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 70: June 2025

Welcome to the 70th edition of the Disconnected Mind Newsletter. Catch up on the latest news from the Lothian Birth Cohorts team between March and June, including updates about our research publications and scientific events, and public engagement and knowledge exchange activities.

Exciting progress in Wave 7 data collection

Our cognitive testing team has completed Wave 7 data collection. Almost two hundred LBC1936 participants returned for a testing visit for the seventh time at the average age of 88: 192 participants met with the LBC1936 team and research nurses at the Wellcome Trust Clinical Research Facility for several hours at a time, one-on-one, taking cognitive tests, surveys, and physical and health exams. Impressively, 131 participants contributed an MRI brain scan at the Edinburgh Imaging Facility at the Royal Infirmary of Edinburgh. We are incredibly grateful for their dedication. With fieldwork complete, our team is now preparing the vast dataset for entry—spanning blood test results, demographics, health measures, genetics, and brain imaging. This meticulous process ensures accuracy before the data becomes available for groundbreaking discoveries. We look forward to sharing the data through new collaborations, advancing scientific discoveries, and keeping participants engaged with the latest findings from the study.

Celebrating the 7th Wave of data collection with an LBC Reunion event

LBC participants at the reunion in Edinburgh Futures Institute

We were thrilled to mark the completion of Wave 7 data collection with a special study reunion on 17 June. Nearly 200 guests—including study participants, collaborators, colleagues, and local high school students—joined us for an inspiring afternoon of talks, reflections, and shared memories. The event was a heartfelt opportunity for the LBC team to express deep gratitude to our incredible participants, whose commitment over the years continues to make the study possible. We were also pleased to recognise the outstanding support of staff from the Wellcome Trust Clinical Research Facility and the Edinburgh Imaging Facility at the Royal Infirmary of Edinburgh—partners whose expertise and dedication remain central to our success. Hosted at the Edinburgh Futures Institute—the LBC team's new home—the reunion marked several important milestones, including the belated 20th anniversary of the LBC1936 cohort, which began in 2004. Professor Ian Deary brought smiles all around with his spirited reading of a ChatGPT-composed poem, A Grand Ode to the Lothian Birth Cohort 1936 at 88, written in the style of William McGonagall—a 19th-century Scottish poet fondly remembered for his dramatically awkward and unintentionally humorous verse. We also celebrated longstanding members of the team: Dr Janie Corley, who has been with LBC1936 since its inception, and Alison Pattie, who returned from retirement to contribute to cognitive testing for the third time—having first worked on the LBC1921 cohort since 1999. The event offered a wonderful chance to reconnect, share emerging insights, and honour the people and partnerships behind the LBC's success. A special edition of the participant newsletter featuring highlights from the day will be available soon.

Celebrating collaboration: LBC team recognised by Royal Society of Edinburgh

Earlier this year, the LBC team was honoured to be nominated for the Royal Society of Edinburgh's prestigious Mary Somerville Medal. Named after the pioneering 19th-century mathematician, astronomer, and science communicator—once dubbed the "Queen of Science"—the medal recognises exceptional achievement in research through teamwork and collaborative endeavour. Although we didn't receive the award this time, being nominated among such outstanding teams was a meaningful recognition of our collective efforts. We take it as a huge compliment, and a reminder of the value of teamwork and collaboration in advancing science.

