CHRISTMAS NEWSLETTER 2022

WELCOME!

THE UNIVERSITY of EDINBURGH
Lothian Birth Cohorts

Welcome to the Lothian Birth Cohorts (LBC) 2022 Christmas newsletter. As always, the LBC team has been very busy all year making great progress with the study. In this newsletter, we will update you on our latest developments, research and publications, and some scientific and public engagement events we've been involved in. We are incredibly grateful for your continued support of the study; none of this would be possible without you.

We hope you have a very happy festive season, and wish you and your loved ones all the best for 2023.

WOULD YOU LIKE TO RECEIVE LBC EMAIL UPDATES?

We know many of you use email to stay in touch with family and friends. If you have an email address and aren't sure whether we know it, please let us know!

We'd be particularly keen to hear from you because in Spring 2023 we will be launching our new **LBC participant email mailing list**! If you, or your friends and family members, would like to receive quarterly newsletters from the LBC team, please send us an email to let us know. We're excited to be able to update you on our progress more often!

CONTACT US

The team are always delighted to hear from you, so if you would like to get in touch with us, please use the contact details found below. Please let us know if your contact details have changed, if you require this newsletter in another format, or if you'd like further information about anything you read here.

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LBC1936 STUDY: WAVE 6 UPDATES

We are delighted to report that Wave 6 of the LBC1936 study has continued to progress very well throughout 2022, and the team have consistently been blown away by our participants' enthusiasm and dedication. When this newsletter arrives with you, we will have seen 290 of you at the Wellcome Trust Clinical Research Facility (WTCRF) for cognitive testing appointments, and 180 will have had an MRI brain scan at the new scanning facility at Edinburgh Imaging Facility (EIF), Royal Infirmary of Edinburgh. We look forward to continue seeing more of you in the New Year.

Janie with Mr Forsyth

It is always particularly special for us when we get to meet the same participants over many years and build friendships with you. Like many of you, our participant Patrick Forsyth has attended all waves since the study began. However, unlike any other, he is the only participant to be tested by the same person at every single wave! This is highly unusual since the testing team and their clinic days have changed across waves. Janie recently saw Mr Forsyth for the sixth time since his first appointment in 2005, at the beginning of the study. We hope we can keep his record going for Wave 7!

Participants Alistair and Margaret at the WTCRF

We also always enjoy celebrating holidays together with you in the clinic. In February, the testing team celebrated Valentine's Day with an unusual coincidence: on 14th February all of our appointments were booked by LBC1936 couples! Participants Alistair and Margaret (pictured above) spent Valentine's Day at the WTCRF completing cognitive and physical tests, and John and Helen (pictured below) spent that afternoon at the EIF each having an MRI brain scan. How romantic!

Participants Helen and John share a romantic moment at the EIF

Wave 6 has also brought about an exciting research development. In collaboration with colleagues in the Alzheimer Scotland Dementia Research Centre (ASDRC), directed by LBC study medic and co-investigator Dr Tom Russ, the team has created a new dataset of important health outcomes including dementia status, from NHS health records of almost all of the participants who were originally invited to the LBC1936 study. This has been helpful for the testing team, who received an up-to-date record of any participants with advanced dementia who need additional support at the clinic. The data will also be an invaluable and unique resource for researchers interested in determining factors related to the development of dementia and other ageing-related outcomes. We are very grateful to the ASDRC team for their hard work on this fantastic project.

CELEBRATING THE ANNIVERSARY OF THE SCOTTISH MENTAL SURVEYS

In June, we celebrated two big anniversaries in the history of the Lothian Birth Cohort studies: 1st June 2022 was exactly 90 years since the Scottish Mental Survey 1932 (SMS1932), and 4th June 2022 was exactly 75 years since the Scottish Mental Survey 1947 (SMS1947). The SMS1932 and SMS1947 represent the foundation of the LBC1921 and LBC1936 studies, respectively. Both surveys were unique in assessing the thinking skills of almost the entire respective populations of 11-year-olds in Scotland under the same conditions. Their importance has only grown with the rediscovery of the records by Professors Ian Deary and Lawrence Whalley in the 1990s, which led to the tracing of two of the most important cohorts in the world: you!

