

# 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 60: December 2022

Welcome to the 60<sup>th</sup> 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.

In this edition, we also reflect on the past year with the LBC Director, Dr Simon Cox.

## Looking back at 2022 with the study director



Dr Simon Cox at the 2019 reunion

This year has been marked by a transition from online interactions and the LBC team working from home to a gradual return to our desks in 7 George Square toward the end of the summer.

We welcomed our first post-pandemic academic visitor, Professor Duke Han of the Keck School of Medicine at the University of Southern California; in June we marked 90 years since the 1932 Scottish Mental Survey which forms the foundation of the LBC1921 study, and 75 years since the 1947 Scottish Mental Survey which forms the foundation of the LBC1936 study; in March we joined the first post-pandemic in-person public event with over 400 attendees, 'Beautiful Brain' at the Edinburgh International Conference Centre; and contributed to a new BBC documentary series that aired in October.

Our work on understanding brain, cognitive and general aging continues to accelerate with further high-impact and high-quality research and discovery, and with new data. We challenged Simon to highlight this year's achievements in five brief points:

### One: Wave 6 data collection close to completion



Beth Jones (left) joined the LBC1936 cognitive testing team this year. In photo with a participant at the WTCRF

*"Throughout the year the LBC1936 team has been continuing their excellent work in bringing in participants for their 6<sup>th</sup> wave of cognitive, medical, physical and imaging assessments, and I am delighted to report that Wave 6 data collection is close to being complete. This is testament to the super LBC team and staff at the Wellcome Trust Facility and, of course, to the participants' generosity and commitment to the study. In spite of the COVID-19 pandemic, the COVID-safe protocols that we still implement, and the additional year between visits, the response from participants has remained characteristically enthusiastic."*

### Two: New data and collaborations

*"In each phase of the Disconnected Mind project, we find ourselves able to collect new types of data. This year, for example, in collaboration with researchers at the University of Dundee, we have invited the LBC1936 participants to contribute to a questionnaire about their experience of chronic pain and childhood adversity, a new important line of data to contribute to life-course effects for later years. The data collection is on-going and we look forward to reporting the results in the new year."*

### Three: Dementia Ascertainment



Dr Tom Russ at the 2019 reunion

*“One of the great achievements of the year is the successful completion of the clinical dementia ascertainment work, led by Dr Tom Russ and colleagues. The team has been systematically going through participants’ medical records to identify dementia diagnoses, with dementia status now available for 865 LBC1936 members who attended the study from Wave 2 onwards. Of these, 13.6% have developed dementia, and sadly those numbers will continue to rise more steeply over the coming years. This work represents a substantial advance in our ability to differentiate normal and pathological profiles of cognitive ageing. These new measures will allow us to return to the wealth of LBC936 data and results collected over 16 years (from mean age 70 to current mean age 86, to understand more about identification of dementia risk, and also make more robust inferences about mechanisms.”*

### Four: Publications

*“We have seen an impressive range of new and important scientific findings, including:*

- *results on how environmental factors across the life-course relate to ageing, arising from our successful collaboration with our colleagues at the School of Geosciences at the University of Edinburgh;*
- *the discovery of how synaptic changes relate to differences in cognitive ageing based on the stem cells and brain tissue samples donated by LBC1936 participants reported in a paper led by Drs Declan King and Tara Spire-Jones;*
- *Dr Federica Conte’s research, who came to visit us from Milan last year, revealing that individuals who show earlier life-course changes in their cognitive abilities are often also those who are at risk of steeper cognitive ageing in later life (published in Psychological Science).*

*We also continue to contribute to understanding of ageing more generally, and to illustrate, I mention an important collaboration with Drs Kristina Kirschner and Tamir Chandra, whose research was published in Nature Medicine. New insights into leukaemia risk were afforded by LBC participants’ longitudinal blood samples. They were critical in enabling more accurate forecasting of the speed with which certain types of mutations in blood stem cells will grow.*

*Finally, I want to highlight a major new output from the core team, very recently accepted at Molecular Psychiatry. Led by Dr Janie Corley, we conducted a detailed analysis of 15 major predictors of cognitive decline across 5 waves of LBC1936. This is a superb and important set of findings at the centre of the study’s mission; see below for further details. I am thrilled by the range and quality of these outputs.”*

### Five: Science communication to the wider public



Dr Judy Okely with LBC participants at the Wellcome Trust Clinical Research Facility during the recording of a BBC documentary ‘Who lives in Scotland?’