Dr Charley Xia promoted to Research Fellow

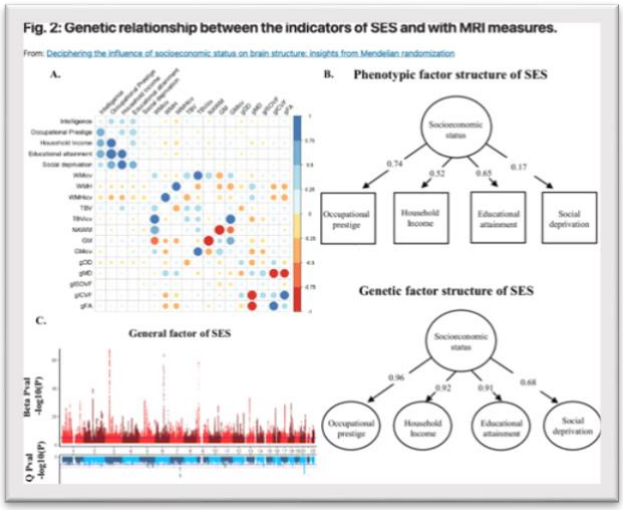
We're thrilled to share that Dr Xiachi (Charley) Xia has been promoted to Research Fellow. Since joining Dr W. David Hill and the Lothian Birth Cohorts in 2020 as a research assistant, Charley has brought his expertise in cognitive epidemiology, neuroimaging, and statistical modelling to explore the trait architecture of cognitive ability and socioeconomic position. His rigorous, thoughtful research continues to shed light on the complex factors that shape brain and cognitive ageing. His recent work—published in *Molecular Psychiatry*—further exemplifies Charley's impactful contributions to the field. Congratulations, Charley!

Congratulations to Katie Robertson on PhD success

We're delighted to share that Katie Robertson has been awarded a fully funded PhD studentship at the University of Glasgow as part of the Precision Medicine Doctoral Training Programme. Katie recently joined the LBC team as an MSc student by research, working with Professor Simon Cox on an Alzheimer Scotland-funded project to investigate the high-dimensional neurostructural hallmarks of traumatic brain injury. Katie will complete her MSc this August and continue her academic journey under the supervision of Dr Michele Svanera, focusing on AI-driven predictive modelling of brain and heart ageing. We're proud to celebrate this exciting next step in Katie's flourishing career. Well done, Katie!

Scientific highlights

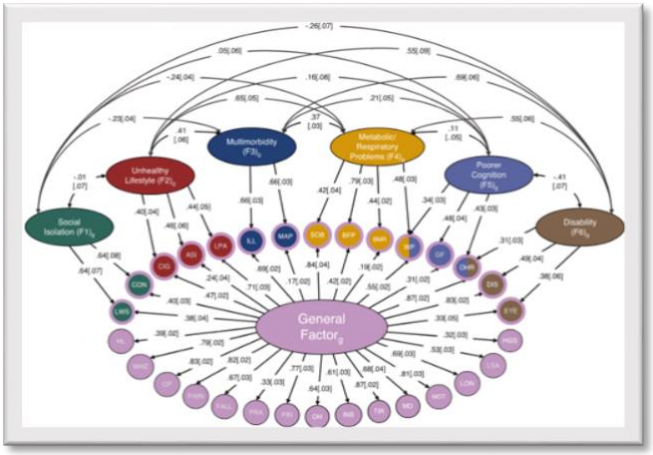
How socioeconomic status shapes brain health: A genetic perspective



Scientists have long sought modifiable levers to safeguard the aging brain. In *Molecular Psychiatry*, an international team led by Drs Charley Xia and David Hill used genetic data to uncover how socioeconomic status (SES) shapes white matter integrity. White matter hyperintensities are MRI-visible lesions that accumulate with age and are associated with slower processing speed and higher dementia risk. First, the researchers ran a multivariate genome-wide association study (GWAS) of four SES measures—education, income, occupational prestige, and area deprivation—in 947,466 participants. They pinpointed 554 genomic loci and distilled a common genetic factor that accounts for three-quarters of SES-associated effects, explaining roughly 9% of SES variation. Next, using these loci as instruments in Mendelian randomization analyses of ~35,000 UK Biobank volunteers with brain MRI, they showed that higher SES causally reduces white matter hyperintensity volume—independent of measured cognitive ability. This work elevates SES from a mere correlate to a potentially modifiable determinant of brain aging. By highlighting a causal link between better social conditions and healthier white matter, it underscores the role of policies—from education access to income support—in bolstering late-life cognitive resilience. *"We have not shown that brain health is genetically determined,"* Dr Xia stresses, *"but that genetic data can be used to reveal SES as a changeable environmental influence on healthy brain aging."* The study includes an extensive FAQ to serve as a guide for understanding how genetic differences can be linked to socioeconomic status differences.

Xia, C., *et al.* (2025). Deciphering the influence of socioeconomic status on brain structure: insights from Mendelian randomization. *Molecular Psychiatry*.

