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Healthy cognitive ageing in the Lothian Birth Cohort studies: marginal gains not magic bullet

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In the face of shifting demographics and an increase in human longevity, it is important to examine carefully what is known about cognitive ageing, and to identify and promote possibly malleable lifestyle and health-related factors that might mitigate age-associated cognitive decline. The Lothian Birth Cohorts of 1921 (LBC1921, $n=550$) and 1936 (LBC1936, $n=1091$) are longitudinal studies of cognitive and brain ageing based in Scotland. Childhood IQ data are available for these participants, who were recruited in later life and then followed up regularly. This overview summarises some of the main LBC findings to date, illustrating the possible genetic and environmental contributions to cognitive function (level and change) and brain imaging biomarkers in later life. Key associations include genetic variation, health and fitness, psychosocial and lifestyle factors, and aspects of the brain's structure. It addresses some key methodological issues such as confounding by early-life intelligence and social factors and emphasises areas requiring further investigation. Overall, the findings that have emerged from the LBC studies highlight that there are multiple correlates of cognitive ability level in later life, many of which have small effects, that there are as yet few reliable predictors of cognitive change, and that not all of the correlates have independent additive associations. The concept of marginal gains, whereby there might be a cumulative effect of small incremental improvements across a wide range of lifestyle and health-related factors, may offer a useful way to think about and promote a multivariate recipe for healthy cognitive and brain ageing.

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Introduction

Promoting successful cognitive ageing is a topic of major importance to individuals and the field of public health. For most, losing one's cognitive abilities, especially memory, is feared more than physical disability (Martin, 2004). Cognitive decline in older age is associated with poorer health and quality of life (Plassman *et al.* 2010), impairments in functional activities, decision-making and independence (Tucker-Drob, 2011; Boyle *et al.* 2012; Jekel *et al.* 2015), and increased health care costs (Brayne, 2007). In the face of shifting demographics and an increase in human longevity, there is a pressing need to evaluate the potential contributions to cognitive function in later life. People differ in their cognitive abilities, both in terms of their overall level, and the rate at which they experience decline in older age (Gow *et al.* 2011). A key question is: why do some people have a better cognitive trajectory than others? Identifying factors that predispose individuals to a faster rate of cognitive decline is an important step

for developing intervention and treatment strategies aimed at maintaining cognitive and brain health into older age.

The main focus of the Lothian Birth Cohort (LBC) studies is people's differences in cognitive and brain ageing. The idea for these studies came about following the discovery of ledgers containing the results of the Scottish Mental Surveys (SMS) (Deary *et al.* 2009c). The surveys had tested the intelligence of almost a whole year-of-birth, twice. On 1 June 1932, almost every child born in 1921 and attending a Scottish school took the same general mental ability test, known as the Moray House Test (MHT) No. 12. The exercise was repeated on 4 June 1947 for almost every Scottish school pupil born in 1936. These were the SMS of 1932 and 1947. Most schools in Scotland participated, yielding test scores on 87 498 (SMS1932) and 70 805 (SMS1947) 11-year olds. From 1999, the LBC studies, based at the University of Edinburgh, recruited men and women in the Lothian region of Scotland who were surviving participants of the SMS of 1932 (to the LBC1921 study) and 1947 (to the LBC1936 study). Other SMS follow-up studies were conducted in Aberdeen, known as the Aberdeen Birth Cohort of 1921 (ABC1921) and 1936 (ABC1936) (Deary *et al.* 2009c; 2004b; Whalley *et al.* 2011).

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The original aim of the LBC studies was to seek the determinants of normal (non-pathological) cognitive ageing from childhood to older age; they were extended to study cognitive and brain ageing within older age. Both cohorts are richly phenotyped, with many data types in common: socio-demographic, medical, cognitive (including the same test as at age 11), magnetic resonance imaging (MRI), carotid ultrasound, retinal imaging, blood biomarkers, physical function and fitness, genetic and epigenetic, lifestyle, psychosocial, personality, and many others (see Supplementary tables 1 and 2). The LBC1921 study has completed five waves of testing since baseline ($n = 550$, mean age 79 years); most recently 54 participants were tested at age 92. No further testing of this cohort is planned. The LBC1936 study has completed four waves of testing since baseline ($n = 1091$, mean age 70 years); most recently 550 participants were tested at age 79. A fifth wave of data collection is planned to begin in the second half of 2017. Follow-up assessments for both cohorts were conducted at ~3-yearly intervals. For further details, see the cohort profile paper (Deary *et al.* 2012a) and the LBC studies website (<http://www.lothianbirthcohort.ed.ac.uk/>). Detailed structural brain MRI was performed at mean ages 73, 76, 79 in the LBC1936 (Wardlaw *et al.* 2011), and at age 90 in the LBC1921.

This overview summarises key results from among the 300+ LBC1921 and LBC1936 peer-reviewed publications, focussing on those addressing cognitive and brain ageing, and placing these findings within the context of the wider, relevant literature. Among the key ageing-relevant factors considered here will be genetic, social, health, biomedical and lifestyles. We introduce the concept of marginal gains to encapsulate the probably many small influences that appear to contribute to differences in people's brain and cognitive health in older age. The marginal gains idea is often applied to performance in elite sports and business. However, based on the work reviewed here, we suggest that the idea could provide a useful framework for understanding and promoting the process by which a possibly large range of potentially malleable risk and protective factors (each of which might show a small association) may lead to an aggregate benefit for cognitive and brain ageing in later life. We stress strongly, though, that the LBC studies are observational and not intervention studies.

Stability and change in intelligence

If we wish to understand the contributions to people's cognitive differences in older age, then arguably the first question one should ask is how much of the cognitive variation in older age is due to long-standing cognitive trait differences. The LBC studies showed

that the biggest factor in explaining why people's cognitive skills differ in older age is childhood intelligence differences. When the same validated intelligence test (MHT) is administered at age 11 years and again to individuals when they are in their late 70s, the raw correlations are between 0.6 and 0.7 (Deary *et al.* 2004b) and are still above 0.5 when the individuals are in their late 80s (Gow *et al.* 2011) and into their 90s (Deary *et al.* 2013). Furthermore, MHT intelligence scores in childhood and older age correlate significantly with scores on well-validated cognitive tests, even at the age of 90 (Deary *et al.* 2013). These correlations imply that about half or more of the variance in intelligence is stable across most of the human life course (see Deary, 2014). The cohorts also provide clear evidence that change in a general cognitive factor accounts for ~50% of the variance in age-related changes across multiple cognitive domains (see Tucker-Drob *et al.* 2014; Ritchie *et al.* 2016).

