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THOUGHT LEADERS INVITED REVIEW

Lessons we learned from the Lothian Birth Cohorts of 1921 and 1936

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The authors are, respectively, the founding and current Directors of the Lothian Birth Cohorts of 1921 and 1936. In this invited and, admittedly, self-regarding and necessarily self-citing piece, we enumerate and explicate some things we learned from working with the cohorts and their data. Some of the lessons are scientific results, some are to do with scientific practice, and some are more general reflections. We hope the paper provides a useful summary of some of the main findings from these too-many-papers-to-read cohorts and an enjoyable account of our building a research team and a network of collaborators. The original aim of assembling the cohorts was to fashion a tool to discover why some people's thinking skills aged better than others'. That tool, we discovered, had many additional uses.

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Introduction

It is nice (we are British, after all) to have been asked by the editor to reflect on what we have learned from the Lothian Birth Cohorts (LBCs). We are happy to do so. One of the benefits this reflection affords is that it can collect a fraction of the large number of the LBCs' widely-dispersed scientific articles in one place and provide a shop window for them (see Publications from the Lothian Birth Cohorts); it can point the way to many more. There are some drawbacks, too, of this exercise. We shall necessarily focus on the LBCs' contributions to scientific questions whereas we know that other cohorts and samples often have made more and better contributions. We shall have to engage in the frowned-upon activity of self-citation. We try to avoid duplicating other synoptic pieces on the LBCs. These coy worries notwithstanding, here are some lessons from 25 years of work on the LBCs.

Not everyone knows what the LBCs are, so this enumerated paragraph is a crib sheet. Here are some key facts that should make the rest of the article more comprehensible.

1. On Monday June 1, 1932, the Scottish Council for Research in Education tested almost every child born in 1921 and attending schools in Scotland on the Moray House Test No. 12 (a test of intelligence that correlated about 0.8 with the Stanford Binet test in 1000 of the pupils in a validation exercise). The *N* was 87,498 and this represented about 94% of the whole Scottish population of that year of birth. This was the Scottish Mental Survey 1932 (SMS1932) (1, 2).
2. On Wednesday June 4, 1947, the Scottish Council for Research in Education tested almost every child born in 1936 and attending schools in Scotland on the Moray House Test No. 12. The *N* was 70,805 and this represented about 94% of the whole population of that year of birth. This was the Scottish Mental Survey 1947 (SMS1947) (2, 3).
3. Beginning in 1999, at a mean age of 79 years, we recruited 550 largely-healthy community-dwelling Scottish people born in 1921 to form the Lothian Birth Cohort 1921 (4). Most had taken part in the SMS1932; therefore, for most of them, Moray House Test scores were available from age 11. They provided demographic and health information; they were tested on cognitive functions, sensory functions, psychosocial factors, and fitness; they provided blood samples for a wide range of biomarkers, genetics, and other 'omics tests; they were linked to death records; a minority had some structural magnetic resonance imaging (MRI) of the brain. They were tested at ages 79, 82, 87, 90, and 92 years (5, 6).
4. Beginning in 2004, we recruited 1091 largely-healthy community-dwelling Scottish people born in 1936 to form the LBC1936 (7). Most had taken part in the SMS1947; therefore, for most of them, Moray House Test scores were available from age 11. They provided all the information that has been collected in the LBC1921, but in more detail and with many extras. For example, their cognitive test battery was much longer, they underwent longitudinal structural magnetic resonance brain imaging, they were linked to medical records as well as death records, they provided white blood cells for stem cell creation, and they consented to provide brain tissue after death. They were tested at ages 70, 73, 76, 79, 82, 86 and, as we write, they are being tested for what will comprise Wave 7 at mean age 88 (5, 6). Figure 1 illustrates the timeline of the LBC1936 study and some of the major types of data that have been collected.
5. We have written the protocols of the LBC1921 and LBC1936 baseline Waves (4, 7), and we have written cohort profiles (5) and cohort profile updates (6) that give details of the variables collected in these two studies. We recommend these articles to those who would like to request data to test their hypotheses on the LBCs.
6. We wrote a summary of what we had found out about healthy cognitive ageing in the LBC1921 and LBC1936 up to 2018 (8).
7. For those interested in the background to the LBCs, the Scottish Mental Surveys, and the smaller but slightly earlier-conducted Aberdeen Birth Cohorts of 1921 (ABC1921) and 1936 (ABC1936) there is the book, *A Lifetime of Intelligence* (2).
8. A key variable that is available in the LBC1921 and the LBC1936 was the retesting in old age of the Moray House Test No. 12. This is the intelligence test that they had taken at mean age 11 years, which was the age of transition from primary to secondary school (at the time, compulsory education continued until the age of 14).
9. Ian Deary founded and directed the LBCs from January 1999 to November 2020 when he retired (just briefly, to be rehired, a few months later, part-time to continue working on the LBCs). Simon Cox has Directed the LBCs since December 2020, having worked with the LBCs since 2009 (for his PhD where Ian Deary was one of his supervisors, then as Study Co-ordinator, then postdoctoral fellow, and then LBC Co-Investigator and leading his own funded work on the neuroimaging aspects of the study).
10. It was a fumbling set of events that led Lawrence Whalley (who died in 2024) and Ian Deary to discover that the SMSs had been conducted and that their data still existed (described in ref. 2). Professor

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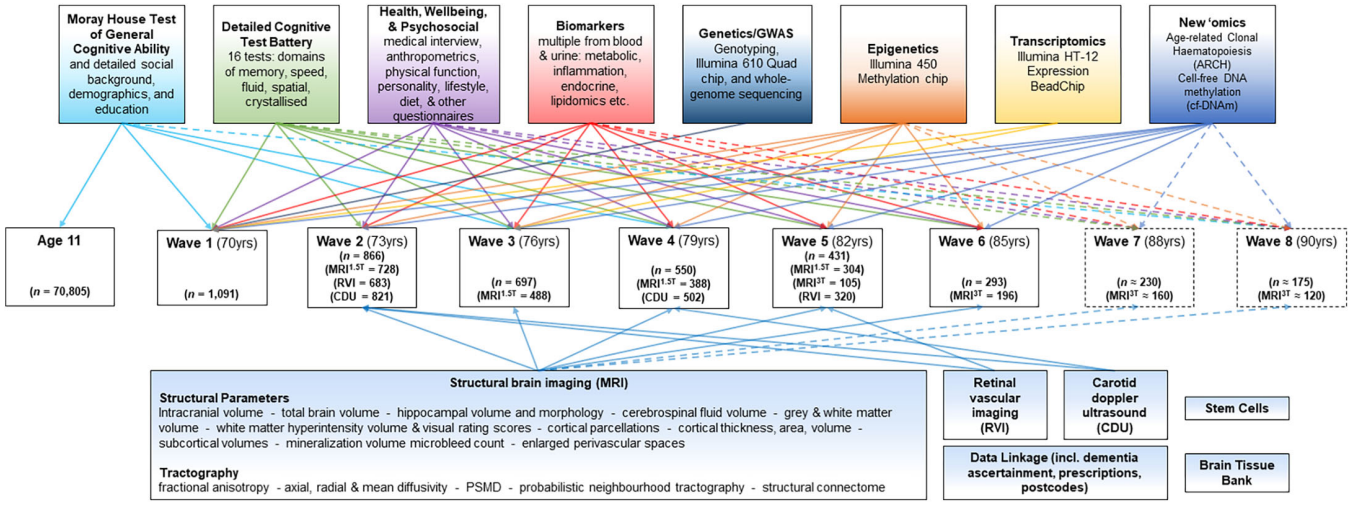

Figure 1. Data collected in the Lothian Birth Cohort 1936. The central row of white boxes denotes each instance of measurement, starting with all age 11 Scottish children who sat the Moray House Test Number 12, and proceeding to the "baseline" (Wave 1) and subsequent assessment visits of the LBC1936 participants. Solid arrows indicate data (top and bottom rows) collected at a given wave; dotted lines and boxes denote ongoing (Wave 7) and planned (Wave 8) data collection.

Whalley (a psychiatrist) led the ABC1921 and ABC1936, collaborating with Ian Deary and geriatric physician Professor John Starr (9). John Starr was the medical lead on the LBCs from 1999 until his death in 2018, after which Dr Tom Russ took up the role. Professor Joanna Wardlaw (a neuroradiologist) is the brain imaging lead on the LBC1936 (10).

Scientific Discovery Lessons

When people ask about the aims of the LBCs, we say something like, "we are trying to discover why some people's thinking skills and brains age better than others". However, the LBCs have proved to be valuable far beyond that remit. They often then ask, "what have you discovered?". After we provide an answer, sometimes it is met with undertakings to make lifestyle changes (e.g., stop smoking), but it is also not unusual to hear the follow-on question, "isn't that obvious?". See what you think...