Professor Godfrey Thomson and the front cover of the 1932 Mental Survey Test

The SMS test scores from thousands of Scottish 11-year-olds offered a rarely available baseline measure to investigate how childhood intelligence relates to cognitive ability, and mental, physical, and brain health in older age. On 1st June 1998, 66 years to the day since the SMS1932, a group of participants gathered in Aberdeen to sit that exact same test as they had completed at age 11. Thus began the LBC1921 and LBC1936 studies; the longest, and one of the most thorough, follow-up studies of cognitive and brain ageing in the world.

Professor Deary reflects: "*I think back almost a quarter of a century to that June 1st 1998 morning in the Aberdeen Music Hall with pain, poignancy, and pride. Pain, because a couple of weeks beforehand, I had smashed up both my elbows in a bicycle accident and my arms were immobile in plaster casts. My daughter Elayne had to accompany me to Aberdeen to manage basic things like doors; however, I managed to read the Moray House Test instructions to the returning participants after 66 years. Poignancy, because the two-and-a-bit decades after that were so busy and fruitful, with the assembling of the wonderful LBCs' participants and team members and collaborators. The years flew by. Pride, because I think we repaid the LBCs' participants' generosity and commitment by producing a lot of high-grade, useful scientific results about human ageing, we trained many super young scientists, and because the LBCs continue at full steam with lots still to discover.*"

LBC1936 TEAM MSC SUCCESSES

Speaking of super young scientists: this year the team celebrated with two members of the team who you may recognise! Study Coordinator Adele Taylor and Research Assistant Danielle Page completed MSc programmes part-time, using LBC data in their theses, while working full-time with the LBC team. We were delighted to announce that Adele received a distinction in her MSc by Research in Psychology, and Danielle received a distinction in her MSc in Human Cognitive Neuropsychology. We are sure you will join us in congratulating them!

SCIENTIFIC HIGHLIGHTS

We are grateful to all of you for volunteering your time and hard work supporting the study, and providing such a range of world-class data over almost 20 years. Here are just a few of the discoveries our researchers and collaborators have made in 2022, using your data:

Blood test could predict future risk of leukaemia

Author: Neil Robertson et al.
Journal: *Nature Medicine*

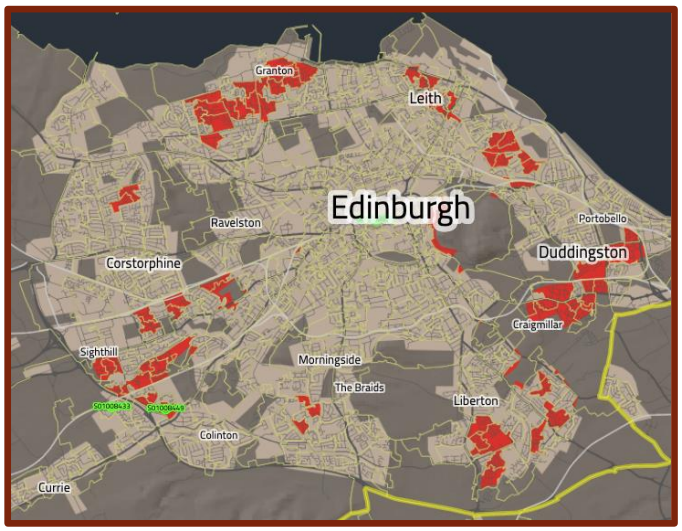
Leukaemia is often the result of the disruption to the fine balance in blood cell production, where old blood cells die and new ones are created. As we age, mutations in some of our blood-creating stem cells can mean that these can have a 'growth benefit' over other blood cells and outnumber them, in what is referred to as 'fitness advantage'. Neil took advantage of unique longitudinal data available in the LBCs to link different types of mutations with different growth speeds of the blood stem cells carrying these mutations. They found that specific mutations give distinct fitness advantages to stem cells in people without leukaemia. This can then be used to forecast how quickly the mutated cells will grow, which determines leukaemia risk. This study was the first of its kind, in attempting to build a predictor of age-related blood cancer risk due to the accumulation of mutations that occur in blood of elderly, healthy people.