*“We have continued actively disseminating our results more widely with talks, science workshops, seminars, festival activities and in interviews with reporters and journalists. Several findings have been picked up extensively by press and media outlets. Our research appeared in national and international outlets, including [the Economist](#), [Guardian](#), [Observer](#), [STV news](#), and our team contributed to a new [BBC documentary](#), news articles and [CNN](#) and [BBC podcasts](#).*

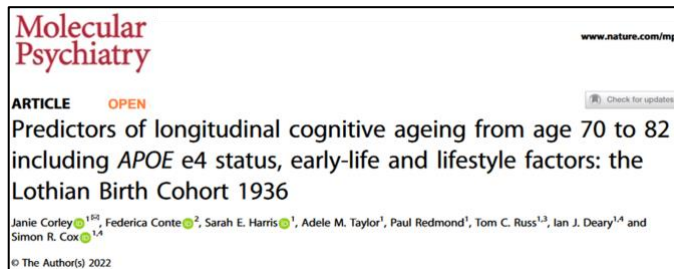
*These efforts have helped us reach thousands of people, online, on paper and in person. We are already making plans for next year and I’m excited to announce this will include our next LBC reunion. Watch this space!”*



## Scientific Highlights

This year the team has led and contributed to over 30 peer-reviewed scientific publications so far, based on LBC data alone. Here we draw attention to some of the recent research that has been published since the last issue of the Disconnected Mind Newsletter in September.

### **APOE e4 linked to accelerated cognitive decline across older age in the LBC1936**



Identifying risk factors for cognitive decline is among the greatest challenges to improve the wellbeing of older people.

Dr Janie Corley led an investigation to examine whether 15 of the most commonly used candidate risk factors in the field of cognitive ageing from across the life-course were associated with longitudinal cognitive change in the LBC1936, using cognitive test scores measured at ages 70, 73, 76, 79, and 82. As we had previously shown in the LBC1936, many factors were associated with higher cognitive function scores at age 70, including a higher childhood cognitive ability and more education, a higher mid-life occupational social class, a healthier lifestyle, better mental health and absence of chronic disease. However, very few of these individual factors were significant unique predictors of cognitive decline, and all had small effects. The only risk factor that consistently emerged from the analyses was *APOE* e4 status. Individuals who carry the *APOE* e4 allele were more likely to experience accelerated cognitive decline across a range of abilities such as memory, visuospatial ability and processing speed, compared to individuals who do not carry this allele.

This highlights the importance of thinking about 'marginal gains' when considering predictors of cognitive ageing. Individual differences in cognitive ageing probably reflect an accumulation of small influences from numerous factors, many of which are likely to be already present in early- and mid-life. We continue to search for more, and to understand their biological bases.

This study is only one of a few in the literature which has examined many life-course risk factors for cognitive decline in the same sample at the same time, an important strategy for determining which factors might protect cognitive ability in later life.

Dr Janie Corley said: *"These latest findings add to the evidence that there are a multitude of factors from across the life course that contribute to better thinking skills in later life. Carrying the APOE e4 gene appears to increase one's risk of accelerated cognitive decline, but it is not inevitable. To enhance your chances of healthy cognitive ageing, a case can be made for being physically active and fit, keeping one's health in check and avoiding smoking. Small and manageable improvements across a broad range of behaviours have potential for maintaining thinking skills in the long term."*

[The study is published in \*Molecular Psychiatry\*.](#)

### **LBC1921 and 1936 DNA-methylation data used to validate two novel epigenetic signatures**



Lifestyle factors like smoking and alcohol consumption may compromise health through biological changes affecting our genes. Tests of biological ageing which assess changes in gene expression – epigenetics – could help us better understand the effects of certain lifestyle factors on our health and may be more reliable than self-reported behaviour estimates which are susceptible to bias.

A study led by Dr Jonviea Chamberlain at Unisanté in Lausanne, Switzerland used data from the Swiss Kidney Project on Genes in Hypertension to create two novel epigenetic signatures of tobacco (EpiTob) and alcohol (EpiAlc) consumption. The epigenetic signatures were then validated in independent cohorts, including LBC1921 and LBC1936, and their association with health outcomes, including cardiovascular disease and all cause and cause-specific mortality were examined.