Uncovering the multivariate genetic architecture of frailty with genomic structural equation modelling

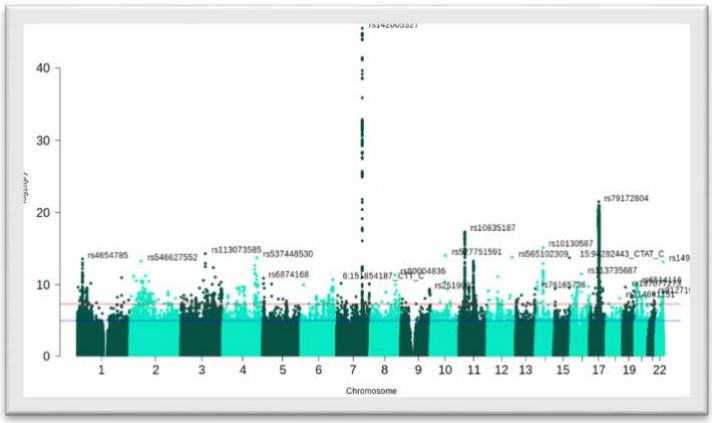


A path diagram of the standardised results for the authors' bifactor model of frailty (Fig. 1 in Foote et al.).

Frailty is a complex state of progressive, multisystem physiological decline that affects over 40% of adults aged over 65 years. It is strongly associated with adverse health outcomes, including increased risk of age-related diseases, hospitalization and disability. We currently know very little about the underlying biological mechanisms of frailty but understanding this could provide new insights into how we can treat or prevent frailty. In this study, a group of researchers from the Lothian Birth Cohorts collaborated with researchers from the US, Canada and Australia to conduct the largest genetic analysis of frailty to date. Historically, it has been very challenging to effectively measure the genetics of frailty because it presents very differently between individuals. For example, one person might have functional disability but be cognitively lucid whereas another might be cognitively frail but mobile. Using new innovative genomic methods that can combine multiple measures of frailty into a single analysis, the team were able to model patterns of shared genetics between 30 different frailty symptoms. This revealed 408 regions of the genome that are associated with frailty either through broad general pathways, or through pathways that are associated with specific subgroups of frailty symptoms. These subgroups included genetics linked to limited social support, unhealthy lifestyle, multimorbidity, metabolic problems, poorer cognition and disability. The team found that when these genetic pathways were combined into a polygenic risk score, they could effectively predict whether someone was frail in the Lothian Birth Cohorts data. These findings provide a much more detailed picture of the underlying mechanisms of frailty that will be fundamental for enabling future studies to identify new ways to prevent frailty in older adults.

Foote, I. F. *et al.* (accepted). Uncovering the multivariate genetic architecture of frailty with genomic structural equation modelling. *Nature Genetics*.

Mapping brain atrophy with a single scan

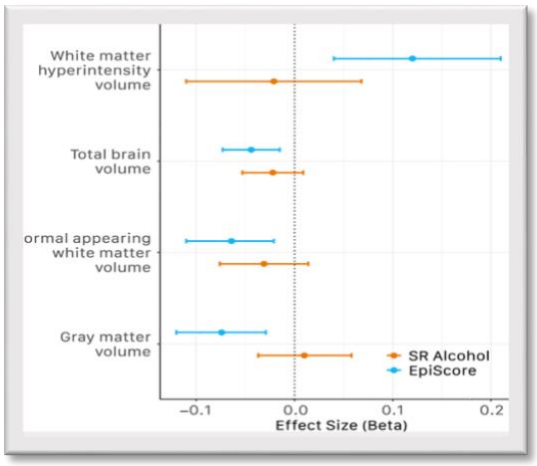


Manhattan plot highlighting WNT16 on chromosome 7 as the strongest genetic signal linked to brain atrophy