Neighbourhood characteristics affect health in older age

Author: Gergő Baranyi et al.
Journal: *American Journal of Epidemiology*

Frailty is a condition that can make older people feel weak and reduce their ability to recover from illness and injury. Age UK estimates that between 25-50% of people aged over 85 live with frailty, so understanding factors which influence frailty is important. Gergő made use of unique data about where LBC1936 participants have lived across their lifecourse to conduct the first study exploring associations between neighbourhood-level factors across the life

course on frailty progression in older adults. Results suggest that people who have spent part of their life living in more socially deprived neighbourhoods are more likely to be frailer in old age. Gergő's study has been featured in the media on STV News, and in The Scotsman, Echo and Evening News.



DNA risk scores predict onset of 11 age-related diseases

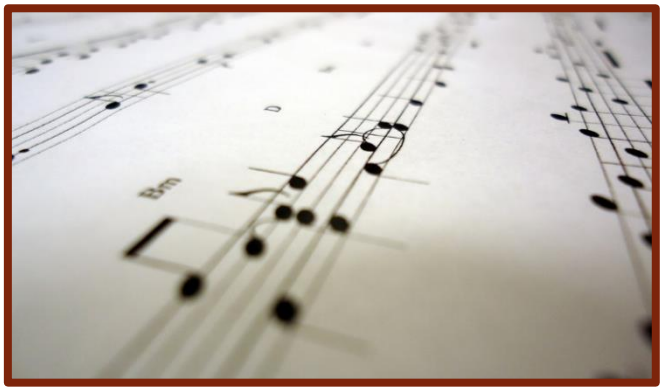
Author: Danni Gadd et al.
Journal: *eLife*

Although our genetic code does not change throughout our lives, our genes can be turned on and off as a result of epigenetics: addition or removal of chemical markers on the DNA. One common epigenetic marker measured in blood samples is known as DNA methylation, which can be linked to levels of proteins in our cells and health outcomes such as risk of developing chronic diseases. Danni explored relationships between DNA methylation and 953 different proteins, which are linked with age-related diseases, in blood samples from the LBCs and a German cohort study. She found 109 proteins for which DNA methylation patterns explained up to 58% of variation in protein levels. She also created 'EpiScores', disease risk scores based on DNA methylation. In a large cohort from the Generation Scotland study, her risk scores reliably predicted onset of 11 major age-related diseases including diabetes, stroke, depression, Alzheimer's dementia, arthritis and types of cancer over 14 years of follow up. DNA methylation and EpiScores for protein levels can therefore be a valuable resource for disease prediction.

Lifetime cognitive change & musical instrument experience

Author: Judy Okely et al.
Journal: *Psychological Science*

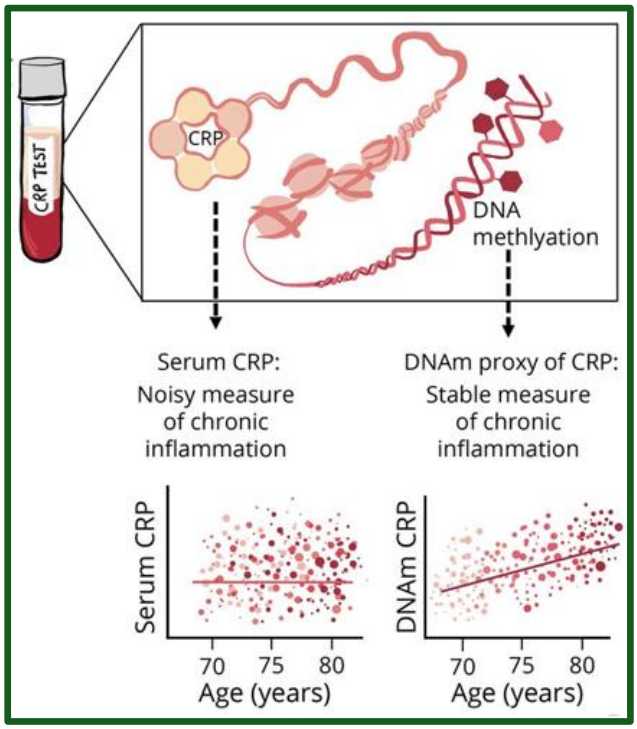
Dr Judy Okely and team tested whether greater experience of playing a musical instrument was associated with more positive cognitive change over almost 60 years. After controlling for the effects of childhood environment, years of education, adult social class, and disease history, greater experience of playing a musical instrument - even in childhood - was associated with more positive cognitive change between ages 11 and 70. This is one of the first studies to indicate that experience of playing a musical instrument is associated with a long-term cognitive advantage.