Some of the Big Findings Appeared Early on

This is not a scientific discovery per se; rather, it is a meta comment. To articulate this, although it has a Pareto-like quality (and some regression-to-the-mean quality), we shall use the comparison of pop/rock bands. Most bands have many songs, only a few of which are large hits and often those hits appear early in their careers (have a look at numbers of plays on Spotify). With the Aberdeen Birth Cohorts (ABCs) and LBCs some of the relatively bigger discoveries happened early on as we picked some low-hanging fruits. Perhaps, with most cohort studies more generally, investigators will have, probably, only a few big hits and many worthy album tracks (have a look at numbers of citations on Google Scholar). Slightly to argue against that, is that longitudinal cohorts gain value from having more waves and, therefore, some larger findings can only appear after several waves of testing, not early on. In what follows we shall provide an as-pithy-as-we-can-manage statement of some of what we found, followed by a bit of explanation and context, and relevant references. There are many hundreds of peer-reviewed articles that analyze LBCs' data and we shall cite, in total, a small minority of them.

Higher Intelligence Test Scores at Age 11 are Related to a Better Chance of Survival to Older Age, and to Lower Risk of Death From Many Major Causes of Mortality

These—the associations between higher childhood (sometimes young adulthood) intelligence test scores and longer life and better health—have been widely replicated, including in very large studies (some having six or seven figure sample sizes). The discovery from the SMSs, that higher intelligence in childhood is associated with living longer (11, 12), properly began the field of cognitive epidemiology which aims to replicate, extend, and explain this set of findings (13). Figure 2 shows the results of linking the Moray House Test scores at age 11 from the Scottish Mental Survey 1947 to major causes of death several decades later. This new field took we psychometrically-oriented psychologists into the statistical analysis world and tools of epidemiologists. The association between childhood cognitive test scores and survival was analyzed mostly using Cox proportional hazard regression and the results expressed as hazard ratios. To give a guide to the size of the typical effects, a one-standard deviation advantage in Moray House Test score at age 11 was associated on average with about 20% to 25% lower chance of dying from most major causes of death up to the late 70s (12). Part of this work has been the picking-apart of the contributions (confounders?, mediators?) of education and social class (which are correlated with intelligence test scores and are themselves related to health and mortality inequalities), and the employing of molecular genetic techniques. We have reviewed this field and, briefly, it appears that childhood (parental) social class does not contribute much if at all to the intelligence-longevity/health association, but that the association might be mediated somewhat by a person's own adult social class (14). With regard to education (or, e.g., health literacy) this is hard to call, not least because intelligence and education and health literacy are quite strongly correlated (15).

About Half the Variance in Intelligence Test Scores in Older Age is the Same as That Found at Age 11

Not long after we discovered that the SMSs' data were extant, we knew that it would be valuable and unusual to be able to find out how strongly childhood intelligence test scores correlated with the same test taken in older age. This provides two useful pieces of information: the obverse is the stability of intelligence differences across most of the human life course (tested using the Pearson [usually] correlation between the test score at age 11 versus the score on the same test in older age); and the reverse of that coin is that it can tell us about the changes with respect to individual differences over that same period. For the former, we've published several papers that describe the correlation between the Moray House Test No. 12 at age 11 and older-age ages in the 60s, 70s, 80s, and 90s (4, 16–18). The broad result is that even the raw correlation from age 11 to the 70s is not far from 0.7 which, when squared, tells us that just under half of the variance in intelligence in older age was there at age 11. This is a lower-bound estimate of the long-term stability of intelligence differences. It is not corrected for measurement error or for the restriction of range in these samples compared with their background populations (which are known because of the comprehensiveness of the Scottish Mental Surveys) (18). For the latter (i.e., the remaining ~50% not explained by early life differences, some of which will be measurement error, of course), understanding what sorts of factors (be they genetic, health, behavioral,

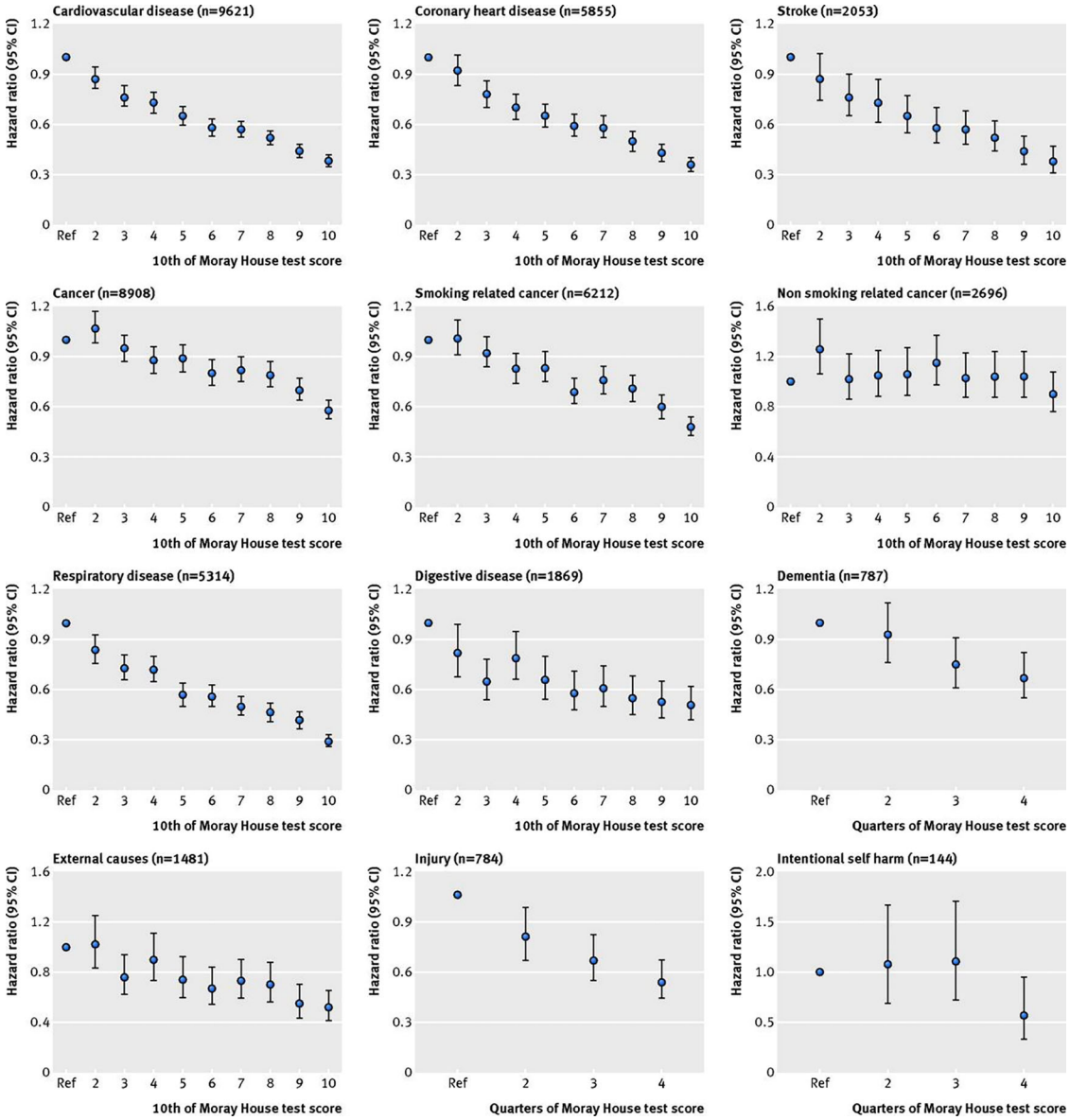

Figure 2. Association between Moray House Test No. 12 score at age 11 and major causes of death up to age 79 in the Scottish Mental Survey 1947. For visualization, the Moray House Test scores were divided into deciles or quarters. The points in the figures are age- and sex-adjusted hazard ratios and 95% confidence intervals; the lowest scoring group is set to 1.0. The analytic sample *N* was 67,765 of whom 25,979 had died. Mean time to follow up was 57 (SD = 18) years. This is Figure 2 from Calvin et al. (2017) in the British Medical Journal, 357, j2708; this article is an open access article distributed under the terms of the Creative Commons CC BY 4.0 license and the figure is reproduced here, with thanks, under that license.

social, etc., though some will be stochastic/random error) perturb people from their childhood ranking has been the basis of many of the earlier LBC discoveries. And it turns out that those who are perturbed less from their 11–70 score ranking are also those that tend—a bit—to also age less steeply into much older age (19). In Figure 3, we show the scattergrams of the Moray House Test No. 12 scores for the Lothian Birth Cohorts at age 11 and age 79. We have previously published a version of this scattergram for the LBC1921 but not LBC1936 and we have not published them together before. We note that, whereas age 79 was the second testing occasion for the LBC1921, it was the fourth testing occasion for the LBC1936 who also took the test at ages 70 and 76.