These results show that individuals who are cognitively more able in youth show a tendency to still show a higher level of cognitive function in older age (Deary *et al.* 2004b; Royle *et al.* 2013). But what about the rate of change in cognitive ageing? That is, in the field of cognitive ageing, it is often asked whether 'ageing is kinder to the initially more able' (Deary *et al.* 1999; Gow *et al.* 2012c). The results are mixed. Some suggest that those with a higher early-life cognitive ability decline in cognitive functioning at a slower rate in later life (Bourne *et al.* 2007), whereas others report no association (Gow *et al.* 2008, 2012c). In the LBC1936, those with higher childhood ability tended to decline more with age in visuospatial ability, but there was no statistically significant association with any of the other cognitive measures (Ritchie *et al.* 2016). Overall, results from the LBC studies suggest that cognitive ability in early life, although it has a strong association with cognitive level in older age, does not confer an advantage with respect to cognitive ageing trajectory (Gow *et al.* 2011; Ritchie *et al.* 2016).

Knowing the long-term stability of individual differences in cognitive abilities is a valuable foundation for estimating which factors account for the other variance in cognitive function in older age. Therefore, if about 50% of the variance in cognitive function in older age is traceable back to childhood, we should seek reliable sources of the other 50%, some of which will, of course, be measurement error. The non-error sources will probably include factors that are outside of our immediate and practical control, and those that might be amenable to change.

Brain correlates of cognitive ageing

Evidence derived from brain imaging studies of the LBCs (Wardlaw *et al.* 2011) supports a lifelong 'trait'

of intelligence and its association with brain structure. In the LBC1936, intelligence at age 11 not only predicts cortical thickness in later life but accounts for over two-thirds of the cross-sectional association between cognitive ability and cortical thickness in later life. Adjusting for MHT scores at age 11 attenuates this association to non-significance (Karama *et al.* 2014). Individuals from the LBC studies who showed less relative decline in cognitive function between age 11 and later life also show better white matter microstructure (Deary *et al.* 2006a; Penke *et al.* 2012b), fewer white matter hyperintensities (WMH) (Valdés Hernández *et al.* 2013), slower progression of WMH (Ritchie *et al.* 2015c, d), less brain atrophy and a larger intra-cranial volume (Royle *et al.* 2013), a bigger brain (Shenkin *et al.* 2009c), less small vessel disease (Staals *et al.* 2015), and fewer iron deposits (Penke *et al.* 2012a; Valdés Hernández *et al.* 2015b). Individuals with better cognitive abilities at age 73 showed less brain volume loss and less WMH growth over a 3-year follow-up period (Ritchie *et al.* 2015a). Coupled changes in white matter microstructure and fluid intelligence are consistent with a longitudinal link between brain ‘disconnection’ and cognitive ageing. The brain correlates of better cognitive ageing point to less shrinkage of the brain tissue generally, better white matter connections in the brain, and fewer hyperintensities in the brain’s white matter (Ritchie *et al.* 2015c, d), and confirm that neuroimaging biomarkers are informative about cognitive changes. The state of the brain’s structure in older age has significance beyond cognitive functioning; the LBC1936 study showed that older brain age (the deviation of the brain’s structure from that expected for a given chronological age) is associated with earlier death (Cole *et al.* 2017).

The determinants of brain changes from age 73 to 76 have been investigated in the LBC1936. Relatively greater deterioration in MRI measures of brain macro and microstructure was associated with lower physical fitness and possession of *APOE* e4. Though other potential risk and protective (physical, health, cognitive, allostatic and genetic) variables were associated with baseline brain structure, they did not predict subsequent brain change over the short (3-year) follow-up period (Ritchie *et al.* 2017).

Genetic influences on cognitive level and cognitive change

In adulthood, twin studies estimate that between 50% and 80% of the variation in general cognitive function is caused by genetic differences (Deary *et al.* 2009b). The LBC studies contributed to a consortium that was the first to use single-nucleotide polymorphism (SNP) data to estimate the SNP-based heritability of

individual differences in human intelligence (Davies *et al.* 2011), which was subsequently expanded (Davies *et al.* 2015). The current estimate is that common SNPs in many genes, each having a very small effect, account for about 30% of the variation in human intelligence differences. This largely refers to contributions to the stable trait of human general intelligence. The emerging view of genetic influences on intelligence, confirmed by work on the cohorts, is that it is likely that a very large number of genetic variants have small effects (Deary *et al.* 2010; Plomin & Deary, 2015).

The LBC studies contributed to a study in which common genetic variants (SNPs) were estimated to account for about 24% (but with a relatively large standard error) of the variability in lifetime cognitive change, i.e. from childhood to older age (Deary *et al.* 2012b). The same study found that the genetic factors contributed the majority influence on the lifetime stability of intelligence. Within that contribution, various candidate genes have been tested. However, other than possession of the ‘risk’ *APOE* e4 allele, which explains around 1–2% of the variance in cognitive change from youth to older age and within older age (Deary *et al.* 2002, 2004a; Luciano *et al.* 2009a, b; Schiepers *et al.* 2012; Ritchie *et al.* 2016; also see Daviglus *et al.* 2010) and is associated with age-related brain structural changes (Ritchie *et al.* 2017), no other candidate genes have been consistently linked to variation in cognitive function or with age-related cognitive decline (Visscher *et al.* 2003; Deary *et al.* 2005b; Kachiwala *et al.* 2005; Houlihan *et al.* 2009; Marioni *et al.* 2014b).

A different approach is to ask whether people’s polygenic risk for disorders related to cognitive decline contribute to cognitive change, even in individuals without the disorders. In the cohort studies, increased polygenic risk of certain diseases, such as coronary artery disease (Hagenaars *et al.* 2016), ischaemic stroke (Harris *et al.* 2016a) and schizophrenia (McIntosh *et al.* 2013), is associated with lower cognitive ability, and greater relative cognitive decline in the case of polygenic risk for schizophrenia (McIntosh *et al.* 2013). Lower cognitive ability in older age was not associated with polygenic risk for diabetes (Luciano *et al.* 2014) or Alzheimer’s disease (Lyll *et al.* 2013a, b, 2014; Harris *et al.* 2014). DNA methylation, which can be used to form an epigenetic biomarker of age acceleration, was associated with cognitive function in the LBC1936, but not cognitive decline over 3 years within old age (Marioni *et al.* 2015a). Apart from cognitive function, the LBC studies showed that a faster running epigenetic clock is associated with earlier death (Marioni *et al.* 2015b).

Thus, the LBC studies contribute to evidence that intelligence level from adolescence to older age is

highly heritable and highly polygenic, and is substantially stable over time, with genetic factors contributing much to the lifetime stability. The existence of some genetic contributions to lifetime cognitive change does not mean that these are not amenable to intervention; with a greater understanding of genes' systems and gene expression pathways (e.g. Johnson *et al.* 2016), genetic contributions might well be modifiable. Establishing the heritability of intelligence and the genetic contributions to cognitive change is important for many reasons, not least because it also helps to elucidate the extent to which environmental influences contribute to lifetime cognitive change.