DNA markers of inflammation related to cognitive and brain measures

Author: Eleanor Conole et al.
Journal: *Neurology*

Low-level chronic inflammation is our body's way of responding to injury and disease, producing a steady but low level of inflammation throughout the body. This tends to increase with age, and is associated with brain ageing and cognitive decline. It is traditionally measured by examining the level of inflammatory proteins such as 'C-reactive protein' (CRP) in the blood, but this method can be unreliable because levels in the blood can change very rapidly.

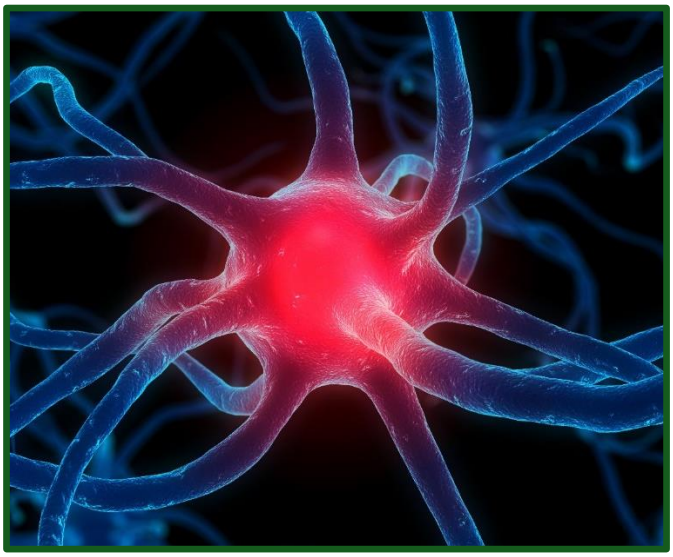


Eleanor showed that another measure of C-reactive protein, DNAm CRP, taken from DNA methylation (changes in the way the body uses DNA) from LBC blood samples, was consistently more strongly related to cognitive and brain imaging measures than traditional blood-based measures. DNAm CRP could be a promising way to more accurately track chronic inflammatory status. This paper was so impressive that it appeared in the scientific journal *Neurology*'s 'recommended' website section earlier in this year.

Synaptic resilience related to cognitive ability

Author: Declan King et al.
Journal: *Alzheimer's & Dementia*

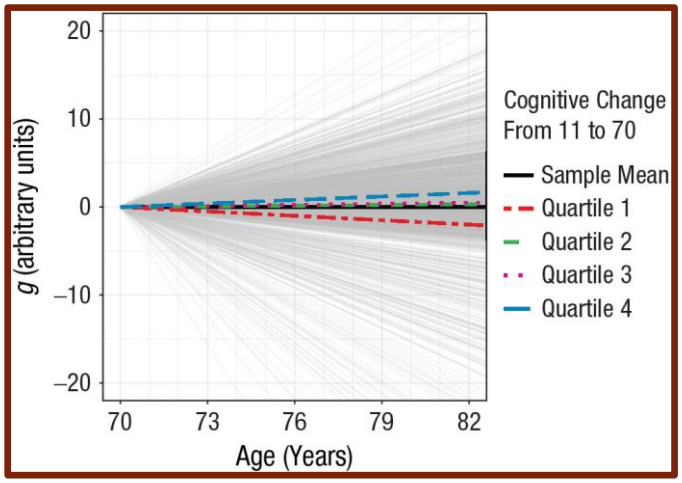
It remains unclear why age increases risk of Alzheimer's disease, and why some people experience age-related cognitive decline but without developing dementia. Declan examined how healthy ageing in the LBC1936 is affected by molecular changes in synapses, the junctions between neuron cells in the brain. He examined post-mortem brain tissue and induced pluripotent stem cells from some LBC1936 blood samples to create data for his 'healthy ageing' cohort, who he compared with two other data sets of individuals who died from Alzheimer's Disease, or who died in middle-age from non-neurological conditions. They found that synaptic pathology (unusual changes in synapses) increased, and expression of the genes in DNA which are involved in signalling in the synapses decreased, in those with Alzheimer's compared to the LBC's healthy agers. This study provides some early evidence to suggest that more efficient synaptic networks in the brain, and less build-up of proteins previously linked to the development of dementia, seem to contribute to resilience to cognitive decline even in people who do not have dementia.