Why do some people's brains shrink faster with age than others? Past studies have tackled this question by tracking brain changes across multiple MRI scans over several years—but because brain imaging is costly, these efforts were often limited in size and scope. This has especially affected genetic research on brain shrinkage, which requires thousands of participants to yield reliable findings. A new study, recently accepted by *Nature Communications* and led by Dr Anna Fürtjes, tests a potential solution in unprecedented detail: the ability to estimate lifetime brain shrinkage using just one MRI scan. Anna and her colleagues did this by comparing a person's current brain volume to the size of the surrounding skull—specifically, the *intracranial vault*, which remains stable in size throughout adulthood. The intracranial vault acts like an "archeaological record," preserving the brain's peak size while the brain inside gradually shrinks with age. The team tested the reliability of this method in five large cohorts, including the Lothian Birth Cohort 1936 and the UK Biobank, and found that it closely mirrored traditional longitudinal measures of brain shrinkage. It also correlated strongly with thinking skills, physical frailty, and clinical markers of brain health. Using this approach, the researchers conducted the largest genetic study of brain shrinkage to date (sample size = 43,110). Their analysis showed that around 40% of the variation in brain shrinkage is down to genetics, and implicated WNT16—a gene previously linked to scale genetic studies of brain shrinkage can be reliably conducted using single-scan data, expanding opportunities for more powerful investigations on an international scale, paving the way for new discoveries into brain health across the life course. The team are now leading an international cross-consortium multi-ancestry follow-up analysis. Watch this space!

Fürtjes, A. E. *et al.* (accepted). Measurement characteristics and genome-wide correlates of lifetime brain atrophy estimated from a single MRI. *Nature Communications.*

Blood-based epigenome-wide association study and prediction of alcohol consumption

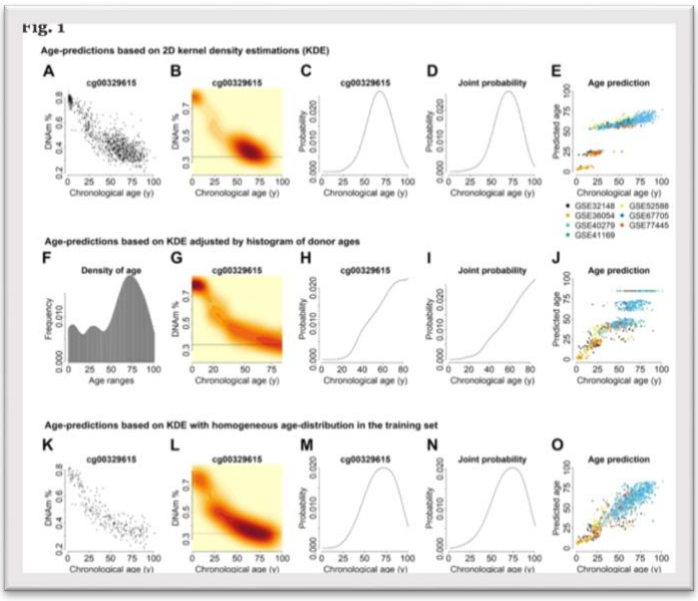


Self-reported (SR) alcohol consumption and alcohol EpiScore associations with global brain imaging in LBC1936

A recent study led by Elena Bernabeu introduces a new method for estimating alcohol consumption using blood-based DNA patterns, rather than self-reported drinking habits. The team developed an epigenetic score—called EpiScore—based on tiny DNA changes known as CpG sites, which can reflect lifestyle factors like drinking. Using data from over 16,000 participants (including the LBC1936 cohort), researchers trained a model to detect DNA patterns linked to drinking. It learned from self-reported alcohol intake during the week prior to blood sampling, helping identify DNA changes tied to consumption. Accuracy improved when predictions were limited to known alcohol-related DNA sites; however, focusing on people with stable drinking habits didn't help significantly. The EpiScore was then validated in more than 10,000 individuals across four independent studies. It showed a moderate correlation with actual drinking behaviour, indicating its potential as an objective measure. Notably, the EpiScore outperformed self-reports in linking alcohol intake to brain health—older adults with higher scores showed signs of poorer brain health on scans, even when their self-reported drinking appeared modest. The study also uncovered two new CpG sites strongly associated with alcohol use, expanding knowledge of how drinking affects the body at a molecular level. Overall, EpiScore presents a more reliable way to study alcohol's long-term impact on health, particularly brain function. Unlike self-reports, which can be unreliable, this DNA-based method offers deeper insights into how drinking habits shape overall health, especially brain health, over time.