The results showed that these epigenetic signatures are well-correlated with self-reported exposure status and are associated with long-term health outcomes. Not surprisingly, the epigenetic smoking signature was associated with lung-cancer and all-cause mortality in the LBC1921 and LBC1936 cohorts. The authors conclude that epigenetic signatures of lifestyle exposure may be a better measure of smoking and alcohol consumption than self-report measures, due to being less prone to reporting and other measurement biases, and may therefore yield more accurate predictions for disease outcomes in future studies.

[The study is published in \*Clinical Epigenetics\*.](#)

### **Synaptic resilience and cognitive ability in ageing**



Why does age increase risk of Alzheimer's disease, and why do some people experience age-related cognitive decline in the absence of dementia?

Dr Declan King led a study testing the hypothesis that resilience to molecular changes in synapses contribute to healthy cognitive ageing. Declan and co-authors used the rare, combined resource of post-mortem brain tissue and induced pluripotent stem cells (iPSC) available from LBC1936 participants, as well as data from other cohorts of middle-aged people who died from non-neurological conditions, and people who died with Alzheimer's disease, to examine synaptic changes associated with age-related cognitive decline.

The study found that synaptic pathology increased, and expression of genes involved in synaptic signalling decreased when comparing tissue from people in mid-life, healthy ageing (LBC1936) and Alzheimer's disease. In contrast, brain tissue and neurons from people who maintained cognitive ability during ageing exhibited decreases in synaptic signalling genes compared to people who had steeper age-related cognitive decline.

The authors concluded that efficient synaptic networks without pathological protein accumulation may contribute to resilience to cognitive decline in ageing.

The study has been accepted for publication in *Alzheimer's & Dementia*.

### **Motoric Cognitive Risk more prevalent in those from lower socioeconomic backgrounds**



Motoric Cognitive Risk (MCR) is a walking speed-based syndrome that is quick and easy to measure and highlights people at increased risk of dementia and falls.

A recent study with LBC1936 data, led by Dr Donncha Mullin, examined the prevalence and risk factors for MCR, and assessed its overlap with Mild Cognitive Impairment (MCI), pre-frailty, and frailty. Participants were classified into non-MCR or MCR groups, and the authors examined baseline risk factors (at mean age 70) for MCR measured years later at mean ages 76, 79, and 82.

The study found that one in 20 of the LBC1936 participants have MCR, with MCR prevalence rate ranging from 5.3 to 5.7% between age 76 and 82. Risk factors associated with MCR varied depending on age at measurement, but included older baseline age, less professional occupational socioeconomic status, and lower scores on a range of cognitive tests of executive function.

Approximately 46% of the MCR group also had MCI, and almost everyone in the MCR group had either pre-frailty or frailty. Those from lower socioeconomic backgrounds were more likely to develop MCR.

The findings highlight the importance of reducing socioeconomic inequalities throughout life.

[The study is published in \*Geriatric Psychiatry\*.](#)

## Early exposure to air pollution associated with faster biological ageing in the Lothian Birth Cohort 1936



Higher exposure to air pollution has been linked to a wide range of diseases, however, little is known about sensitive periods during the life course when air pollution might have a stronger impact on our health, or whether the effects of air pollution are cumulative over time.

A study, led by Dr Gergő Baranyi at the School of Geosciences at the University of Edinburgh, explored associations between air pollution exposure across the life course and biological ageing. The researchers examined DNA methylation-based markers of biological ageing derived from participants' blood samples, taken between ages 70 and 79 respectively, in relation to estimated air pollutant concentrations linked to participants' residential addresses from across the majority of their' lifespans, in 1935, 1950, 1970, 1980, 1990 and 2001.

The study found that living in more polluted areas around birth and during young-to-middle adulthood was associated with small but detectable differences in rates of biological ageing, and the impact of air pollution is likely to persist across the entire life course.

These findings are of great interest to diverse audiences. Dr Baranyi shared the results at a number of national and international conferences and said: *“Although the audiences of these conferences could not be more diverse, participants were equally engaged to hear about our latest results. They were particularly impressed about the availability of residential history for almost the entire life course of the cohort participants, a unique feature of the LBC1936.”*

[The study is published in \*Environment International\*.](#)

## Knowledge Exchange

### What's good for the mind?

After two years of online engagement with school pupils we were delighted to have finally returned to in-person science workshops. In November, as part of the national Being Human Festival, the team visited Broughton High School to meet with two groups of S1 11- and 12-year-olds to chat about the LBC research.