Early-life and demographic factors

Positive early-life factors, including birth parameters (Shenkin *et al.* 2001, 2004; Grove *et al.* 2017), education (Stern, 2002; Banks & Mazzone, 2012; Clouston *et al.* 2012; Ritchie *et al.* 2016), and childhood environment (Johnson *et al.* 2010; Ritchie *et al.* 2016), appear to have modest associations with better cognitive capacities in later life and better brain health according to only some MRI indices (Shenkin *et al.* 2009a; Cox *et al.* 2016; Field *et al.* 2016). However, we have not found evidence that early-life factors offer protection against cognitive decline in the LBCs or other studies (Shenkin *et al.* 2009b; Tucker-Drob *et al.* 2009; Zahodne *et al.* 2011; Gottesman *et al.* 2014; Ritchie *et al.* 2016). That is, they might be associated with long-standing cognitive level, but possibly not with cognitive trajectory.

Education is hypothesised to boost so-called cognitive reserve (Tucker & Stern, 2011). However, we acknowledge that some users of this term make it ambiguous, because sometimes it refers to higher pre-morbid cognitive level, and sometimes to less steep decline. Longer schooling in the LBC1936 was a significant predictor of higher scores on a latent general cognitive factor at age 70, independently of childhood IQ score (Ritchie *et al.* 2016), and of greater cross-sectional cortical thickness in areas linked to the flexible integration of semantic knowledge (but not to other brain MRI markers; Cox *et al.* 2016). However, there was no evidence of an association between education and a latent factor of cognitive change from age 70 to 76 (Ritchie *et al.* 2015b, 2016). Though more education associates with better general cognitive abilities in later life, it appears, after adjustment for childhood intelligence, to be associated with some specific cognitive skills (Ritchie *et al.* 2015b), and does not appear to improve more fundamental aspects of cognitive processing, such as reaction time and inspection time (Ritchie *et al.* 2013). Education's effects might therefore be limited to specific aspects of intelligence tests, such as knowledge and perhaps reasoning, rather than a

general factor of intelligence, and might offer no protection against cognitive decline (Ritchie *et al.* 2015b).

Some established correlates of lower intelligence test scores in youth, including low parental socio-economic status (SES), poor maternal nutrition, maternal smoking, and poor perinatal nutrition, are related to maternal intelligence, suggesting that these associations might in part be accounted for by the genetic link between mother and child (Shenkin *et al.* 2004; Deary *et al.* 2005a; Rääkkönen *et al.* 2009). Indeed, parents pass on genetic variants associated with both intelligence and aspects of the socio-economic environment to their children (Deary *et al.* 2010; Marioni *et al.* 2014a; Hill *et al.* 2016). Yet, though social background (parental or environmental circumstances) may provide opportunities for educational and occupational attainment, results from the LBC studies suggest that childhood SES alone does not appear to have strong associations with cognitive decline in later life (Johnson *et al.* 2010; Ritchie *et al.* 2016). It may be that the choices that individuals make (personal life history variables), rather than early-life social milieu, have the greatest effects on cognitive abilities in later life (Johnson *et al.* 2010). Not only is childhood intelligence the strongest direct contributor to later life intelligence, it may contribute directly to one's ability to obtain education, and a safe and well-remunerated job, the typical indicators of SES (Deary *et al.* 2005c).

Consistent with the 'use it or lose it' hypothesis, researchers often ask whether a more intellectually demanding job in adulthood contributes to better cognitive function (Hultsch *et al.* 1999). Occupational complexity was associated with better cognitive performance in the LBC1936 at age 70 (after adjusting for age 11 IQ, education and social deprivation), accounting for 1–2% of the variance (Smart *et al.* 2014). Gender differences identified in the 1936 cohort, in relative IQ change between youth and age 70 (with an effect size of 0.19) favouring men (Johnson *et al.* 2011), an effect also reported in the LBC1921 (Deary *et al.* 2004b), might reflect men's greater involvement in the workforce in these samples and its potential to retard cognitive decline with age. However, not all studies report beneficial long-term effects of occupational characteristics on cognitive ageing (Finkel *et al.* 2009; Gow *et al.* 2014). More stimulating environments may help preserve cognitive ability in later life, but engagement in complex and intellectually stimulating activities may also be a consequence of individual differences in prior cognitive ability (Gow *et al.* 2012b); a dynamic longitudinal association seems likely.

Lifestyle and psychosocial factors

A number of factors potentially under an individual's control might improve cognitive ageing prospects

and reduce the risk of cognitive decline and impairment (Lee *et al.* 2010; Baumgart *et al.* 2015). The LBC team have been investigating what these factors are and estimating the size of their effects. We preface this by stating that effect sizes are typically small, and so, like many potential behavioural changes for health, they would possibly have a detectable effect at population level rather than a manifest result for any individual.

Smoking

It is well documented that smoking is a risk factor for cognitive decline and dementia (Anstey *et al.* 2007; Peters *et al.* 2008). Evidence for past smoking is less consistent (Daviglius *et al.* 2010). In the LBC1936, those still smoking at the age of 70 performed more poorly than ex- and never-smokers on most of the concurrently performed cognitive tasks (Corley *et al.* 2012). Cigarette smoking in older age was found to be associated with slightly lower scores in general cognitive abilities and in speed of information processing, accounting for 0.7% and 0.6% of the variance, respectively. Past smoking was not associated with significantly poorer performance when compared with never-smokers in any cognitive domain. Lower childhood IQ predicted more likely onset and less likely cessation of smoking in the LBC1936. In the LBC1921 at age 80, current smokers had significantly lower MHT scores in older age than never- and ex-smokers after adjusting for childhood IQ (Deary *et al.* 2003; Starr *et al.* 2007). A lower childhood IQ predicted cessation but not uptake of smoking, perhaps reflecting social attitudes to tobacco over this particular historical period (Taylor *et al.* 2003).

Our results suggest that cessation of smoking in adulthood may 'buffer' the cognitive ageing experienced by those who continue to smoke, perhaps via decreased progression of WMH volume (Dickie *et al.* 2016), or decreased cortical thinning (Karama *et al.* 2015). When accounting for the amount of lifetime smoking, Karama *et al.* found that the cortex of subjects who stopped smoking appeared to have partially 'recovered' (the study was cross-sectional, so this was inferred) for each year without smoking. Although complete cortical recovery in affected areas was estimated to take on average 25 years in this sample, these important findings suggest that partial recovery is possible. In terms of public health implications, findings which hint at underlying neurobiological mechanisms such as these are valuable. Here we suggest that there might be both cognitive and cerebral benefits to quitting smoking, in addition to the better known health benefits, even for older adults who have been smoking for many years.