The Genetic Influences on Intelligence Differences are not All the Same in Childhood and Older Age

Most of the individual genetic contributions to intelligence differences are tiny (really tiny, like too tiny to work on). Don't do candidate gene studies (apart from *APOE*). So, three lessons there. The first lesson was based on an early finding with the LBC1921 in which we found that possession of the *APOE* e4 allele (assessed by testing for the two single-nucleotide polymorphisms [SNP] that determine *APOE* e4 status) was not associated with Moray House Test No. 12 score at age 11, but was associated significantly with the same test taken by the same people at age 79 (on average, those with the e4 allele scored lower) (20). The second lesson became obvious as we conducted genome-wide association studies (GWAS) which grew in sample sizes from four to five to six figures. In GWAS, one examines the association between the outcome (in this case the cognitive test scores) and hundreds of thousands of SNPs that capture genetic variation in humans (see Ref. 21) for a description of this and other genetic methods). The LBCs and ABCs formed the majority of the participants originally (22) and still contributed to the larger consortia studies (23, 24). One thing that did not change hugely as the studies grew in size was the estimated heritability of intelligence differences based on SNPs—it

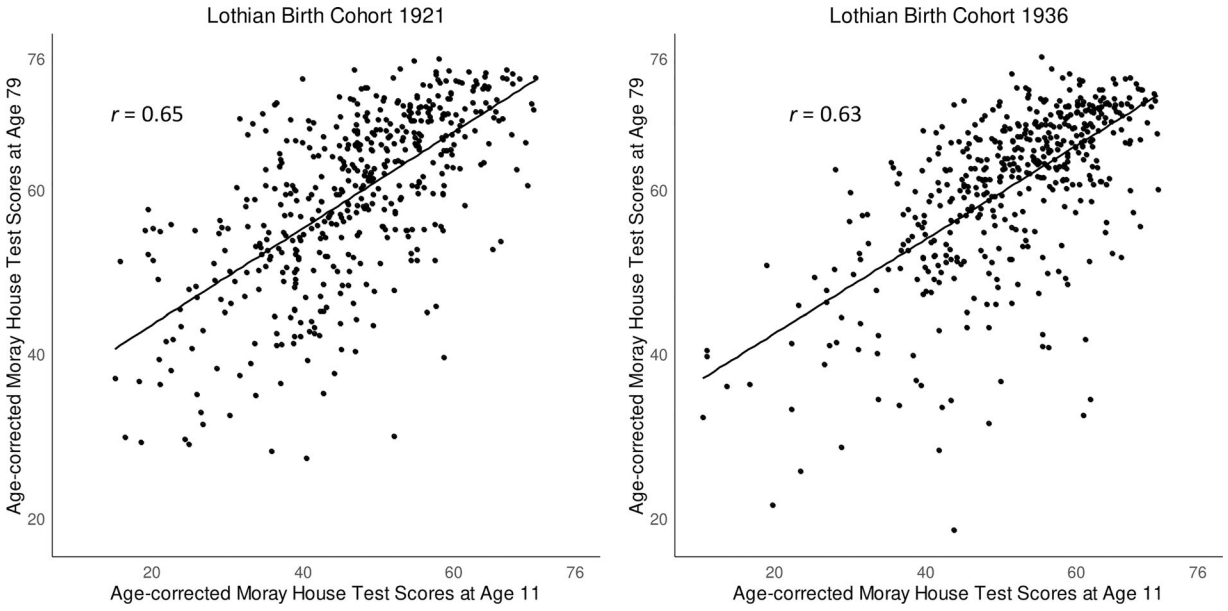

Figure 3. Stability of individual differences in intelligence from childhood to old age. Associations between Moray House Test Number 12 scores taken at age 11 and age 79 in the Lothian Birth Cohort of 1921 (left; $N = 483$) and Lothian Birth Cohort 1936 (right; $N = 468$). Pearson's r are displayed in the top left of both panels ($p < 2.2 \times 10^{-16}$). Scores have been corrected for age in days at testing. Outliers ±3.5SDs were removed from the pairwise correlations based on full available samples ($N = 3$ for LBC1921, $N = 7$ for LBC1936) for visualization purposes. Correlations with outliers included are: $r = 0.66$ (LBC1921, $N = 486$; $p < 2.2 \times 10^{-16}$) and $r = 0.61$ (LBC1936 $N = 475$; $p < 2.2 \times 10^{-16}$).

remained at about half, or a bit less, of that estimated from twin studies. That heritability, to date, is made up of at least hundreds of tiny individual associations between SNPs and intelligence test scores. We summarized this field, with consideration of what this means for understanding the biological mechanisms that found part of intelligence differences (21). The third lesson was learned from our early experience with the LBCs and ABCs and the work of others which concluded that, apart from variation in *APOE* (25, 26), associations between variation in candidate genes and intelligence test scores in modestly-sized studies have not replicated. With large errors around the point estimates, we estimated that genetic factors accounted for about two-thirds of the stability in intelligence from childhood to older age but about only a quarter of the changes in intelligence rankings across the same period of the life course (27).

Some of the Expected "Exposures" (Independent Variables) to Later-life Cognitive Ability Turn Out to be "Outcomes" (Dependent Variables) of Early-life Cognitive Ability (Reverse Causation or Confounding)

When we set up the LBCs we wanted to include as wide a range of potential contributors to people's differences in cognitive ageing as was feasible/tolerable. In testing the cognitive outcomes, we selected a broad battery of cognitive tests to cover the main domains of cognitive function; in assessing the exposures, we tried to be inclusive as was practicable and included genetic, health, fitness, sensory, biomarker, brain imaging, psychological, demographic, and social variables (6). We began to find that some of these latter, supposedly exposure/independent-variable factors, although they did associate with cognitive function in older age, also correlated with intelligence tested at age 11, many decades previously. Thus dissolved the sometimes-false separation we had made between our cognitive ageing and cognitive epidemiology investigations. Among the putative variables that were involved in our realizing this were, for example, C-reactive protein (28), physical fitness, Typical Intellectual Engagement, social and other activities (29), alcohol intake, tendency to type 2 diabetes (30) and allostatic load; there were others; some of these are listed and discussed by ref. 8. To spell this out, we found that children with a higher intelligence test score at age 11 tended to be fitter, healthier and more socially and intellectually engaged in older age, and to drink a wee bit (not a lot—not to excess) of alcohol; that is, sometimes, but not always, the association between the given factor and age-11 intelligence test could reduce the association between the factor and older-age intelligence to nonsignificance. Thus we discovered "reverse causation"/confounding by early-life intelligence test score. This does not necessarily rule out the causal nature of a given factor whose association with later life functioning is attenuated, since it could also be that people's differential exposures to cognitive-ageing-inducing factors can be predicted, at least in part, by earlier life factors. What it does do, though, is cast those factors which are not attenuated by age-11 intelligence into much sharper focus as factors of interest. The life-course timing of factors that might or might not influence people's differences in cognitive aging—including contributions made by the LBCs—is discussed by others also (31).

People Have Very Different Experiences of Brain and Cognitive Ageing

When analyzing the things that might explain differences in brain and cognitive ageing, one needs to have variability in those outcomes-of-interest. However, quite how much of a difference there is between people has been one of the striking findings of the work. The LBCs can offer a valuable window into this because all participants are the same age. The brain scans that were taken during the second wave of LBC1936 testing are a stark illustration of just how variable same-age people's brains are in terms of key features of biological ageing. Figure 4 shows a selection of 73-year-old LBC1936 brain MRIs (over 700 were brain-scanned at this age), showing atrophy (where the brain shrinks away from the intracranial vault and also the cerebrospinal fluid-filled ventricles at the center of the brain enlarge to replace space vacated by the diminishing cerebral tissue; Panel A) and white matter hyperintensities (ageing-related damage to the brain's connecting fibers; Panel B). They are both ordered from top-left (least affected) to bottom right (most affected). We and others have indicated that these and other important aspects of brain structure are important for cognitive ageing differences (see below). We have of course also shown this wide variability in the ageing experience elsewhere, with statistical figures and analyses for both brain and cognitive ageing, and for their subsequent changes into older age (which also show wide variability) (32, 33). Nevertheless, this figure remains one of the most engaging ways to communicate to others some of our central research aims; how can one arrive at older age with a brain that looks like those in the top left, and what can one do to avoid having one that looks like those toward the bottom right? And how can we maintain that for as long as possible as we