LBC team at Broughton High School with cognitive tests and 3D-printed brains during the Being Human Festival

The children tested their thinking skills with LBC cognitive testers, Beth Jones and Danielle Page, explored what happens to the brain as we grow old as they compared a pair of healthy and unhealthy 3D-printed brains and factors that influence the process, and joined Arish Mudra Rakshasa to discover what mice have to do with loneliness, how the lockdown affected the LBC participants, and how mental health relates to cognitive ageing. It was a fabulous morning with over 40 energetic and curious children who were keen to explore and ask questions, and air their views and answers about brain health and ageing!

Beth Jones said: *“I had a lovely time visiting Broughton High School. Danielle and I ran a table about cognition and different types of thinking abilities, with examples of the tests administered to the LBC participants at the clinic. The children were very engaged, took part in the tests and asked many questions. One boy wanted to know if he got any skills from video games, which led to a great discussion about visuospatial abilities and what ‘thinking skills’ are needed to play video games. We also had some S4 helpers, who did a fantastic job explaining instructions and running reaction time and block design tests. Overall, I thoroughly enjoyed the day and think it was a rewarding experience for all.”*



## Looking smart



In her article [‘In the frame: a close look at the world of spectacles’](#) for *The Observer*, Emma Beddington, a freelance writer and a spectacle wearer, focuses on eyesight and takes us on a journey through the history of sight correction and myopia. The article reminds us that those of us who wear spectacles can take some comfort in a finding by a major genome-wide association study, led by Dr Gail Davies of the LBC, published in [Nature Communications](#).

In a large dataset from over 300,000 people aged between 16 and 102, including LBC data, the study revealed a small but significant correlation between near-sightedness, or ‘myopia’, and cognitive ability at a genetic level, and that wearing glasses is correlated with greater scores on tests of cognitive ability.

Gail’s article has recorded 52,000 views and a spectacular Altmetric score of 1412, with 255 citations and 76 mentions in news outlets. You can read an accessible summary of the study in *The Guardian’s* original 2018 article, [‘Wearing glasses may really mean you’re smarter, major study finds’](#).

## Which musical instrument will you learn to play?



Learning to play a musical instrument may be challenging. It might require hours of practice and patience from those around.

But that’s not a reason to give up. The benefits are worth the effort. Dr Judy Okely’s recent study with Lothian Birth Cohort 1936 shows that participants who had more musical instrument experience in early life tended to show greater gains in general cognitive ability by age 70.

*“These results add to the evidence that activities that are mentally challenging, such as learning to play a musical instrument, might be associated with better thinking skills,”* says Judy.

Judy’s paper has been featured in *The Guardian*, *The Times*, *The Independent*, *The Scotsman*, *The Daily Telegraph*, *Evening News*, *The Economist*, *The Herald*, and *The Irish Daily Mirror*.

You can read an excellent summary of this research in an article [‘Learning a musical instrument may confer lifelong cognitive benefits’](#) by Emma Young in *The Psychologist*, a monthly newsletter by the British Psychological Society.

## Lothian Birth Cohorts featured in a new BBC documentary



In May, we were invited to take part in filming a segment of a new series, ‘Who Lives in Scotland?’ with Martin Geissler for BBC Scotland.

In the episode, titled ‘Health, Wealth and Happiness’, Martin explored some of the challenges Scotland faces with an ageing population, such as the increasing numbers of people living with dementia as more people begin to live longer.

The Lothian Birth Cohorts were presented as a unique example of studies aiming to better understand how people can stay healthy and sharp into older age.

On the show, former LBC Director Professor Ian Deary explained just how unique the LBCs are, and what we have uncovered so far about factors which influence healthy cognitive and brain ageing.

Dr Judy Okely presented the findings of her research on cognitive ability and musical experience in the LBC1936, and two LBC1936 participants, Alex Peden and Moira Hepburn, represented the LBC studies by taking part in some cognitive tests on camera. The programme included many positive messages about getting older and if you missed it on November 1<sup>st</sup>, you can watch it on the BBC iPlayer:

<https://www.bbc.co.uk/programmes/m001dtzz>.

### The importance of place for healthy ageing



Professor Catharine Ward Thomson, our collaborator in the School of Geosciences, was invited to present her research on outdoor environments and quality of life, including their impact on older people at the Advanced Care Research Centre's Symposium on '*Understanding ageing and reshaping health and care*'.