Physical activity

A higher level of participation in physical activity in later life was associated with better general cognitive abilities and processing speed in the LBC1936 at baseline, accounting for 0.7% and 1% of the variance, respectively (Gow *et al.* 2012b), and less cognitive decline over 11 years of follow-up (from age 79 to 90) in the LBC1921 (Gow *et al.* 2017). The lack of association between a cumulative activity score (spanning the ages of 20–75) and cognitive ability indicates, there may be specific periods in which engagement in physical activities may be particularly beneficial. Our findings of better cognitive functioning with greater physical engagement supports the wider evidence that physical activity has a significant role in determining healthy cognitive ageing (Lee *et al.* 2010; Blondell *et al.* 2014; Carvalho *et al.* 2014; McKee & Schüz, 2015). Other studies have demonstrated that even mild activities, such as walking, were found to be protective in later life (Weuve *et al.* 2004). The results of a meta-analysis of prospective studies suggest that all levels of physical activity offer significant and consistent protection against cognitive decline (Sofi *et al.* 2011). Yet, despite this promise, randomised controlled trials of physical activity are equivocal; some report positive effects on cognitive function (Lautenschlager *et al.* 2008), whereas others find no improvements in global or even domain-specific cognitive abilities (Sink *et al.* 2015). However, a meta-analysis of 29 studies reported modest improvements in attention, processing speed, executive function and memory, with exercise training among non-demented adults (Smith *et al.* 2010). Type and intensity of exercise may be a factor; aerobic training programmes in older people lead to significant improvements not observed in those doing strength and flexibility exercises or in controls (see Bherer *et al.* 2013), suggesting a role for cardiorespiratory fitness in healthy cognitive ageing.

The biological mechanisms by which cognitive function might be enhanced through physical exercise training remain to be completely elucidated. Physical exercise in later life may exert a cognitively protective effect via preservation of brain microstructural integrity; more physical activity at age 73 was associated with less brain atrophy and fewer white matter lesions in the LBC1936 (Gow *et al.* 2012a). Associations with higher fractional anisotropy and higher normal-appearing white matter volume became non-significant in the fully adjusted model. Another study showed that exercise training increases hippocampal volume and improves memory (Erickson *et al.* 2011). These results, and others (Marks *et al.* 2007; Voss *et al.* 2013; Tian *et al.* 2014), offer evidence for

neurotrophic effects of physical activity on brain structure. Exercise may, of course, enhance cognition indirectly by improving psychological wellbeing (Herring *et al.* 2012a, b), improving sleep quality and minimising pain (Reid *et al.* 2010), all of which may secondarily impact neurocognitive functioning (Reppermund *et al.* 2011). It remains to be seen whether these factors in fact mediate any positive effects that exercise has on cognitive and brain health.

Alcohol

Findings on the association between alcohol use and cognition were less clear, consistent with other research (Daviglius *et al.* 2010). In the LBC1936, a higher intake of alcohol, particularly of wine, was associated with better memory function at age 70 after adjusting for age 11 IQ, accounting for around 1% of the variance in scores (Corley *et al.* 2011). An almost exclusive preference for wine among women alluded to a potentially beneficial effect of wine or of its components. However, memory performance was better in men with a higher overall alcohol intake and not necessarily due to wine intake *per se*. In the same sample, the use of Mendelian randomisation demonstrated that individuals with a higher genetic ability to process alcohol showed relative improvements in cognitive ability with more consumption, whereas those with low processing capacity showed a negative relationship between cognitive change and alcohol consumption with more consumption (Ritchie *et al.* 2014). This study indicates that any protective effects of alcohol consumption on cognitive change may be contingent on an individual's genetically influenced capacity to metabolise alcohol.

Diet and nutrition

Certain dietary components (Loef & Walach, 2012; Morris, 2012) and dietary patterns (Féart *et al.* 2010; Tangney *et al.* 2011; Allès *et al.* 2012) have been linked with better cognitive ageing in the literature, yet the results from the LBC studies have been mixed. In the LBC1936, the proportion of total variance in cognitive function at age 70 years accounted for by the age 70-reported intake of the nutrients B2, B12, folate, vitamin C was <1% (McNeill *et al.* 2011). In the same study, supplement use was associated with better cognitive function, but this was accounted for by a higher IQ in youth. Individuals adhering to a Mediterranean-type dietary pattern (Corley *et al.* 2013) and consuming a greater intake of dietary flavonoids (Butchart *et al.* 2011) and more caffeine (Corley *et al.* 2010b) had better cognitive skills at age 70, but these associations largely disappeared upon adjustment for cognitive ability in youth. Individuals with a higher intake of these dietary

components were more likely to have a higher IQ in both childhood and old age. In the same sample, those with a higher Mediterranean diet index score showed less total brain atrophy over a 3-year period (Luciano *et al.* 2017). However, the effect size was small (0.5%) and not corrected for multiple comparisons, and so replication studies are needed. In other analyses, healthy (nutrient-dense) dietary patterns were associated with significantly lower levels of circulating inflammatory markers (Corley *et al.* 2015). Given that chronic low-grade inflammation is a putative predictor of cognitive decline, a relationship between diet and cognitive decline via pro-inflammatory processes may be a promising avenue for future research. Dietary intake of iron was assessed in relation to brain ageing in the LBC1936, since brain iron accumulation is involved in neurodegenerative diseases. However, neither iron nor calorie or dietary cholesterol intake, at the levels found in normal western diets, was directly associated with iron deposition load assessed on structural MRI scans (Valdés Hernández *et al.* 2015a). It appears that at least some aspects of diet that are associated with cognitive function in older age are confounded with prior cognitive ability, and probably the lifestyle changes associated with cognitive differences.

Dietary assessment was not included in the LBC1921 study, but lower serum B12 at age 79 was associated with greater cognitive decline between ages 11 and 79. By contrast, serum folate at age 79 correlated with age 11 IQ, and controlling for this reduced the correlation with IQ in old age to almost zero (Starr *et al.* 2005).

Intellectual activity

Performing socio-intellectual activities (examined using a latent factor) was no longer associated with general cognitive ability, processing speed or memory in the LBC1936, following adjustment for childhood IQ (Gow *et al.* 2012b). Intellectual activities were not associated with any of the structural brain parameters assessed (Gow *et al.* 2012a). However, we reported a positive effect of being bilingual on later-life cognition, even in those who acquired their second language in adulthood (Bak *et al.* 2014). These effects could not be explained by other variables, such as childhood IQ, SES, immigration or gender. Early *v.* late acquisition showed differential effects, depending on childhood IQ. Overall, individuals with higher intelligence seem to benefit more from early acquisition and those with low intelligence from late acquisition, but neither group showed negative effects. Furthermore, learning a second language was related to better conflict processing, irrespective of initial childhood ability or social class (Cox *et al.* 2016).