Cognitive change age 11-70 predicts cognitive change during older age

Author: Federica Conte et al.
Journal: *Psychological Science*

Researchers have discovered some protective and risk factors for cognitive decline, but many studies focus on a limited age range, and how cognitive change happens is not well understood. Federica, who came all the way from Milan to visit us and work with the LBC data, modelled the rate of change in cognitive ability between childhood and older age. Those who experienced greater improvements in cognitive ability between age 11 and age 70 tended to experience less cognitive decline in later life between age 70 and age 82. This adds to evidence suggesting that some factors which influence cognitive change in later life could be operating much earlier in one's lifetime, before we reach older age.



Mediterranean diet not associated with longitudinal brain volume change

Author: Michelle Luciano et al.
Journal: *The Journal of Nutrition, Health & Aging*

Eating a Mediterranean diet, with high volumes of fruit, vegetables, legumes and cereals, and moderate consumption of fish, dairy products and wine, seems to have physical and mental health benefits. However, Michelle found no association between consuming a Mediterranean diet at age 70 and total brain volume change later between ages 73 and 79, after controlling for other health factors. Further investigation may be needed, but this suggests that previously found associations which linked diet and brain structural changes over a shorter time period (age 73-76) may not be long-lasting, or may become less important as ageing-related conditions account for greater variation in brain volume change.

Rare DNA variants associated with Processing speed

Author: Jan Bressler et al.
Journal: *Translational Psychiatry*

In previous studies, low scores on tests of processing speed, such as our 'reaction time' test, have been associated with mild cognitive impairment and dementia, and these scores could help identify those at risk of diseases like dementia. In twin studies, up to 67% of variation in tests of processing speed seems to be genetic. Using nine cohort studies including LBCs, Jan examined processing speed scores of 36,334 individuals. Scores were slightly but significantly associated with rare variants of one gene, 'RNF19A', in most cohorts. Previous studies have not been able to explore genetic associations in such detail; the LBCs' and other cohorts' detailed genetic data have allowed this topic to be explored for the first time.

LBCS ON THE BBC!

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 with dementia as more people begin to live longer. He asked the study to appear 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 Prof 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. Martin also interviewed Dr Judy Okely about her research on cognitive ability and musical experience in the LBC1936. Of course, we were keen to involve participants too: two LBC1936 participants, Alex Peden and Moira Hepburn, also kindly represented the LBC studies by taking part in some cognitive tests on camera, to show the sort of things we do at our clinic appointments.

The programme, which aired on November 1st, was excellent and included many positive messages about getting older. If you missed it, and you have access to the internet, you can watch it on the BBC iPlayer television app by searching for 'Who Lives in Scotland?', or find it on the BBC iPlayer website using the following link: www.bbc.co.uk/programmes/m001dtzz

LBC MUSIC RESEARCH RESONATES WITH THE MEDIA

And, speaking of Judy Okely: her recent article, which we summarised in the 'Scientific Highlights' section, found a small, but significant positive association between greater experience of playing a musical instrument and greater gains in cognitive ability between ages 11 and 70. The paper is one of the first studies to indicate that experience of playing a musical instrument is associated with a long-term cognitive advantage, and the media have – quite rightly – gotten very excited over these results. The distinguished British Psychological Society included a summary of the paper as their headline article in the September edition of their monthly research digest, and the paper has now had