In her talk '*Understanding Ageing: the importance of Place (and of salutogenic landscapes)*', Professor Ward Thomson covered two-decades worth of research engaging with older people on links between outdoor access, quality of the outdoor environment, and healthy ageing. The presentation included work with the LBC1936 in the UKRI-funded project, '*Mobility, Mood and Place*', in collaboration with Professor Ian Deary, and Drs Jamie Pearce, Mark Cherrie and Niamh Shortt from the department of Health Geography, which demonstrated the links between less access to parks and green space over the life-course and cognitive decline, anxiety and depression in older age.

Catharine also covered findings from the more recent ESRC-funded '*Lifecourse of Place*' project using LBC1936 data, led by Professor Jamie Pearce in collaboration with LBC's Simon Cox, Ian Deary and Gergő Baranyi, among others. The project aimed to examine links between neighbourhood deprivation and air pollution over the life course, and healthy ageing that include frailty indicators and measures of brain health and biological ageing.

The symposium was attended by over 50 participants, including researchers, government, policy-makers, business, third sector, and public representatives.

## Happy Holidays from the LBC1936 team!

We hope you enjoyed reading the final issue of the Disconnected Mind Newsletter this year and we look forward to sharing our news with you in the New Year!



LBC1936 team 2022. Left to right: Danielle Page, Simon Cox, Adele Taylor, Janie Corley, Beth Jones, Alison Pattie.

### Contact

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



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

### New publications since September 2022

#### Accepted / In Press

King, D. et al. (2022). Synaptic resilience is associated with maintained cognition during ageing. *Alzheimer's & Dementia*.

Lu, A.T. et al. (2022). DNA methylation GrimAge version 2. *Ageing*, 14 (23), 9484-9549.

Weihls, et al. Epigenome-wide association study reveals CpG sites associated with thyroid function and regulatory effects on KLF9. *Thyroid Journal Program*.

#### Published

Baranyi, G. et al. (2022). Life-course exposure to air pollution and biological ageing in the Lothian Birth Cohort 1936. *Environment International*, 169, 107501.

Baranyi, G., et al. (2022). Association of life-course neighborhood deprivation with frailty and frailty progression from ages 70 to 82 years in the Lothian Birth Cohort 1936. *American Journal of Epidemiology*, 191(11), 1856-1866.

Bernal, J. et al. (2022). Assessment of perivascular space filtering methods using a three-dimensional computational model. *Magnetic Resonance Imaging*, 93, 33-51.

Chamberlain, J. D. et al. (2022). Blood DNA methylation signatures of lifestyle exposures: tobacco and alcohol consumption. *Clinical Epigenetics*, 14(1), 1-12.

Clancy, U. et al. (2023). Are neuropsychiatric symptoms a marker of small vessel disease progression in older adults? Evidence from the Lothian Birth Cohort 1936. *International Journal of Geriatric Psychiatry*.

Conte, F. P. et al. (2022). Cognitive change before old age (11 to 70) predicts cognitive change during old age (70 to 82). *Psychological Science*.

Corley, J. et al. (2022). Predictors of longitudinal cognitive ageing from age 70 to 82 including APOE e4 status, early-life and lifestyle factors: the Lothian Birth Cohort 1936. *Molecular Psychiatry*, 1-16.

Higham, J. et al. (2022). Local CpG density affects the trajectory and variance of age-associated DNA methylation changes. *Genome Biology*, 23(1), 1-28.

Lahti, J. et al. (2022). Genome-wide meta-analyses reveal novel loci for verbal short-term memory and learning. *Molecular psychiatry*, 1-13.

Mullin, D. S. et al. (2022). Prevalence and predictors of Motoric Cognitive Risk Syndrome in a community-dwelling older Scottish population: A longitudinal observational study. *International Journal of Geriatric Psychiatry* 37(11), 1-10.

Okely, J. A., Overy, K., & Deary, I. J. (2022). Experience of playing a musical instrument and lifetime change in general cognitive ability: Evidence from the Lothian Birth Cohort 1936. *Psychological Science*, 33(9), 1495-1508.

Stevenson, A. J., et al. (2022). A comparison of blood and brain-derived ageing and inflammation-related DNA methylation signatures and their association with microglial burdens. *European Journal of Neuroscience*.



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