Social factors and psychological wellbeing

In analyses including social networks, social support and loneliness, loneliness was the only factor which contributed to the prediction of poorer old age cognitive abilities, explaining about 2% of the variance at age 79 in the LBC1921 (Gow *et al.* 2007). In the LBC1936, less loneliness, more social support and shared living arrangements were most consistently associated with aspects of cognitive ability, though these associations appeared to be partly accounted for by fewer symptoms of depression (Gow *et al.* 2013a). In the same sample, lower levels of anxiety were associated with more favourable relative change in cognitive function between ages 11 and 70 (Johnson *et al.* 2010). However, a large multicohort study (including the LBC1921) of mental wellbeing in relation to cognitive function found that associations in older people are small and may be confounded by personality trait differences (Gale *et al.* 2012).

Health

Intelligence in youth and older age is associated with important health outcomes (Deary *et al.* 2010), and age-related disease increases the risk of cognitive decline (Deary *et al.* 2009a). An individual's cognitive trajectory is the result of a combination of shared influences with the rest of the body. However, some health conditions are modifiable via lifestyle changes and medication.

Physical fitness

In the LBC1921, grip strength and reasoning were correlated at each wave of testing in the ninth decade, but their trajectories of decline were not (Deary *et al.* 2011). A latent trait of physical fitness – derived from lung function, grip strength and walking speed – accounted for over 3% of the variance in cognitive change between ages 11 and 79 years in the LBC1921, after adjusting for childhood IQ (Deary *et al.* 2006b). The same physical fitness trait was associated with better 6-year cognitive change in the LBC1936, yet when physical measures were assessed individually, they showed few associations (Ritchie *et al.* 2016). Declining physical fitness over a 3-year period was associated with less brain volume at baseline in the LBC1936 sample, and did not diminish when covarying for education, social class, and health status (Aribisala *et al.* 2013), and longitudinally with age-related changes in brain structure (Ritchie *et al.* 2017). These results suggest that higher general fitness is protective against cognitive decline and brain ageing; this is important given that it is potentially modifiable.

Cardiovascular risk factors

The LBC studies have shown us that people's vascular health in later life are in part associated with early-life intelligence in addition to being associated with age-related cognitive change (McGurn *et al.* 2008). In the LBC cohorts, lifestyle-related risk factors for cardiovascular disease (CVD) – diabetes, low high-density lipoprotein (HDL) cholesterol, and being overweight/obese – were (independently) associated with poorer cognitive function at age 70, but statistical significance was lost following adjustment for age 11 IQ in each of these analyses (Corley *et al.* 2010a, 2015; Möttus *et al.* 2013; Aslan *et al.* 2015).

A higher childhood IQ was found to predict lower hypertension in adulthood in a sample comprising the LBC1921 and MIDSPAN study such that there was a 3.15 mmHg decrease in systolic blood pressure and a 1.5 mmHg decrease in diastolic blood pressure for each standard deviation increase in childhood IQ (Starr *et al.* 2004b). However, individual differences in childhood IQ only partly accounted for the association between hypertension and lower adult cognitive function, suggesting that lifestyle factors have a part to play. Lower ankle-brachial index, a frequently used measure of generalised atherosclerosis, was associated with worse cognitive performance in older age, independently of prior cognitive ability, especially in the oldest old (>85 years), possibly because of long-term exposure to atherosclerotic disease (Laukka *et al.* 2014). Multivariate analyses of the LBC1936 data suggest that diagnoses of CVD, hypertension or diabetes are not uniquely associated with cognitive performance (with the small exception of CVD and slower processing speed), or with cognitive decline, beyond the other predictors in the model (Tucker-Drob *et al.* 2014). Following adjustment for age 11 IQ, Ritchie *et al.* (2016) reported that the associations between CVD history and cognitive level in later life were attenuated by 90%.

In contrast, brain MRI studies in the LBC1936 indicate a small negative association between vascular risk factors (VRFs) and brain health, independently of prior ability. VRFs combined explained 1.4–2% of WMH variance, of which hypertension explained the most (Wardlaw *et al.* 2014). A lower HDL cholesterol level (Dickie *et al.* 2016) and poorer glycaemic control (in those who carry the *APOE* risk e4 allele) (Cox *et al.* 2017), were identified as important independent CVD risk predictors for the progression of WMH from age 73 to 76. Hypertension is associated with increased WMH but research carried out by the LBC team has indicated that they may be associated indirectly, via increased arterial stiffness (Aribisala *et al.* 2014).

The current prevailing view is that VRFs are potential aetiological factors for cognitive decline but that the association is age-dependent. For some VRFs, such as obesity, hypertension and hypercholesterolaemia, it is mid-life levels that seem to be more important than those measured at older ages for cognitive outcomes (Ballard *et al.* 2011; Qiu & Fratiglioni, 2015). Many clinical trials and epidemiological studies, including the LBCs, have been conducted among older adults >65 years when VRFs probably no longer act as risk factors and might be more likely to be modified by age-related concomitant disease.

Medications

Taking a greater number of medications is associated with a relative worsening of cognitive function from childhood to old age, explaining about 2.2% of the variance in cognitive change in the LBC1921 (Starr *et al.* 2004a). The total number of medications prescribed is a proxy indicator of disease burden, and, therefore, it is unclear whether it is the drugs themselves or the underlying disease for which they are prescribed that is causing the relative decline in IQ. In the same sample, however, taking statins, as indicated for CVD, was associated with a relative improvement in cognitive change across the life span, explaining about 2.8% of the variance (Starr *et al.* 2004a). Statin users in both LBC cohorts had lower childhood IQs, but the cross-sectional associations with cognitive function at age 70 in the LBC1936 were not robust in the final models, which adjusted for total cholesterol levels (Corley *et al.* 2015). In other literature, there is no consistent epidemiological evidence that exists for an association of cognitive decline with statins, anti-hypertensive medications or anti-inflammatory drugs (Davignus *et al.* 2010).

Health literacy

Health literacy was related, in the LBC1936, to childhood IQ and to IQ change from age 11 to 70, independently of SES, education, personality, and with worse general fitness, greater body mass index (BMI) and fewer natural teeth (Murray *et al.* 2011; Möttus *et al.* 2014). Both studies found that health literacy is related to general (not health-specific) cognitive differences, and therefore raise the possibility that 'health literacy' measures are little more than cognitive ability measures. The results of Möttus *et al.* suggest that health literacy measures do not add additional variance to the already present cognitive–health associations. Lifelong health may be associated with health literacy via the effect of general cognitive abilities on health knowledge and health management, of the sort an individual may require when diagnosed with an illness.