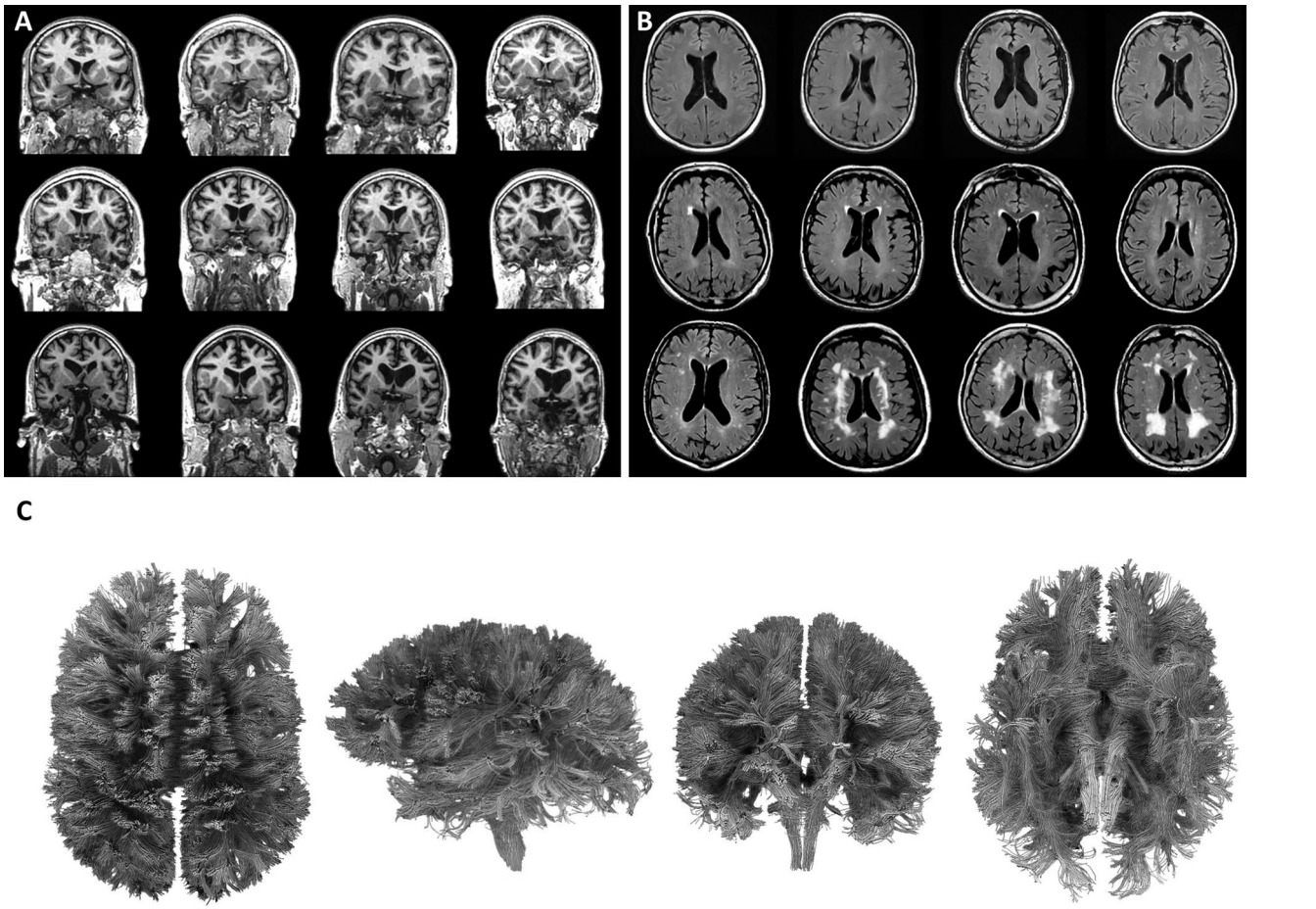

Figure 4. Brain structural (MRI) scans from a selection of individuals from the Lothian Birth Cohort 1936 taken during Wave 2 (when all participants were about 73 years old). **Panel A** shows global atrophy (brain volumetric shrinkage) ordered from least (top left) to most (bottom right). **Panel B** shows total white matter hyperintensity volume (increasing from top left to bottom right). Panels A and B are reproduced from Cox and Deary (2022) in Brain Aging, 2, 100032 (74); this article is an open access article distributed under the terms of the Creative Commons CC BY 4.0 license and the figure is reproduced here, with thanks, under that license. **Panel C** shows white matter pathways of a middle-aged male adult, identified using diffusion MRI. Views from left to right: superior, lateral, anterior, inferior.

continue to age? It also offers a ray of hope to those of us on the journey to our 70s (where IJD has just arrived) that adverse brain and cognitive ageing outcomes are not an inevitability.

Brain Size Really is (Modestly) Related to Intelligence. Whether More Intelligent People Tend to Have a Larger Brain was a Debated Issue Over Many Years

The nadir of respectability for this question might have been with Stephen J. Gould's book *The Mismeasure of Man*. The arrival of MRI to assess brain size settled the issue. Early meta-analyses, an LBC1936 study that was the largest study at the time it was published (34), and data from the UK Biobank study (35) agree that the association (correlation) between general cognitive ability and total brain volume as assessed in MRI is about 0.27. We caution that, in older-age samples such as the LBC1936 and UK Biobank, there might be sources of variation in total brain volume that are associated with intelligence test scores that are not present or as marked in younger-age samples. Therefore, it is important to study the association at different ages. Why does one do this work?: because it's the brain that thinks and we want to know how variations in its biological parameters associate with thinking skills through the life course. We recognize (see following sections) the importance in understanding what it is about a larger brain that makes, on average, for more efficient thinking. But, of course, there is much more to thinking skills than just having a large brain, including other brain variables (34, 35), and we cover some of that in the following section.

Brain White Matter Matters for Intelligence

As we just said, there is much more to thinking skills than just having a large brain. Around the time that the LBC1936 began, there was increasing realization of, and interest in, measurements of the brain's white matter and their importance for studying ageing. Our team's decision to measure participants' white matter microstructure using new diffusion MRI (see Figure 4, Panel C) was in response to this, and our intention to address this was writ large in our application to the charity Age UK for funding as "The Disconnected Mind project" (10). With the LBCs' brain imaging data, we discovered that the health of the brain's connections—the white matter—in the main brain tracts were all positively correlated, that is, healthy brain white matter in one tract was strongly related to having healthy white matter elsewhere in the brain (36). We subsequently also replicated this important finding in other healthy adult samples with a wider age range such as UK Biobank (37), and also found it in neonates and among psychiatric patients with schizophrenia (38, 39). Moreover, having computed a general component of this white matter health (using principal components analysis), we found that people's differences in brain white matter health were modestly associated with cognitive functioning (40). Thereafter, we found that these two variables change together in a synchronized fashion over time: on average, those with steeper ageing of their brain white matter pathways are those whose general cognitive functioning declines more steeply (41). This is another result that has been replicated elsewhere. Moreover, the so-called white matter lesions

that accumulate in some people more than others as they age are also related to intelligence differences and...

Brain Grey Matter Matters for Intelligence, Too (and Carefully Putting Many Brain Imaging Measures Together is Advantageous)

There are other brain variables—including grey matter parameters for the cortex and subcortex, and aspects of brain vascular health—to consider with respect to intelligence/cognitive ageing associations (34). MRI-derived variables don't stand still; we have expanded these to include detailed properties of the cortex, brain connectomics, "brain age," and other aspects of the health of the brain's white matter (33, 42–44). One lesson from this accumulation of brain imaging–derived variables is that some are strongly correlated with other such variables and that one needs to ascertain the independence of brain imaging variables from each other when firing them at intelligence differences. This avoids old-wine-in-new-bottles scenarios, but has also allowed us to: i) identify more precisely how far everyone experiences the same aspects of brain ageing; and ii) map the extent to which information gleaned from these many aspects of brain grey and white matter are all uniquely relevant for differences in cognitive ageing. We have learned that they often account for some small unique proportion of cognitive differences in older age. That is, whereas some classes of brain features are partly overlapping, having lots of information about different facets, regions, and tissues helps us to improve our understanding of differences in cognitive ageing (44, 45).

The generosity of the LBC1936 participants in providing their brain tissue after they die (more about this important and striking legacy in the sections below) has also enabled us to look deeper still into the hallmarks of better and poorer cognitive and brain ageing, identifying features like synaptic resilience and neurogranin as important aspects (46, 47). We are also using new methods to put LBC data together with large-scale postmortem data from many other sources to learn more about the regions of the brain that are most important for cognitive and cognitive ageing differences, such as gene expression patterns across the cerebral cortex (45). We are optimistic about the opportunities that these approaches promise, and we gratefully recognize that they can't happen without the sad aggregation of munificent brain donations by members of the LBC1936.

