScores were associated with cognitive function in LBC1936, suggesting broader applicability beyond metabolic traits. Overall, the study highlights the potential of DNA methylation-based predictors in understanding and measuring metabolic health across diverse populations.

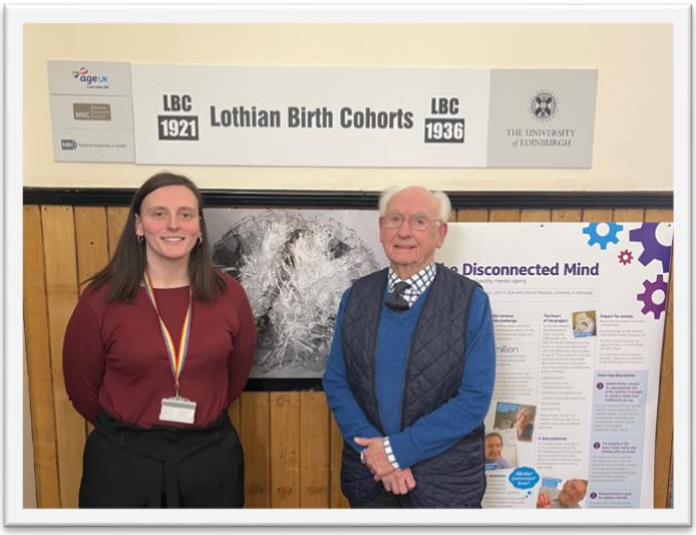
Smith, H. M., et al. (2025). DNA methylation-based predictors of metabolic traits in Scottish and Singaporean cohorts. *The American Journal of Human Genetics*.

Knowledge Exchange

A call with the Financial Conduct Authority

Don't worry, we're not in financial hot water! Our founding Director, Professor Ian Deary, was asked to talk to the Financial Conduct Authority (FCA) about the Lothian Birth Cohorts' research on healthy brain and cognitive ageing as part of the FCA's diversity work. On the 9th of January 2025, Ian gave a talk via Zoom to over 30 people from the FCA on 25 years of work on the LBCs. "*It's always a slightly disorienting experience speaking to one's computer screen*," said Ian, "*but the FCA staff on the call were very interested. There were many complimentary comments in the 'chat' facility of the call, and they used that to ask many good questions which were relayed to me by the excellent chairman. The staff were from around the UK—concentrated in London, with an office in Edinburgh too—and they were fascinated by the original Scottish Mental Surveys and how we used those to find and recruit members of the now-famous LBCs. They were impressed by how much the participants do on each research visit, and by the variety, number, and quality of the research outputs—and how well those are communicated to policy makers and the public. These much-younger-than-me people were lapping up information about how to look after their brains and thinking skills.*" Ian tells us that it is likely that we shall have a return visit to the FCA. Among the LBC data that Ian listed in his talk were three instruments that we use to assess financial matters, including how well older people handle bank information and their proneness to scams, and how those relate to cognitive capability and cognitive ageing. While Ian's broad talk was not the time to go into those in detail, the FCA staff were delighted to come across this seam of highly relevant (to them) information and we intend to describe the results to them in the near future.

Building on lived experience of LBC participants



Hannah Smith and LBC1936 participant, Mr Gordon Milne

Hannah Smith is a final year student in the Translational Neuroscience PhD programme funded by the Wellcome Trust. The aim of her PhD project is to identify blood-based biological markers of cognitive function, neuroimaging markers of brain health and dementia using several large cohort studies, including the Lothian Birth Cohorts. One of the requirements of her PhD training is to work alongside an individual with lived experience related to her PhD topic. This is how Hannah has started working with one of the LBC1936 participants, Mr Gordon Milne. In their meetings they discuss Mr Milne's experience of ageing as well as his experience of being a participant in a longitudinal research study like the Lothian Birth Cohort. Hannah said: *"I have benefitted enormously from our discussions which have encouraged me to think about research questions that still need to be answered that I did not set out to investigate during my PhD."* The partnership has helped to shape her questions and how she conducts her research. It is also a valuable opportunity to provide the partner with information about how scientific research is performed and some of the challenges researchers face in their projects. Mr Milne said: "*I found this partnership an interesting insight to Hannah's research and findings and as a harbinger of what was to follow. Whilst the times spent in discussion were a two-way benefit for both of us, I see Hannah's Doctoral Thesis significantly furthering the contribution to a legacy engaging the ensuing generations' research and understanding. Since 2004 the extensive research output by LBC1936 has been and will continue to be of great importance to the advancement of knowledge. I am honoured to be a small part of that unprecedented rich data base.*" Hannah adds: *"Working with a lived experience partner has given me a great appreciation for the participants who contribute so much to our research. I hope to continue with these partnerships throughout my career as I believe it is essential to include individuals with lived experience in research."*

Drs David Hill and Charley Xia talk about their research on PPLS Perspectives Podcast