Biomedical factors

Allostatic load (AL)

AL has been proposed as a general framework for understanding the cumulative effects of life stress on individuals. Greater AL, which we and others have tried to capture as a compendium measure of a range of inflammatory, cardiovascular, and metabolic measures (e.g. Booth *et al.* 2013b), was associated in LBC1936 with poorer general cognitive ability, processing speed and knowledge, but not memory or non-verbal reasoning, and with brain volume measures (especially lower white matter volume) (Booth *et al.* 2015). The associations of AL with cognitive abilities were not mediated by the brain volume measures. AL at age 73 was associated with IQ scores at age 11 but did not predict cognitive change from age 11 to 73. In this first study to consider AL, cognitive ability and neuroimaging measures of brain volume, the results suggest that the cumulative wear and tear on the body from a lifetime of stress responsivity is associated with both brain structure and cognitive ability in early- and later life but not with cognitive change from childhood to the early 70s.

Elevated levels of salivary cortisol (often considered an important component of AL) were related in a subsample of the LBC1936 to poorer lifetime cognitive change, but only for levels taken in response to a mild psychological stressor, and not for diurnal levels (Cox *et al.* 2015a, b, 2017). This effect was significantly mediated via poorer white matter microstructure, but was unrelated to differences in hippocampal volume or shape.

A potential contributor to AL is infection from the cytomegalovirus (CMV). The LBC team reported that significant inverse CMV infection and cognitive ability associations were confounded by early-life cognitive, demographic and environmental factors (Gow *et al.* 2013b). In those who were CMV-infected, however, higher CMV antibody level was significantly associated with lower general cognitive ability and processing speed, accounting for around 1–2% of the variance, even after controlling for potential confounds. This indicates a potentially detrimental effect (via lifelong wear and tear) of increased antibody response rather than CMV infection *per se*.

Other biomedical factors

Few other biomedical factors examined in the cohorts have yielded robust associations with cognitive ageing. Research covering inflammation (Luciano *et al.* 2009c; Aribisala *et al.* 2014), thyroid function (Booth *et al.* 2013a), renal function (Munang *et al.* 2007), telomere length (Harris *et al.* 2006, 2012, 2016b), and retinal

blood vessel parameters (Patton *et al.* 2007; Henderson *et al.* 2011; Laude *et al.* 2013; McGrory *et al.* 2016) all show weak-to-null associations with the level and change of cognitive domains or a variety of brain measures. Of those that were initially significant, many became non-significant or were markedly attenuated following adjustment for childhood IQ scores, i.e. they are examples of confounding or reverse causation. The association between inflammatory markers (particularly fibrinogen) and processing speed was an exception; significance was maintained in the presence of childhood IQ and/or CVD risk factor adjustments. This might reflect variation in physiological integrity (Luciano *et al.* 2009c). However, inflammatory processes, long implicated in cognitive decline and the development of mild cognitive impairment (MCI) and dementia, were only weakly associated with markers of cerebral small vessel disease (Aribisala *et al.* 2014).

Genetics and environment: a lifelong interaction

Accepting the importance of both genetic and environmental contributions to people's differences in cognitive ageing acknowledges their interplay across the life course and constitutes a new challenge for future research. Indeed, there is moderate-to-strong heritability of lifestyle factors that is stable over age (McGue *et al.* 2014), unsurprising, given that most behavioural characteristics are (partly) inherited. However, genetic influences can be modified by physiological and environmental influences, and these may play a larger role in the expression of cognitive impairments (Mortimer *et al.* 2005; Stern, 2012). Alcohol (Ritchie *et al.* 2014) and glycaemic control (Cox *et al.* 2017) have been highlighted here as potential targets for mitigating cognitive and brain ageing in those who fall into a risk group with a greater genetic predisposition towards such deleterious effects. Heritability should not be erroneously interpreted as evidence for unalterable genetic determination of behaviour. An illustration of the variable determinacy of genetic factors was the LBC1936 study in which polygenic scores for type 2 diabetes were more strongly associated with glycated haemoglobin in those with lower childhood IQ scores when compared with higher IQ scorers (Möttus *et al.* 2015). Behavioural change may be challenging, but it is possible either by individuals or by clinicians, as part of a delivered health-care intervention.

A multivariate approach to cognitive and brain ageing

Many of the studies reported above, take in essence, a univariate approach; that is, given that they do have

some appropriate covariates, they focus mostly on a single potential determinant of cognitive level or change. Of course, some of these potential determinants will themselves be associated, and so we cannot simply make a list of determinants and assume they will have additive associations. Therefore, the LBC studies have recently taken a more complex multivariate approach in which important predictors were modelled simultaneously on cognitive level (age 70) and change (between ages 70 and 76 in LBC1936) using latent growth curve models (Ritchie *et al.* 2016). In these analyses, univariate correlates of age 70 cognitive ability level (at the same time measuring lifetime cognitive change from age 11 to age 70) were many; those individuals with better general cognitive function at age 70 were younger when tested, had higher childhood intelligence, were more educated, were from more professional occupational classes, lived in more affluent areas, were fitter (on all three performance indicators), had lower BMI, were less likely to smoke, and were less likely to have cardio-metabolic illness. Carriers of the *APOE* e4 allele also performed less well on the visuospatial and speed domains. Following multivariate adjustment, however, only age, sex (female), higher age 11 IQ, more education, and better forced expiratory volume remained significant correlates of better general cognitive ability level. Importantly, none of the social or health variables remained significantly associated with cognitive ability level when modelled together with other covariates (and correcting for multiple comparisons).

Likewise, few predictors of less cognitive decline between the ages 70 and 76 in LBC1936 survived multivariate modelling, with the exception of *APOE* e4 non-carrier status, sex (female) and better grip strength. The predictors included in these analyses together accounted for 80.5% of the variance in cognitive level, and 16.1% of the variance in general cognitive decline.

Predictors of longitudinal changes in brain structure have rarely been examined using multiple heterogeneous variables simultaneously. In a recent multivariate investigation of neurostructural changes in the LBC1936 (Ritchie *et al.* 2017), many variables significantly correlated with baseline (age 73) brain structure, but few could account for significant heterogeneity in subsequent brain change (between 73 and 76). Better physical fitness and *APOE* e4 non-carrier status were the most consistent predictors of differential rates of brain ageing, though effect sizes were small. Education and prior intelligence were correlates of brain structure, but not related longitudinally to ageing-related changes in brain structure. The distinction between cross-sectional and longitudinal analyses of brain ageing is important: in cross-sectional studies, it is not possible

to differentiate between developmental processes that occur in earlier periods of life from effects that are specifically ageing-related (Tucker-Drob & Salthouse, 2011). Subsequent waves of the LBC1936 will bring more occasions of brain imaging over longer periods, providing a larger target for our predictors of differential brain ageing.