Intelligence is Far From All That Matters (at Any and Every Age as a Human)

It might be possible—given the statement of LBCs' aims given above—to imagine the LBCs as having, as outcome (dependent variable), a bullseye labelled cognitive functioning and, as exposures (independent variables), hundreds of arrows (genetic, health, lifestyle, biomarker, psychosocial, etc.) fired towards it. That would be wrong. From the beginning of the LBCs, the noncognitive variables we included sometimes became outcomes additional to the cognitive ones. We became interested in health, fitness, personality, mood, life satisfaction, social position, social engagement etc. as part of healthy ageing and studied the associations of these outcomes too (48–50).

The Age of People's DNA (by Comparison with Their Chronological Age) Predicts (to a Wee Extent) How Long People Will Live

This provides a useful lesson regarding the LBCs' expansion with respect to both exposures and outcomes. By this stage, we had already genome-wide scanned the LBCs' DNA samples for SNPs. But one's DNA nucleotide sequence is not the whole story with respect to how the DNA works (i.e., eventually leads to protein production). Along DNA strands there are, attached, methyl (CH3) groups which have effects on gene expression; these are one form of epigenetic (in this case DNA methylation: DNAm) marks. People show differences in these marks which are, in part, due to genetic differences ((51)) and, in part, to environmental causes (e.g., smoking (52)). We undertook methylome-wide scanning in the LBCs. We thought that individual differences in DNA methylation might be informative about cognitive differences and age-related cognitive changes, which they were to an extent (53). Methylation marks on DNA change with age, and we were aware of the concept of epigenetic age, that is, that some people's DNA had methylation patterns that looked older or younger than is typical for their chronological age. We found that younger methylation age at baseline (age 70 for the LBC1936 and age 79 for the LBC1921) was associated with how long people lived. This replicated in other samples. This was outside of our field but is one of our citation hits (51). Pursuant to some of the Scientific Strategy points listed below, DNAm research has been a successful and interesting collaboration. It emerged that how methylated your genes are correlated quite strongly (according to Funder and Ozer (54) rather than Cohen [see the subsection directly below]) with smoking, BMI, and inflammation, to name a few, and that these in turn are also related to brain and cognitive differences (53, 55–57).

Get Ready to Enjoy Small Effect Sizes, Moving From the Psychologists' Crud (Meehl, 1990 (58)) Value of About 0.3 Down to the Epidemiologists' 0.1 and Below

We and others saw and discovered in the LBCs for ourselves early on that effect sizes in cognitive ageing are typically small; a fitness variable, or possession of the *APOE* e4 allele, or smoking or just pick your favorite candidate variable that contributes to individual differences in cognitive ageing and about the best you can expect from any of these is that, net of cognitive capability in youth, they will, if you are lucky, contribute about 1% of the variance to cognitive capability in older age. We summarized this reality in our paper entitled *Marginal gains not magic bullet* (8). Mind you, and this seems too obvious to have to write (but we see papers and statements that refute that), it is important to keep in mind that, in cognitive ageing, what one is seeking is factors that are associated with *change* in cognitive capability, whether that change is from youth to middle to older age, or just change within older age itself when more decline takes place. To underline even more, an association between a putative "cognitive ageing" factor and a cognitive test score assessed on one occasion—whether it is cross-sectional or whether the putative predictor was assessed some time previously—is not informative about cognitive ageing. There is less variance in cognitive change than there is in cognitive status, and cognitive change is noisier, and such changes are accordingly harder to account for with predictors. Here's an example. In a 12-cohorts consortium that included LBC1936, there was a significant cross-sectional association between telomere length and various cognitive test scores (59). However, in a study that included only the LBC1936, there was no association between change in telomere length and change in cognitive test scores (or with change in physical abilities) across three waves of testing at ages 70, 73, and 76 (60). It is also worth noting that measured change is also rarer (since it is harder and more costly to measure/fund), which also detracts from the relative power of longitudinal studies on within-person differences as compared to cross-sectional studies of between-person differences (as illustrated by the 12:1 ratio in the telomere example above).

Beyond genetics—the given—what can an individual do if they want to age well, including cognitively?: play the numbers; maybe by getting oneself on the right side of the many (many of which are not confirmed) possible cognitive ageing variables one might be leaning in the right direction toward healthier ageing. Some have explained that small associations, though they can mean a lot for large populations (e.g., blood pressure control for the avoidance of stroke) are not practically informative—when considered in isolation—for individuals (61); however, we would argue again that staying on the correct/sunny side of the many small putative effects is the best choice for improving one's healthy cognitive and brain ageing (and general health) odds. With regard to the points we made in this section, and elsewhere, Walhovd et al. (31)—sometimes citing LBCs' results—made a strong case for, "sobriety regarding the timing and quantity" of influences on brain and cognitive ageing; we agree—we have tried to stay sober too, and we encourage others to do so.

Multivariate Analyses of Cognitive Ageing are More Bracing Than Univariate Analyses

Yes, it gets worse. Just as we discussed for the variety of brain imaging variables (you have to ask what each brain measure is telling you about cognitive differences that is unique), one has to ask the same about the other lifestyle, health, genetic, and other candidate predictors of cognitive ageing; that is, do they survive when entered together? There are few reliable associations with cognitive changes (usually declines, on average) in older age. And their effect sizes are small. It is not unusual for research reports to include (in addition to some sensible, basic covariates)

a single predictor of cognitive ageing. Indeed, we have had experiences of finding such reports easier to publish than when we have included multiple predictors/exposures. But life is not like that; we don't experience influences on our ageing in isolation from each other. We have conducted, with the LBC1936's longitudinal data, two studies in which we threw in a couple of handfuls of popular (from the scientific literature) determinants of cognitive ageing (32, 62). First, we looked at them as predictors of cognitive change one at a time. Then, we popped them together in a multivariate analysis. What happened?: positive findings fell like snow off a dyke (as we say in Scotland about such ephemera) as most of the significant univariate findings left possession of *APOE* e4 and the occasional other variable looking rather lonely in their continued significance. That is not to say that the unique contributions of those many factors mightn't be additively important (we examine this in this paper—(62)), but that their unique effects are likely even smaller; accurately quantifying how much smaller will require even bigger samples and consortia effort (to which we are contributing) with comparably deep phenotyping.

You Will Bet on Some Duds, But Null(-ish) Results are Valuable Too

With the LBCs we have tried to scan the horizon for possible contributors to cognitive ageing differences from many fields of study. Among these, we have kept an eye on biomarkers of ageing because that seemed like a likely source of tractable contributors. Looking back, one could say that earlier work was conducted in the time of candidate biomarkers and that we are now in a time when multi'omics platforms provide the capability to examine hundreds and even thousands of proteins/peptides, lipids, glycans, other metabolites etc. And these will be used in hypothesis-free(ish) studies and will probably deliver some replicable and probably small effects. But the point here is that we sought expert collaborators in likely biological variables related to cognitive ageing, found the resources to assess them and then sometimes found not very much when it came to looking at the results. This applies to, for example, retinal vessel topography (63), and see telomere length, above. It should quickly be said, by way of being positive, that these variables proved useful in other studies with other variables and that null results—knowing what is probably not associated with differences in cognitive ageing—provide knowledge too. One should not have an emotional reaction to a scientific result, but we confess to mild pleasure at finding a null association between childhood intelligence and life satisfaction in old age (64).

It Helps to Have a "theory" but Theory Does not Always Help Scientific Progress in This Field

We have put theory, there, in sneer quotes for the reasons that one of us has already written at length regarding the assessment of the quality of theories in the psychology of cognitive capability and most of that critique applies here (65). This lesson was learned from some referees and editors who have from time to time enjoyed our manuscripts but have wanted for some "more theory." And sometimes a nonharmful sprinkling of that condiment will suffice; we do not wish to appear cynical, but it helps to have a theory to be published, although theories in our field are often skyhooks rather than cranes (66). Some of the so-called theories that circulate in the field of cognitive ageing include brain/cognitive reserve (67, 68), brain maintenance (where others have similar reservations to ours about whether these two aforementioned "theories" constitute explanations or not (69)), common cause (70), and processing speed (71). The latter two are circumscriptions of interesting empirical regularities and the first two vary between a useful trellis on which to hang cognitive ageing studies to a diversionary soup stone (72). The one suggestion from our team that others have taken to be a theoretical articulation was the notion of "system integrity" which was posited in our first cognitive epidemiology study using data from the SMS1932 (11). We took the opportunity thereafter to clarify what it might mean and might not, and what its weaknesses and predictions were. If it deserves a name it is probably hypothesis rather than theory (73); is it a trellis or a soup stone?—neither perhaps, being more like a sticky note to remind us to explore this possibility (both theoretically and empirically) a bit more. In the field of cognitive and brain ageing we would prefer a very-large-N dataset with well-measured, relevant variables rather than an apparently "well-aimed" so-called "theory" (cf. GWAS versus candidate gene studies). We trust that this short mention of theory is not too glib, and we refer the interested reader to our longer discussions of theory (8, 65, 74, 75) and to a handbook that has a section on "models of cognitive aging" (76).