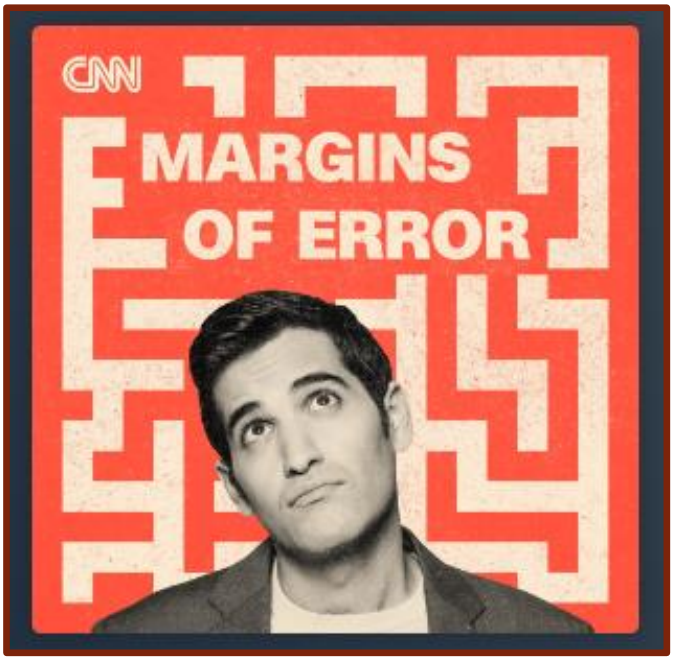
media coverage in The Guardian, The Times, The Independent, The Scotsman, The Daily Telegraph, Evening News, The Economist, The Herald, and The Irish Daily Mirror. This impressive media coverage shows that the public are fascinated by research showing factors which can positively impact the ageing process; research which simply would not be possible without LBC participants' dedication!

DR SIMON COX & PROF IAN DEARY PUBLISH 'BRAIN AGEING' OPINION PIECE

In February, Former and Current Directors of the Lothian Birth Cohorts, Professor Ian Deary and Dr Simon Cox, were asked in their capacities as world-class researchers in cognitive and brain ageing to write an Invited Opinion article for journal *Aging Brain.* In their article, "Brain and cognitive ageing: The present, and some predictions (about the future)", they discuss the lessons we have learned and what we still have to learn from neuroimaging research, including many questions we have answered – or are in the process of uncovering – with the LBC studies. Simon said, '*It was great fun to discuss how we might address the many remaining gaps in our knowledge, but we went about the task of addressing the future with heavy caveats, in the spirit of the well-known Danish parliamentary howler "It is hard to make predictions, especially about the future".'*

CNN PODCAST: GENETICS, VISION, AND COGNITIVE ABILITY

In the podcast 'Margins of Error' on CNN audio, presenter Harry Enten aims to break down data, translating the numbers into saying something about who humans are and what they believe. In a new episode in May, Harry discussed the topic of vision, and in particular, whether there is any truth in the stereotype that those who wear glasses are more intelligent than those who do not. LBC Co-investigator Dr Michelle Luciano appeared on the podcast to discuss findings from a genetic study including the LBCs, in a paper she co-wrote with team member Dr Gail Davies, which revealed a small but significant correlation between near-sightedness and cognitive ability at a genetic level. What a good reason to keep wearing your specs!



HOW TO STAY SHARP IN OLDER AGE: THE NEXT GENERATION

The team are always keen to spread the word about what we know from the LBC studies about how to keep our thinking skills sharp in older age. This year we've had many opportunities to teach children about the LBCs and what we know about healthy aging!

Susana at Whitehill Junior School

In February, team member Susana Muñoz Maniega attended a 'Meet the Scientist' event at Whitehill Junior School in Hitchin, Hertfordshire. Susana taught their P7 class - who were 11 years old, just as you were at the time of taking the SMS1947 test – all about the LBC studies, the cognitive tests we do, and how MRI brain scans work and what we learn from them. The children were absorbed hearing about the LBC studies, and just how important the SMS1947 test turned out to be.

Danielle teaches children about our research

Danielle Page also delivered her LBC Primary School workshops to nearly 100 P7 pupils, all also aged 11, from 3 different schools in March, May and November. The children tried out some of the cognitive tests we give to you at the clinic, learned how the study of thinking skills and memory relates to the brain, and found out what they can do even at age 11 to keep their thinking skills sharper as they get older.

Colin demonstrates our Augmented Reality brain visualisations with LBC participants

Finally, in November as part of the national Being Human Festival, the team visited Broughton High School to teach their S1-S2 students about the LBCs, cognitive testing, brain ageing, and mental health. Danielle Page and Beth Jones put the students through their paces with the same cognitive tests we give to you at the clinic. Colin Buchanan talked to them about your brain scans and let them see augmented reality visualisations of brain scans using our AR glasses, which some of you may remember trying at our 2019 reunion event. Arish Mudra Rakshasa also taught them about what we've learned about mental health and cognitive abilities.