Drs Charley Xia and David Hill interviewed for a PPLS podcast

PPLS Perspectives is a podcast series that brings together students and academics to explore the research carried out by the University of Edinburgh's School of Philosophy, Psychology and Language Sciences and the impact this work has on the society. In the first episode of 2025, Dr Charley Xia, a statistical geneticist, interviewed Dr David Hill to discuss their work on genetics of cognitive ability and socio-economic status. Dr Hill is an LBC collaborator who currently leads an MRC-funded project examining genetic and environmental links between cognitive ability, socio-economic position, and health. He uses genetic methods to examine complex relationships between genetic variation and traits that are seemingly unrelated to genetic inheritance, and how one genetic variant can affect multiple traits. For example, some of the genetic variants that influence educational attainment and income may do so through their links with traits such as personality or dyslexia. In this sense, income can then be viewed like other heritable traits and be influenced by genetic variation. These traits, David explains, are polygenic, resulting from the cumulative effect of many alleles with a small – and on their own insignificant – effect. This is also illustrated in a recent genome-wide association study David led, which used Mendelian randomization to examine the effects of socio-economic status on brain structure in older age and found that a higher-level socio-economic status is a causal factor resulting in lower levels of white matter hyperintensities, which are a risk factor for cognitive decline. Here, David emphasized the importance of clear communication to avoid misinterpretations, particularly regarding genetic determinism. He notes that genetic variants account for about 10% of socio-economic status differences, with the remaining 90% likely attributed to other factors. David added: *"Our research indicates that the genetic variants themselves have a small effect on socio-economic status, about 10% of the differences. This doesn't mean that it explains 10% of any individual's socioeconomic status nor does it mean that the genetic variant will always influence socio-economic status in the individuals […]",* highlighting the complex interplay between genetics and environment in shaping socio-economic outcomes.

The LBC team celebrates the International Day of Women and Girls in Science

Left to right: Sarah McGrory, Barbora Skarabela, Sabela Mendez, Sarah Harris, Janie Corley, and Jo Moodie

The International Day of Women and Girls in Science is celebrated annually on the 11th of February. Established by the United Nations General Assembly in 2015, this day aims to promote women's and girls' full and equal access to and participation in science, technology, engineering, and mathematics (STEM) fields. The International Day of Women and Girls in Science serves as a reminder of the ongoing efforts needed to achieve gender equality while celebrating the achievements of women scientists who make significant contributions to their fields. The majority-female LBC team is proud to support the effort. LBC Co-Investigator Dr Janie Corley says on behalf of the women on the LBC team: *"As women in science, we have the opportunity to shape research on cognitive ageing, influence policies that promote healthy ageing, and support future generations of women in STEM."*

Professor Simon Cox delivers two talks at the University of Southern California (USC)

In early December, LBC Director Professor Simon Cox delivered two talks in two days at the University of Southern California. In Part I, for the Psychology Department's Bosco Tjan Colloquium Series, he focused on the LBC team's ongoing work on characterising brain and cognitive ageing trajectories, and understanding the neurobiology that underlies those relationships. The following day, he gave Part II to the School of Gerontology Multidisciplinary Research Colloquium, covering some of the work on the environmental and genetic predictors of cognitive ageing (Marginal Gains), as well as new results from our dementia ascertainment work.

Around these two talks, he also had a busy schedule of meetings with numerous excellent researchers and graduate students across both faculties. "*It is rare to have the time to cover so much of the team's outstanding work in such detail – having two well-attended talks with highly relevant and engaged audiences was a treat. It was a superb visit, packed with interesting discussions, plus new and exciting opportunities for future collaboration. It was also a delight to be so thoughtfully hosted by Prof Duke Han, who will be visiting us in late March, and with whom we collaborate on our financial research.*"

Publications Update

Bernabeu, E., et al. (2025). Blood-based epigenome-wide association study and prediction of alcohol consumption. *Clinical Epigenetics*. https://doi.org/10.1186/s13148-025-01818-y

Cox, S. R. (2024). Neurocognitive aging. *Annual Review of Developmental Psychology*. https://doi.org/10.1146/annurev-devpsych-010923-102441

Davyson, E., et al. (2025). Insights from a methylome-wide association study of antidepressant exposure. *Nature Communications*. https://doi.org/10.1038/s41467-024-55356-x

de Kort, F. A. S., et al. (2025). Cerebral white matter hyperintensity volumes: Normative age- and sex-specific values from 15 population-based cohorts comprising 14,876 individuals. *Neurobiology of Aging*. https://doi.org/10.1016/j.neurobiolaging.2024.11.006

Huguet, G., et al. (2024). Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes. *Cell Genomics*. https://doi.org/10.1016/j.xgen.2024.100721

Jutila, O.-E. I., et al. (2025). Life-course exposure to air pollution and the risk of dementia in the Lothian Birth Cohort 1936. *Environmental Epidemiology*. https://doi.org/10.1097/EE9.0000000000000355

Smith, H. M., et al. (2025). DNA methylation-based predictors of metabolic traits in Scottish and Singaporean cohorts. *The American Journal of Human Genetics*. https://doi.org/10.1016/j.ajhg.2024.11.012

Contact

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

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