Irrespective of the Large Amount of Data you do Have, People Will (Rightly) Ask About the Data you don't Have

Running a longitudinal study of older adults inevitably results in the sad truth of dropout and missing data. Since the baseline of both LBC studies, attrition is typically about 20% per every 3-year cycle between waves of assessment. About half of the attrition is due to mortality, with the remainder being—anecdotally—a mixture of people not wishing to come back because they have "done enough," because of the development of illnesses, or being unavailable due to caring duties for grandchildren or—increasingly—for a spouse/significant other. Understanding how and why participants "drop out" of the study is important. It has important statistical implications for our core aim of characterizing cognitive and brain ageing, and asking what correlates with differences in those trajectories. We know that, on average, people who drop out are likely doing less well in terms of their brain and cognitive ageing, and general health, than those who keep coming back ("completers"; e.g., ref. 62). We also, therefore, know that, when we plot the average changes in just completers, we mostly underestimate the amount of cognitive decline in our sample (e.g., ref. 77). To ensure that we don't bias our estimates against the least healthy participants (who are just as important and informative), we will often use full information maximum likelihood (FIML) to include all available data to estimate those declines. However, reviewers often ask whether we are doing the correct thing here, since FIML assumes that the patterns of missingness are either random or mostly accounted for by variables included in our models. Whereas we are unable to account completely for the patterns of dropout we observe (e.g., refs. 32, 78), we have previously indicated that the further reduction in variance/greater range restriction in an already self-selecting sample would likely yield a slight underestimation of effect sizes (e.g., ref. 79) as well as substantially lower statistical power.

Scientific Strategy Lessons

Some of the lessons that we learned from the LBCs pertain more to how to go about the process of scientific enquiry rather than results from analyzing the data.

"Maximum Strategic Intransigence, Maximal Tactical Flexibility" (with Thanks to S. Reicher)

Our original stated aim was to investigate nonpathological cognitive ageing. We've stuck to that. Notwithstanding that continued focus, it soon became clear that we had useful data with regard to other aspects of healthy ageing and we investigated those—though never as a mainstream of the work. Also, as the participants grew older, some of them developed dementia, and we began to ascertain that and to use the information sometimes as an exclusion criterion and sometimes as an outcome (80).

Sometimes One Finds Something That is Too Good not to Develop

Indeed, that's what happened when we discovered that the SMSs' data were extant. Both Lawrence Whalley and Ian Deary were busy doing research but the opportunities seemed too important not to develop, that is, the possibility to study lifetime cognitive ageing with a childhood baseline cognitive test, and the chance to conduct linkage studies and find out whether childhood cognitive ability was related to survival (and, if so, why). Change of strategy? And the good luck of finding the SMSs' data was followed by the discovery of other data and the decisions about whether time spent in pursuing those was worthwhile. For example, we discovered birth records (including birth weight) of some of the people born in Edinburgh in 1921 (81). And we found out that some of the SMS1947 participants had had more information collected from them at age 11 and some into their 20s. We followed up both of these with add-on studies of, for example, cognitive ageing, cognitive epidemiology, personality, and life-long wellbeing (82–85). And we also found out that the Scottish "Midspan" studies had had many people born in 1921 and we obtained permission to link them to the Scottish Mental Survey 1932. This resulted in several contributions to our cognitive epidemiology work (86–90) and to our work on social mobility (91).

Only Set Up a Cohort if it has Something That it Can do That Others Cannot

Leading a cohort takes over one's life. The LBCs never had guaranteed funding beyond a 3- or 5-year grant-funding period. Yet, they have been funded continuously since January 1999. This means that the Director and co-investigators go home each evening with the responsibility to retain the cohort and the research team. Therefore, especially with the ease of accessing and analyzing secondary data from existing cohorts (with UK Biobank providing a current apogee for some investigations), one must ask why one is taking the trouble to set up a cohort, which will then put other people to the trouble of taking part. The why is that the cohort should be able to address an important set of scientific questions in a way that is valuable, that is, by being the only sample that can address the questions or at least by adding usefully to what can already be done in other samples. When we began the ABCs and LBCs, we knew of no other cohorts that could adjust for such a well-validated cognitive test in youth. About the best we were aware of was the cognitive surrogates employed in the Nun Study, which we found impressive.

Make the Cohort a Hub That Concentrates the Team's Scientific Expertise and Then Attach High-quality Spokes to Enhance the Cohort's Scope

The LBCs began with four people involved in the hub that designed, ran, and analyzed the LBC1921 study: Ian Deary (trained in medicine and psychiatry and a PhD in differential psychology), John Starr (geriatric physician), Martha Whiteman (PhD in psychology), and Alison Pattie (nurse and research assistant). Thus, the hub had expertise in cognitive testing, multivariate statistics (including structural equation modelling), other aspects of psychological differences, gerontology, and geriatrics. With time, the hub/core team enlarged—especially with the beginning of the LBC1936, at which time we added full-time individuals to look after the growing databases. Even early on though, we realized that we needed additional expertise, some of whom came from our Department of Psychology, some of whom were also from our University of Edinburgh, and some of whom were from other UK and overseas universities. Let's call these experts and their teams spokes to our hubs. (We shall see below that some spokes become part of the hub [yes, there, the metaphor breaks down a bit]). What spoke expertise did we add?: we brought in experts in molecular genetics, statistical genetics, brain imaging, ophthalmology, biomarkers, medical database linkage, telomere biology, neuropsychology, epidemiology, education, environmental geography, music, qualitative methods, physical activity, stem cell biology, postmortem pathology, molecular neuroscience, psychiatry, hematology, epigenetics, immunology, transcriptomics, lipidomics, proteomics… There are probably more and more will come, and we apologize to any whom we have forgotten to list. Oh, and we've tended to work with very good experts. It would be invidious to pick out a few, so the reader can spot them as co-authors on our articles. Finally, working with superb experts also means that some of that know-how in a new field rubs off on you—not a huge amount and we would never claim to be experts in our non-native fields—but enough that you are in a better position to spot new opportunities to occasionally contribute to new discoveries or perspectives in unexpected fields.

Consider Whether to Add an Expertise to the Core Team or to Outsource it to a Spoke

Looking at the LBCs' hub/core team as it is now, that is, those located in the same place in Psychology in 7 George Square at the University of Edinburgh, there are in-house geneticists and brain-imaging experts, for example, who would previously have been in spokes. Earlier on, a sole geneticist or brain imager would not have had an environment that would have nourished their expertise. Therefore, it was as we were able to attract more of such experts that we had a community that could help each other. Now, with >1 numbers of psychologists, brain imagers, geneticists (all of whom are also expert in multivariate analyses) in one place they can not only help their colleagues in the same field, they can conduct cross-disciplinary studies easily because they are colocated.

For Each Proposed Additional Variable, Ask Whether it is of Use in This Cohort

Generally, when we have decided to conduct an analysis or measure a variable in the LBCs we have asked ourselves these related questions: does the LBC make a valuable contribution to this literature?; and could this be done in any cohort or sample? In summary, we have tried to play to the strengths of the LBCs' information which means, a lot of the time, having childhood intelligence test scores in older people. However, as the LBCs' databases grow, other valuable opportunities emerge. For example, having longitudinal data on clonal hematopoiesis of indeterminate potential (92, 93) and DNA methylation, their linkage with existing LBC data was highly valuable and hard to replicate elsewhere. So, the more data that have been collected, the more opportunities there are for possibly-unique/at-least-valuable collection of still more (to some extent, and within what is practical and is sometimes driven by opportunity and/or serendipity) because there are so many data already collected to which they might be tested for association. Also worth saying is that the value in collecting new data during the later waves as sample sizes sadly dwindle also means that power is affected and there is less reason to add new data; to counterbalance that, there are lots of innovative ways in which one can continue to collect new data on the full sample by capitalizing on emerging methods and possibilities—for example, retrospective geocoding based on linked lifetime addresses in the full sample (e.g., ref. 94), medical record data linkage, analyzing blood samples stored from prior waves, and so forth. Thus, people become more rather than less interesting as they grow older.