Children being fascinated by the LBCs!

Your data isn't just helping us produce world-class research: it's helping us to teach children how to protect their thinking skills from age 11 to age 86 and beyond!

THE LBCS: KEY FOR EXAMINING IMPACT OF AIR POLLUTION

In recent years, there has been increasing interest in the impact of air quality on our health. LBC Co-investigator and study medic, and director of the Alzheimer Scotland Dementia Research Centre (ASDRC), Dr Tom Russ, has a particular interest in this topic. Since 2021 he has published two papers: the first, a review of environmental risk factors for dementia, concluded that air pollution may increase the risk of accelerated cognitive decline and dementia in older people. The second was the first paper to examine air pollution exposure across the lifespan: using your LBC lifetime address data, Tom found exposure to air pollution in early life and in utero was associated with greater decline in cognitive abilities from age 11 to 70.

These findings are fascinating, and they are already having great influence on policy: in July, the Committee on the Medical Effects of Air Pollutants, who advise the UK Government, published a report examining the possibility that exposure to outdoor air pollution could increase the risk of cognitive decline and dementia. They reviewed evidence of the link between pollution, cognitive ability and the brain, including both of Tom's papers. They also identified the LBC studies as one of only three existing groups with sufficient data to fully examine these potential long-term relationships. Another example of how important and influential your data can be!

THANK YOU FROM THE LBC TEAM

As a member of the LBC1936 cohort, your contributions are helping to further our knowledge and understanding of cognitive, brain, and general ageing. Thank you for your continued interest and involvement; we look forward to seeing you in 2022 and beyond.

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

LBC PUBLICATION HIGHLIGHTS 2022

- 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.*
- Barnes, A., et al. (2022) 'Topological relationships between perivascular spaces and progression of white matter hyperintensities: A pilot study in a sample of the Lothian Birth Cohort 1936'. *Frontiers in Neurology*.
- Brouwer, et al. (2022) 'Genetic variants associated with longitudinal changes in brain structure across the lifespan'. *Nature Neuroscience*.
- 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. (2022) 'Adherence to the MIND diet is associated with 12-year all-cause mortality in older adults'. *Public Health Nutrition*.
- Gadd, D. A., et al. (2022) 'Epigenetic scores for the circulating proteome as tools for disease prediction'. *ELIFE*.
- Iveson, M. H., et al. (2022) 'Intergenerational social mobility and health in later life: Diagonal reference models applied to the Lothian Birth Cohort 1936'. *The Journals of Gerontology*.
- Jochems, A. C. C., et al. (2022) 'Contribution of white matter hyperintensities to ventricular enlargement in older adults'. *NeuroImage*.
- King, D., et al. (2022) 'Synaptic resilience is associated with maintained cognition during ageing'. *Alzheimer's & Dementia*.
- Lee, M., et al. (2022) 'Pulmonary Function and Blood DNA Methylation: A Multi-Ancestry Epigenome-Wide Association Meta-Analysis'. *American Journal of Respiratory and Critical Care Medicine*.
- Luciano, M., et al. (2022) 'Mediterranean-Type Diet and Brain Structural Change from 73 to 79 Years in the Lothian Birth Cohort 1936'. *The Journal of Nutrition, Health & Aging*.
- Mccartney, D. L., et al. (2022) 'Blood-based epigenome-wide analyses of cognitive abilities'. *Genome Biology*.
- Mishra, A., et al. (2022) 'Gene-mapping study of extremes of cerebral small vessel disease reveals TRIM47 as a strong candidate'. *Brain.*
- 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*.
- Okely, J. A., et al. (2022) 'Experience of Playing a Musical Instrument and Lifetime Change in General Cognitive Ability: Evidence From the Lothian Birth Cohort 1936'. *Psychological Science*.
- Robertson, N. A., et al. (2022) 'Longitudinal dynamics of clonal hematopoiesis identifies gene-specific fitness effects'. *Nature Medicine*.
- Sliz, E., et al. (2022) 'Circulating Metabolome and White Matter Hyperintensities in Women and Men'. *Circulation*.
- 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*.