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

A new way to estimate biological age using patterns in genetic data



Chronological age is easy to measure, but it doesn't always reflect how well your body is ageing. Scientists are increasingly using DNA methylation—a natural process that modifies DNA as we age—to estimate biological age, which may be more closely tied to health and lifespan. In this study, researchers developed a new method called w2D-KDE (weighted 2D kernel density estimation). Unlike traditional "epigenetic clocks," which predict a single biological age, this approach provides a range of possible ages, offering both an estimate and an indication of stability in ageing-related DNA changes. The researchers tested this method using data from large studies, including the LBC1921 and LBC1936 cohorts. Their results showed that this new measure was just as effective as existing tools for estimating chronological age, but it also provided extra insights. For example, individuals whose biological age markers showed less variation tended to have better health and live longer—especially in the LBC1921 group. Beyond ageing, this method helped identify biological differences linked to diseases such as HIV and leukaemia. It also distinguished more clearly between healthy and unhealthy ageing. By offering a more nuanced and flexible way to measure biological age using DNA, this approach could improve how we assess ageing and health risks in the future.

Perez-Correa, J. F. *et al.* (2025). Weighted 2D-kernel density estimations provide a new probabilistic measure for epigenetic age. *Genome Biology.*

Knowledge Exchange

LBC research in the spotlight: From grip strength to gardening and reaction times

Recent media coverage has highlighted the valuable contributions of Lothian Birth Cohorts research across various fields, demonstrating the lasting impact of long-term studies on health, cognition, and ageing. One standout example is the renewed attention given to grip strength research, following a *Times* article referencing the landmark study *Grip Strength across the Life Course: Normative Data from Twelve British Studies (2014)*. This widely cited research, which includes data from the LBC1921 cohort, provides important insights into muscle strength as a predictor of overall health and longevity. Its continued relevance underscores the importance of studying physical function across the life course. Meanwhile, the BBC Future explored the benefits of gardening, touching on themes central to ageing and cognitive wellbeing. With increasing recognition of how outdoor activities can boost mental health, physical resilience, and social connections, LBC research, led by Dr Janie Corley, continues to inform discussions on lifestyle factors that promote healthy ageing. Janie's paper on the topic has been widely cited in 64 news stories from 61 national and international outlets. Additionally, Professor Simon Cox lent his expertise to a recent article discussing reaction times, further showcasing the breadth of LBC's contributions to our understanding of cognitive and brain ageing. Reaction speed is a key indicator of brain health, and insights from long-term cohort studies like LBCs help researchers understand how cognitive abilities change over time and what factors may support sharper thinking in later life. These media highlights reinforce the significance of LBC research in shaping discussions on ageing, brain function, and overall wellbeing—connecting decades of scientific inquiry with real-world applications that continue to inform and inspire.

Exploring the role of proteomics in disease: A symposium led by Dr. Sarah Harris

Speakers and chairs at the proteomics symposium. Dr Sarah Harris in the centre front row.

Proteins are the building blocks of life, controlling nearly every function within our cells. Studying them—through the field of proteomics—gives scientists vital insights into health, disease, and potential treatments. On 9 May, the University of Edinburgh hosted the *Molecular Epidemiology Symposium: The Role of Proteomics in Disease*, co-organised by Dr. Sarah Harris and Professor Riccardo Marioni, Principal Investigators working with the Lothian Birth Cohorts. Around 100 researchers from academia and industry came together to discuss the latest advances in proteomics technologies, including SomaScan, Olink, and mass spectrometry—powerful tools that allow scientists to detect and study thousands of proteins in biological samples. Dr. Harris presented her research, funded by the National Institutes of Health (NIH), on proteomic biomarkers that may signal cognitive decline before dementia onset. Meanwhile, Professor Marioni led a thought-provoking Q&A with Dr. Robert Scott from pharmaceutical company GSK, exploring the impact of proteomics on drug development. Keynote speakers highlighted the critical role proteins play in diseases such as Alzheimer's, providing new perspectives on how studying them could transform healthcare in the future. The symposium, supported by One Health Genomics Edinburgh and sponsored by bioXcelerate AI, was a day filled with inspiring discussions and knowledge-sharing. Reflecting on the event, Dr. Harris remarked, *"It was a highly educational day filled with inspiring talks."* As proteomics continues to advance, events like this help bridge the gap between research and real-world applications, bringing hope for future breakthroughs in disease prevention and treatment.