Cover the Bases When Testing the Cohort

From our interest in contributors to nonpathological cognitive ageing, we knew those variables could come from a wide range of domains. Therefore, we had to gather a wide range of data. Of course, we looked around at other cohorts for guidance. We needed data from cognitive functioning, other aspects of psychology, social and demographic factors, lifestyle and health behaviors, demographics, biological and genetic factors, and medical information and fitness. These can be seen in our LBCs' study protocols and profile articles (4–7). One is inhibited from collecting what seems like too much, wishing not to fatigue the participants or discouraging them from returning. Our lesson was than older people can and will do more than you think. Initially, we were cautious with LBC1921 and more detailed and wide-ranging with the LBC1936 (who started with us when they were younger).

Even if They are not Perfect, Retain the Same Variables in the Next Wave of Testing

In psychology and in medicine and beyond, the ways of measuring things do not stay still. One chooses, say, cognitive and personality and mood and fitness tests (to pluck out a few from many types of data) for the baseline study. Sometimes, a newer and seemingly better test will appear after one has collected the data. What should one do? Hold your nerve: unless there is a big problem with the original test, collect the same thing again. There is value in longitudinal data with the same measures. Of course, if we have had time, we have included the better measure and the older measure at the next wave, but we have tended not to drop variables and we have been glad of that when it comes to longitudinal analyses.

If You Have Only 2 Min to Test a Person in a Cognitive Ageing Study, do the Wechsler Digit Symbol Test (Other, Equivalent Tests are Available)

Scores on this test age badly, that is, it declines more steeply than other cognitive tests and domains, and so it provides what one is looking for in a cognitive ageing study. Individual differences in the ageing of its cognitive domain—processing speed—correlate strongly with the individual differences in the ageing of other cognitive domains such as reasoning and memory.

Add the National Adult Reading Test if you have another two minutes (other, equivalent tests are available). This test will give you a decent estimate of the persons' peak prior cognitive ability, even when they have mild cognitive impairment or early dementia (82, 95). To an extent, it will

make up for not having the early life cognitive test scores that the ABCs and LBCs have, though it took these studies to establish that.

Add grip strength if you have another 2 min. It is a handy (pun intended) index of fitness and, in large samples, is predictive or mortality (tighter grippers live longer) (96, 97).

Do What You Can with Sufficient Power on Your Own and Join a Bigger Gang When You Can't

We have done under-powered studies. Many people have. We try not to. We set up the LBC1936, especially, with $N > 1000$, to be powerful in phenotypic studies looking at determinants of cognitive ageing. With over 700 of the LBC1936 having brain imaging data, it was one of the larger single-cohort studies of cognitive ageing with such data at the time. For *APOE* genetic studies, it was adequate in power. However, as soon as we began doing GWAS, with one exception (see below) we knew we had too little power to do anything that would be robust and so we collaborated. First, we had a UK-based gang that included us, the ABCs and the Manchester-Newcastle studies (22). It soon became clear that that was too small and we joined the CHARGE Neurology consortium, which had a cognitive group. That took the Ns to five and then six figures and only then did it seem that replicable results were appearing (24). Another example is the debate about replicable brain-behavior associations requiring thousands of samples (98). We also joined ENIGMA and other consortia because we recognize a similar situation in the brain imaging domain, though of course there remain things that can be done in LBC that aren't easy to find appropriate datasets for replication. By adopting multicohort approaches in the brain-imaging analyses, we lead we have shown that, actually, the LBC1936 solo results don't stack up too badly (45).

Having a Cohort That is Successful at Some Things Makes One all the More Appreciative of Other Cohorts That Can do Some Things Better

There are lots of studies out there with their different strengths. In the field of cognitive ageing, where we could pick out many good studies, we have a strong "we're not worthy" response to the ROSMAP studies which have an astonishing range of varied and good variables, a wonderful retention rate, and a terrific sign-up rate for postmortem donation. We have a similar response to UK Biobank, which is why we have spent so much time analyzing their data on topics relevant to the LBCs. The vision to collect such a large *N* (500,000)—with a very bold aim to collect with brain imaging data from 100,000 of them—means that the UK Biobank data is used world-wide.

Feel Free to Moonlight with Other Cohorts to Test Hypotheses That You Care About

Bearing in mind that we are interested in variation in brain and cognitive variables and their ageing, we have felt the need to be unfaithful to the LBCs when we can answer questions more powerfully elsewhere. The list is too long to name them all, but we have analyzed data and published results from UK Biobank, Generation Scotland, NLSY1979, The three British birth cohorts (1946, 1958, 1970), the West of Scotland Twenty-07 Study, and others.

Your Sample Can be a Control Sample for the Illnesses They Don't Have

Members of the Lothian Birth Cohort have been proud to appear as healthy controls in various medical studies. To pick out just two examples, they have been controls in genetic studies of colorectal cancer (99) and motor neuron disease (100).

You Will Regret the Things You Did Not Test

One can't go back and test at baseline again. One has to live with the decisions that were made. The LBC1936 will never have baseline brain imaging data at age 70, though they do have those data at every wave after that. So, think carefully about that initial testing wave. Related to that, you will bemoan, often, what the cohort does not have and perhaps envy other cohorts for having those data. For example, there are no contemporaneously-collected data in the LBCs between age 11 and older age (though we managed to find—via linkage to the Scottish Midspan study—data from middle age in some participants of the Scottish Mental Survey 1922 in our cognitive epidemiology work (86–90, 101)). It would have been helpful to have more early- and mid-adult variables collected in the LBCs. We have done our best to fill these gaps by retrospective self-reports and other techniques such as geo-linkages for past home addresses. One practical example from LBC1936 is that we did not ask for linkage to participant's medical records at the first wave of their testing at age 70; we corrected that, but we kicked ourselves for having omitted to request that from participants from the beginning.

Consider What Size of Cohort and Team is Optimal for Purposes (to Retain Focus) and Quality of Life (Though the Cohort will Take Over Your Life)

We have kept the LBC team to a moderate size. If one counts the PIs, the team that runs the study, the employed and ad-hominem/feminam postdoctoral fellows and research assistants—that is, mostly keeping it to the hub—the numbers vary around a score. All members of the team are encouraged to contribute to analysis and write-ups. We have no purely clerical staff—all are trained in science, usually psychology and/or genetics and/or brain imaging. Most are located in the same corridor or nearby.

If Something is Exciting, do it, Even if it is not in Your Field

We gave the example above of finding that DNA-methylation age was related to longevity. It was too exciting not to do. Even less related to our core mission than that was at the time when we had recently obtained the genome-wide scanning of SNPs in the LBCs. As an exercise for our newishly-appointed statistical molecular geneticist, we ran some biomarker variables through a GWAS procedure. We found three SNPs that accounted for 18% of the variance in activated partial thromboplastin time, and important measure in hematology (102). There was then the search for who had reported this already. No one had. We ran with it, with added hematological expertise. It was an interesting result and it was a good exercise in the analyzing and writing-up of GWAS. Perhaps even further from this was our involvement with clonal hematopoiesis (92, 93) which, again, seemed both too exciting and important not to become involved with.

We Learned That There Are Multiple, Partly Overlapping-Camps of Cognitive Ageing Research

Let's call these individual-differences psychology, experimental psychology, and medically-oriented. The individual differences approach might be exemplified by, say Timothy Salthouse or Warner Schaie, using large community-dwelling cohorts to examine patterns of cognitive ageing in different cognitive domains and what they share. The sample is all one group. Sometimes these studies are cross-sectional and sometimes longitudinal and sometimes cross-sequential. The experimental psychology approach might be exemplified by, say Michael Rugg, and is more likely to use smaller, separate samples of older and younger individuals and compare them on cognitive test scores. There are then more medically-oriented studies that focus on mild cognitive impairment and dementia. Sometimes these are case-control studies and sometimes cohorts that are followed into and through cognitive impairments.

Much of our work with the LBCs has been done within the individual differences framework. In part, this can involve data reduction statistical techniques (principal components analysis, factor analysis, sometimes in a structural equation modelling framework)—the bread and butter of differential psychology methods. However, the necessity of doing multivariate longitudinal modelling taught us that, with the LBCs, we were in one of the more technical analytical fields of psychology and also that the measurement of and determination of differences in cognitive (and other) change was, to say the least, much-discussed and sometimes fraught. Our team became familiar with, for example, growth curve modeling (32, 41, 62, 103). If one wants to study cognitive change and its determinants, one has to be prepared to learn to drive some heavy and complicated statistical machinery.