Collectively, the LBC studies suggest that a number of environmental factors may have small associations with cognitive abilities in later life. It is likely that many of these factors covary. If there are multiple univariate predictors, and few that survive the multivariate model, then one possibility is that some might mediate others via testable pathways. To understand the data more fully requires techniques such as structural equation modelling, which can explicitly explore mediation effects, latent traits and multiple outcome variables; there are many examples of these in the LBC reports. Multivariate techniques – considering many predictors together – may provide a more realistic consideration of the predictors of cognitive and brain ageing.

Discussion

In this paper, we have described some of the follow-up studies of people who took part in the SMS of 1932 and 1947, and given overviews of ~100 LBC papers that pertain to cognitive ageing across the life course, and to brain ageing, in the context of some existing literature. Broadly, the LBC studies have found two things from the cognitive ability test scores at age 11 years: first, those with higher childhood intelligence tend to be healthier and more cognitively able in old age; second, that some people got to older age with better or worse cognitive function than one would predict given their ability at age 11. Observations by the LBC studies over the past 15 or so years have helped to identify which candidate determinants are associated with these differences in lifetime cognitive resilience and brain and general health, across genetic, socio-demographic, health, and lifestyle domains.

Overall, the findings support the link suggested by Juvenal (first to second century AD) between a healthy body and a healthy mind. An older body, which is physiologically fitter and engages in regular physical activity, is associated with a higher childhood IQ score, tends to experience less cognitive change over the life course, and less cognitive decline and deleterious brain changes within old age. VRFs, such as smoking, hypertension and cholesterol, and greater cumulative AL, may have important associations with cortical thinning, brain white matter integrity, and brain atrophy in later life. All of this is in line with research, which provides evidence that the ageing brain retains a considerable functional plasticity which

is very much dependent on the interaction of individuals with their environment (see Mora, 2013).

The multivariate results to emerge from work on the cohorts suggest that when many potential predictors are modelled simultaneously, only a subset of correlates of cognitive level and brain structure are predictive of differences in cognitive and brain ageing, at statistically significant levels (Ritchie *et al.* 2016; 2017). One possible reason for stronger results in the cross-sectional data is that determinants have had most of the life course to contribute to brain and cognitive variance. In the change analyses within older age, we report only 3-year change in MRI data, and 6-year change in cognitive markers. Even though it is during a period of time when change over time is greater, it is still hard reliably to detect very subtle changes over such a short period. Nonetheless, our findings are complementary to those of systematic reviews and meta-analyses (see Daviglus *et al.* 2010; Plassman *et al.* 2010), which report that few observational studies had sufficient evidence from which to draw conclusions about particular behavioural, social and economic factors, and their association with cognitive decline. Where there are few reports of significant associations with cognitive change, then interventions may be less likely to succeed. However, where there are more consistent significant associations with cognitive change, given that observational studies cannot address causality, then even this does not necessarily mean we have identified a target for intervention.

Strengths and limitations

As birth cohort samples (who share the same year of birth), there is a natural control for much of the confounding effects of chronological age. The LBCs are unusually well-phenotyped samples, which benefit from multiple later-life waves of follow-up. The use of multimodal neuroimaging in concert with these other data can help elucidate some potential underlying mechanisms. A major strength of these studies is the availability of cognitive data at distinct time points (age 11 and later life) creating a rare opportunity to distinguish factors that might have a true effect on later-life cognitive ability – possible causal factors – from the potentially confounded factors (i.e. confounded by childhood IQ). Ideally, the influence of premorbid cognitive ability on cognitive ability in later life is best assessed by using the earliest possible direct measure of cognitive ability to avoid the ‘contamination’ by lifestyle, adult SES, and health factors that may affect cognitive abilities, even by early adulthood. Childhood cognitive ability scores are rare in studies of cognitive ageing and shine fresh light on aspects rarely addressed by other observational investigations.

The LBC studies have limitations. Given that our samples are self-selecting, they are biased towards high-functioning, well-educated, motivated volunteers, as is the case in many studies of cognitive ageing. Nonetheless, potential incipient cognitive impairment among participants, as yet clinically undetected, must be acknowledged. Although the LBC studies can measure relative cognitive change from childhood to older age, they have not documented the cognitive changes that occurred from childhood to early adulthood and from there to age 70 (LBC1936) or age 79 (LBC1921). It is possible that changes over these periods of the life course are associated more strongly with some of the proposed predictors. Some lifestyle behaviours including those that influence cardiovascular and metabolic risk may be most influential in midlife compared with late life (Kuh & Cooper, 1992; Carlson *et al.* 2008; Lee *et al.* 2010; Rovio *et al.* 2010). A particularly salient example of this is cholesterol (van Vliet *et al.* 2009). Finally, due to the synergistic effect of lifestyle factors, the extent to which the apparent effects of one health behaviour is attributable to (i.e. confounded or mediated by) another is unclear. For example, other studies show that physical activity and exercise are increased by active social networks (Leroux *et al.* 2012), and that smokers tend to have poorer dietary choices than non-smokers (Woodward *et al.* 1994). The focus on single associates/interventions may underestimate the effect of multimodal or combined approaches.

Confounding and reverse causation

One of the most consistent observations to emerge from the LBC studies is that the apparent causes of cognitive ageing may not be causes at all. Some of the putative health and lifestyle determinants of cognitive ageing differences are themselves predicted by long-ago measured childhood differences in intelligence (Whalley *et al.* 2006; Deary *et al.* 2009a; Deary, 2010). Therefore, a cross-sectional association between a variable such as diet and cognitive ability in older age might – in part or whole – be the result of childhood IQ predicting both. Physical function and disease states may in part be acting as proxy markers of lower childhood IQ, and this might account for portions of the variance in cognitive ability years later. The repeated demonstration of confounding by prior ability across multiple areas in the LBC studies covering lifestyle, health and biomedical markers, and MRI indexes of brain health, is relevant to the debate on what is called ‘differential preservation’ *v.* ‘preserved differentiation’ (Salthouse, 2006; Bielak, 2010; Gow *et al.* 2012d; Bielak *et al.* 2014). Central to this theory is the critical question of whether certain factors alter

the trajectory of age-related cognitive decline (differential preservation) or are associated with enhanced baseline cognitive ability (preserved differentiation). In searching for determinants of cognitive ageing, researchers aim to identify evidence of differential preservation. This important distinction highlights the need to design studies that will shed light on directionality when empirically feasible.

However, does childhood IQ represent a true causal link in some of the reported associations? One could argue that confounding by prior IQ does not necessarily rule out a protective or adverse effect of a predictor. Twin studies provide some reassurance for this (e.g. Crowe *et al.* 2003; Gatz *et al.* 2006). The role of lifetime IQ might, more realistically, be one of substantive causation; that is, higher IQ might have a direct impact on the uptake of healthy behaviours via better health literacy, better decision making, and a greater understanding of the consequences of one’s behaviour. In essence, higher IQ individuals may be more likely to engage in a lifestyle that is protective against cognitive decline. With these theoretical considerations in mind, it seems most plausible that there is a dynamic cycle involving IQ, self-management of health, and ultimate cognitive outcomes.