Celebrating Brain Awareness Week at St Francis Primary School

P7 students at St Francis Primary School trying out cognitive tests

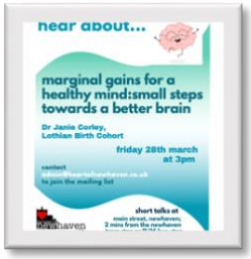
On 12 March, nearly 50 enthusiastic P7 pupils at St Francis Primary School took part in Brain Awareness Week workshops, delving into the fascinating world of brain health and cognitive ageing. Supported by volunteers from the Lothian Birth Cohorts (LBC) research team and Boroughmuir High School, the sessions provided an interactive and engaging introduction to how our thinking skills change throughout life. The pupils learned about the groundbreaking LBC studies, which follow individuals who first took cognitive tests as 11-year-olds in 1921 and 1936. They explored how these long-term studies have helped scientists understand memory, brain function, and ageing over time. To bring these ideas to life, the children played “Who Gets to Be 100?”, a board game designed to introduce key concepts from the LBC research. Competitive spirits ran high as they tackled questions and tested their own cognitive skills! They also tried practice questions from the original tests taken by children in 1921 and 1936, worked through cognitive challenges in teams, and examined 3D-printed brain models created using LBC data. The excitement was clear, with pupils eagerly asking, *“Can you come back tomorrow?”* Many questions and discussions followed, showing a deep interest in how the brain works. The Boroughmuir High School volunteers added to the collaborative energy, making the sessions even more engaging. As a fantastic finale, the children created a poster showcasing what they had learned about brain health—sharing advice on how to keep their minds active and healthy for life. Thank you to the teachers, pupils, and volunteers for making this such a memorable and insightful event.

Exploring Psychology: A workshop for families

Rita Dargham, a PhD student in Translational Neuroscience with *IntoUniversity* participants, playing the Game of Life

On Saturday 10 May, families from Glasgow and Craigmillar came together at the University of Edinburgh for an inspiring workshop designed to spark curiosity and foster a love for lifelong learning. Hosted in collaboration with the University’s Widening Participation Team, the event welcomed a group of 40 P6 and P7 students and their parents and carers working with *IntoUniversity*, a UK-based charity that provides local learning centres to support young people from disadvantaged backgrounds in achieving their aspirations—whether in higher education, employment, or work-based training. The workshop featured hands-on activities and engaging discussions about psychology and brain health. Families explored these themes through interactive sessions, including the "Bridge Your Mind" walking tour, led by Jana Tomastikova, a fourth-year Psychology student, who connected Edinburgh’s landmarks with key insights from the Lothian Birth Cohort studies. Children took part in "The Game of Life: Who Wants to Be 100?", an interactive experience that highlighted how lifestyle choices—such as staying active, learning a new language, or playing a musical instrument—can shape brain health and reduce dementia risk. Meanwhile, parents and carers participated in a Q&A session, learning more about cognitive and brain health, as well as the impact of research from the Lothian Birth Cohorts. The IntoUniversity team praised the event for its accessible and engaging content, with participants highlighting the enthusiasm of volunteers and the impact of the presentations. Families shared positive feedback, with one parent remarking, *"The tour was really nice—I learned alongside my children and found it useful to think about educational opportunities for both them and myself."* Another participant shared, *"Excellent experience, learned a lot!"* while others expressed their excitement for future workshops, saying, *"I would like to attend whenever I get this opportunity."* The success of the event was a testament to the enthusiasm and expertise of our volunteers from the Lothian Birth Cohorts and PhD students in Translational Neuroscience, who helped make this initiative informative, engaging, and fun!