Take Biological Samples, Even if They do not Have an Immediate Use

From early on in our work with the LBCs we stored blood, plasma, and serum. We knew we needed these for basic health biomarkers (e.g., blood chemistry, hematology, glycated hemoglobin, etc.) and for genetics. We knew that more biomarkers would appear and that some would need to

be measured longitudinally. It is hard to exaggerate now how useful these samples have been. An indication of their uses can be seen in our cohort profile articles.

Future-proof the Cohort in Their Afterlife

The data from the LBCs will be analyzed after they are no longer with us and, we hope, after we are long-gone, too. However, there is a more biological meaning to this lesson. Having drawn cells which can be transformed to stem cells that can then be differentiated to many cell types means that the LBC1936 participants have provided material that can be used, in vitro, to test hypotheses about neural and other cell ageing (104). Related to that, the postmortem brain tissue donated by some of the LBC1936 participants who have died has already been used to investigate the biology of cognitive ageing, though the numbers to date are still very small (cf. the ROSMAP studies) (47, 105). Such discussion of attempted future-proofing of the LBCs reminds us to mention that this—and, indeed, the panoply of the LBCs—takes place within the strictures of consent and ethics and that these, during our work, have been moving targets. The consent required for different aspects of the studies has become more detailed as waves have passed, and postmortem brain tissue collection and storage and stem-cell creation and storage have each needed their own detailed consent procedures and ethical approvals. Other aspects of the study, such as linkage to medical records required additional (additional, i.e., to the ethical/consent work for the collection of the data within each wave) ethical/consent applications. From the beginning of the LBCs until the present we have proceeded via the ethical committees of the national Health Service in Scotland; that is, we have taken a medical rather than a psychological route to ethical approval and consent, which reflects the broad and health-related content of the studies.

Realize the Responsibility of Assembling a Longitudinal Cohort and Involve Them

One lives with a cohort. They are not like a convenience sample that one will thank and never see thereafter. One must form relationships with the cohort. One must listen to them and make channels for that to happen. With the LBCs, we have: newsletters (read some of them here: https://edin.ac/4dN8unc) at the ends of waves and at Christmas and at some other notable times; reunions at the ends of waves and at notable anniversaries (there are talks on the new results and question and answer sessions and information about the future plans; see our 20-year anniversary booklet here: https://edin.ac/3VnQiLi); and the LBCs' participants have made many national television, radio and newspaper appearances. There have been historical and art exhibitions (portraits some of the LBCs' participants and the research team) about the LBCs. There was a play about the LBCs performed at the Edinburgh International Fringe Festival. A film was made about the LBCs. A book was written recounting the personal histories of some of the participants and some of the team. The LBCs' participants have featured in umpteen science festivals, and knowledge exchange events for schoolchildren and members of the public. There's a summary here: https://edin.ac/4dTXQee. LBCs' participants and team members have twice been to the UK House of Lords to describe what their findings were to expert groups. When we wrote, above, that one must listen to the cohorts' members, that was not empty virtue signaling. Here's an example. At one of the reunions of the LBC1936, a participant asked why, given that we had collected so much information on them, we had not asked for their brain after death. That began a long process of obtaining permission for and setting up the LBC1936 Brain Tissue Bank (which has multiple small samples from brains, and not whole brains).

Being in an Observational Study Can be an Unintended Treatment

This probably has not happened often or to any large extent. However, being a participant in the LBCs, it would be impossible not to be alerted to aspects of cognitive and brain and more general ageing. To give just one example, one LBC1936 participant enrolled for and successfully completed a degree in philosophy with the UK's Open University because she thought she should use her brain more.

Referees and Journal Editors Want Longitudinal Data in Cognitive and Brain Ageing, but Funders Don't Want to Fund Them (Unless You Have New Hypotheses at Each Wave)

As we said above, the LBCs have never had guaranteed funding. However, we have had, for example, consecutive grants from Age UK that spanned the years between 2004 and 2020 for the LBC1936. We have also had multiple grants from the UK Research and Innovation bodies, especially BBSRC and MRC. Here, we are referring mostly to grants for core aspects of the study; there are many other grants for specific projects and for fellowships. But, as we note in parentheses above, it has never been sufficient to state, when applying for funding, that we were collecting another valuable wave of data from the LBCs. Almost always, we have had to develop fresh hypotheses for each wave. Although we have been able successfully to do this, and keep the show on the road (and deliver the specified work), the process of focusing on some specific hypotheses—from cohorts that have a solid track record of being a rich substrate on which to test so many hypotheses—was not easy.

Have a Good Succession, Even if it Happens During a Pandemic

Our cohorts have lasted a long time, beyond the full-time career of Ian Deary, for example. We were able to keep the LBC1936 cohort and research team going through the Covid-19 pandemic (106–108) and they are now (the second half of 2024) passing through Wave 7 at age about 88. The Deary-to-Cox succession is built not just on that one positive working relationship, but also upon great loyalty and continuity of team members and participants and collaborators. We still have, working in the team, Alison Pattie, who was first employed at the start of the LBC1921 in 1999, and Janie Corley, who was first employed at the start of the LBC1936 in 2004. Directing a cohort study is an intricate business, and we both count ourselves lucky to have benefitted from a superb and dedicated team, without whose continuity the whole operation would have been impossible to keep on the road.

Appreciate One's History

The history of the SMSs and the research environment in Scotland and nationally and internationally that brought them about has been a source of interesting study in itself. Central to that was the interesting figure of Professor Sir Godfrey Thomson, a giant in education, intelligence, and statistics and who is unfairly relatively unknown (109–113). His portrait hangs in the current director's office (along with an appreciation of *in umeris gigantum stamus*) as it did in the founding director's. Here is a link to a video covering the exhibition devoted to Thomson that we produced in 2016: https://www.youtube.com/watch?v=ZObidTDX4lI

And, now that the LBCs are 25 years old, they fold into and become part of that history. The next few years will see the age-90/Wave 8 testing of the LBC1936. Allied with that will be an effort to take our very large, securely-stored paper records and digitize them, so that every mark made for every test for every participant at every wave can be made available to future researchers. Also, the present authors have (it's a mug's game, though) tried to predict what might happen, scientifically, in the brain and cognitive ageing field over the next while (74).

Enjoy What You do

The LBC cohorts, the LBC research team, our collaborators, our funders (here, we make a special mention of Age UK, with whom we had a long and rewarding relationship), and the University of Edinburgh (with a special mention for the School of Philosophy, Psychology and Language Sciences and its various Heads for their support) are and have been enjoyable to work with. We value and humbly appreciate personal, social, and scientific premiums that return from that positive environment. The LBCs have opened doors that other types of research involvement wouldn't have: we and they met several members of the British Royal Family (including the late Queen Elizabeth II), Lords and MPs, and stars of stage and screen. Fuelled by the LBCs, we have seen junior researchers rise to professorships and to other valued vocational destinations; the LBCs have seeded cognitive and brain ageing researchers in other places.

Concluding Thoughts

The research with the Lothian Birth Cohorts was often summarized as something like, "to discover secrets of healthy cognitive ageing." In

various ways that handy-but-crude statement dissolved: first, we were sometimes confirming/incrementing others' findings rather than discovering (i.e., for the first time); second, we accepted that we should have to study pathological as well as healthy cognitive ageing, as the participants experienced dementia in larger numbers; and we expanded our outcomes remit beyond cognitive functioning. Those belt-loosening changes to our original methodological purity notwithstanding, we hope that discoveries from the LBCs, as enumerated in the "Scientific Discovery Lessons" will be useful to scientists in cognate fields. We also hope that our discoveries and incremental contributions to the fields in which we work will help people to make better choices regarding healthy lifestyles and provide understanding regarding contributions to individual differences in cognitive and brain ageing and ageing more broadly (alongside other teams' findings); we hope that scientists and lay people will appreciate that what they think are outcomes can be exposures and vice versa (reverse causation/confounding); this was all summarized in our "marginal gains" approach (8). We also refer the reader to our various policy-influencing attempts and contributions (here https://edin.ac/4dTXQee and here https://edin.ac/48te7G9) and also mention that we have undertaken hundreds of media and in-person appearances/activities to spread the word about good science and healthy ageing. These activities cover all ages from primary schools to older-people's groups and use educational programs, games, and art. Finally, we hope to have encouraged readers to find and read more of our publications and to keep up with those that appear in the coming years; they are listed here: https://edin.ac/3UixD26.

Data Availability Statement

No original data were generated in this work that requires public dissemination. Information about data access and collaboration for the Lothian Birth Cohorts of 1921 and 1936, the LBCs' data dictionaries, the LBCs' data summary tables, the LBCs' cohort profile articles, the LBCs' data request form, and data request contact information are all available here: https://edin.ac/3YkR3Ev.

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Author Contributions

Both authors contributed equally to all aspects of this work.

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Author Disclosures

The authors have confirmed that no conflict of interest exists.

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