Dr Janie Corley talks about healthy brain ageing at the Heart of Newhaven Community



On 28 March, members of the Heart of Newhaven Community gathered for a discussion on brain ageing, led by Dr Janie Corley. This volunteer-led group, based in the historic Victoria Primary School, connects people to reduce isolation and promote community wellbeing through engaging activities, talks, and events. Dr. Corley shared insights from the LBC studies, offering a unique perspective on how our thinking abilities evolve as we grow older and what factors may influence healthy brain ageing. The discussion was lively, with attendees showing great enthusiasm for learning more about brain health and ageing. A special highlight was the presence of one of the LBC study participants from the local area, adding a personal touch to the conversation. The meeting fostered meaningful exchanges, encouraging questions and discussions about ways to maintain cognitive health as we age. Attendees expressed interest in follow-up activities and further opportunities to explore brain and cognitive health in everyday life. Janie said: *"Thank you to the Heart of Newhaven Community for hosting such a warm and engaging event. It was inspiring to see the community's eagerness to learn and connect over such an important topic, reinforcing the power of shared knowledge in promoting lifelong wellbeing."*

LBCs at the CAHSS Research Showcase: A morning of insight and collaboration

Alzheimer Scotland Dementia Research Centre

On Monday, 10 March, we attended a special event hosted by the University fundraising team to thank supporters of the Alzheimer Scotland Dementia Research Centre (ASDRC). Dr Tom Russ and colleagues expressed deep appreciation for donor contributions, and Professor Simon Cox highlighted the value of the Lothian Birth Cohorts for ageing and dementia research. Dr Charlotte Squire and Katie Robertson discussed their projects, while Dr Barbora Skarabela shared insights at the LBC display table. Attendees included donors, charity reps, Brain Scotland members, and academics such as Professor Susan Shenkin (ACRC). Guests explored ASDRC research through interactive posters and conversations with students. The LBC team's 3D-printed brain models sparked interest and were later featured in Dr Catherine Pennington's "Your Amazing Brain" workshop at the Edinburgh Science Festival. The event welcomed around 30 guests and fostered lively discussion, collaboration, and enthusiasm for future engagement in brain health and dementia research.

Castlebrae Community Science Festival

Maria Paula Huertas Caycedo, a PhD student in Cardiovascular Science, assisting with Augmented Reality glasses

On 21 March, the Castlebrae Science Festival, organised by the community engagement team at Edinburgh BioQuarter, brought together over 200 attendees for an exciting afternoon of hands-on exploration and discovery. The event was a wonderful community celebration, where families, students, and teachers gathered to engage with science in a welcoming and familiar space. After last year's success, we brought back our interactive display table, featuring 3D-printed brains and augmented reality glasses that visualise brain ageing based on real data from LBC and UK Biobank data. Throughout the afternoon, children and parents had the chance to explore, ask questions, and engage with scientific concepts in a fun and accessible way. We were fortunate to have volunteers from Edinburgh Neuroscience, whose expertise and enthusiasm helped bring the experience to life. Their support ensured that visitors had meaningful and engaging discussions about brain health, ageing, and the importance of scientific research. A particularly heartwarming moment was when students and teachers from St Francis Primary and Niddrie Mill Primary stopped by, recognising our team from previous school visits. Their excitement and curiosity reflected the lasting impact of engaging young minds with science. The feedback from attendees was overwhelmingly positive, with all respondents rating the festival 5 out of 5. Parents especially appreciated the opportunity to learn about science alongside their children, fostering a shared sense of curiosity and discovery. Many described it as a wonderful opportunity for children, reinforcing the importance of community-driven learning experiences. A huge thank you to our colleagues at Edinburgh BioQuarter, who organised the event, and everyone who participated, supported, and helped make this festival such a success, including our dedicated volunteers and the enthusiastic families who joined us. We look forward to creating more opportunities for hands-on science engagement in the future!

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

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Foote, I. F. et al. (accepted). Uncovering the multivariate genetic architecture of frailty with genomic structural equation modelling. *Nature Genetics*.

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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.

Email lbc1936@ed.ac.uk to reach the LBC1936 cognitive testing team, or lbc.ke@ed.ac.uk for knowledge exchange, public engagement, media inquiries, and policy.

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

LBC team in June 2025 in 7 George Square

UKRI

NIH National Institutes of Health

THE ROYAL SOCIETY

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