Another possibility is that associations between candidate determinants and cognitive health may be caused by some third confounding variable or set of variables and may be the result of a more basic factor(s) affecting both the apparent cause and effect. Thus, many researchers are interested in whether there are general ageing effects, known as the ‘common cause’ theory of ageing that occur across cognitive and physical modalities attributable to core biological processes that deteriorate with age (Schaie, 2005). However, recent evidence from the LBC studies has cast doubt on this idea. Not only did physical functions appear to age separately, there was also no compelling evidence for coupled change across cognitive and physical functions in later life (Deary *et al.* 2011; Ritchie *et al.* 2016). Contrary to the ‘common cause’ hypothesis, these findings suggest multiple largely independent causes of ageing across bodily systems.

Marginal gains: a modest multivariate recipe for healthy cognitive ageing

From our LBC results overall, it seems likely that, other than intelligence scores from youth, a large number of genetic and other predictors have small associations with cognitive efficiency in later life. The most consistently cited factors linked to cognitive ability or ageing – smoking, physical activity, and variation in the *APOE* gene – have effect sizes of the same magnitude, often accounting for 1–2% or less of the variance in

cognitive outcomes (Whalley *et al.* 2005; Deary *et al.* 2009a, b). Though small in statistical terms, modifying some of such factors or their downstream effects could have substantial benefits at population levels. It is important to know what these effects are, so we can discover the combination of factors that might help people age better.

In terms of preserving mental abilities or delaying cognitive decline, the available evidence suggests that there is no magic bullet. Thus, the small effects we find, even if replicable and causal, might be useful at the population level, but are not necessarily good predictors at an individual level. Perhaps a helpful way of thinking about successful cognitive ageing can be gained from the theory of marginal gains, a concept that has become commonplace in the world of elite sport (see Clear, 2015, <http://jamesclear.com/marginal-gains>). The principle behind the marginal gains idea is that if you improve in every variable (or lifestyle factor) underpinning or influencing your performance (in our case, cognitive abilities) by just 1% or so, then, cumulatively, you get a significant improvement, or an 'aggregate of marginal gains'. In terms of Team Sky (GB's professional cycling team), every aspect of cycling was decomposed and improved. A programme of small changes was implemented from addressing nutrition, to the ergonomics of the bike seat, clothing, bedding, sleeping position, and even handwashing techniques to prevent infections. Within 3 years, the team had won three Tour de France competitions and 70% of all track cycling gold medals at the 2012 Olympic Games.

Mutatis mutandis, an approach, which recognises the complexity of the factors influencing brain and cognitive health in later life might provide a useful framework for promoting healthy cognitive ageing. At an individual level, it encourages a proactive approach, in finding and exploiting small margins for improvement at every stage. Small changes, as suggested by marginal gains theory, may help individuals to overcome the perceived barriers to behaviour change (e.g. self-confidence and self-efficacy), which often prevent people from embarking on a new and often overwhelming regime. Clearly, some contributions to cognitive ageing are more open to interventions than others. Over time, whereas it may not be apparent, each small positive lifestyle change, such as going out for a walk every day, could add up to a significant advantage in terms of improving physical health (reducing risk of hypertension, dyslipidemia and metabolic syndrome, obesity), mental health (loneliness and social isolation, depression) and cognitive health, and this is likely to have a cumulative population-level effect. Tailoring interventions that take into account individual differences in risk genotypes might help to target an optimal set of gains. The 'magic' may lie in

the accumulation of many such gains over time to put individuals, in elite sporting terms, 'ahead of the opposition'. Let us not fail to mention that 'marginal gains' would be a life-course approach; e.g. given that childhood cognitive ability accounts for about half of the variance in cognitive function in older age, then any effective boost to cognitive level in youth will be some insurance against descending to lower cognitive levels in older age.

More to life than cognitive function

Cognitive function is critical for mental and physical health. However, happiness and satisfaction with life are also key indices of successful ageing. Life satisfaction in the cohorts was unrelated to IQ in either childhood or late adulthood or to cognitive change over the intervening period. It may be that an individual's subjective wellbeing comes from having sufficient cognitive ability for the important aspects of one's life (Gow *et al.* 2005). Life satisfaction is also partly a result of personality factors, mood states (Brett *et al.* 2012), and social factors, such as having a strong social network (Gow *et al.* 2007). Although space prohibits more detailed discussion, some of our reports in the LBCs have focussed on health and happiness/well-being in older age, both quantitatively (Zammit *et al.* 2012, 2014) and qualitatively (Carpentieri *et al.* 2016, 2017; Lapsley *et al.* 2016).

Conclusions

People start off at different cognitive levels and vary in how much their cognitive functions change with age, even in those who do not have dementia or other neurodegenerative changes. The LBC studies suggest that cognitive and brain ageing are most likely the result of a multivariate accumulation of disparate influences. Potential risk and protective factors include contributions from genetic, medical, lifestyle and psychosocial domains (see Box 1). Identifying these factors is a key priority for research aiming to address the challenges associated with demographic ageing. Lifestyle factors can be promoted or discouraged, as appropriate, via interventions aimed at delaying, ameliorating or even reversing age-related cognitive decline. We must hope that even genetic contributions, linked to cognitive change and decline, have discoverable mechanisms which might afford interventions. But, whereas predictors of cognitive level in old age are numerous, predictors of cognitive decline's slope – that is, correlates of differential preservation – have, as yet, been few and far between, often with very small effect sizes.

Further longitudinal investigations of potentially malleable factors and cognitive decline in the LBC

Box 1. Key points

- **A Good Start** – Intelligence differences in youth are the largest contributor to cognitive ability differences in older age.
- **Stable Minds** – Intelligence differences measured at age 11 are relatively stable across the life course, even into the ninth decade.
- **Genetic Contributions** – Common genetic variants account for about 24% of change in general cognitive ability between youth and old age. Variation in *APOE* is part of this.
- **Few Clear Determinants of Change** – There are multiple correlates of cognitive ability *level* in later life but as-yet few reliable genetic, lifestyle, health and psychosocial predictors of cognitive *change*.
- **Clearest Results** – The most consistently-cited lifestyle and health factors linked to brain and cognitive ability or cognitive ageing are smoking, physical activity and fitness, and allostatic load.
- **Social Factors** – Education and occupational complexity might also contribute to healthy cognitive ageing in terms of level but not of slope.
- **Confounding/reverse causation** – Some factors, such as body mass index, diet, and inflammation, are associated with cognitive function in older age but these associations largely disappear after adjusting for childhood IQ, implying that the latter might be a confounder that is associated to the supposed exposure.
- **Cortical Disconnection** – Declines in brain white matter microstructure are coupled with declines in cognitive ability in some, but not all, cognitive domains.
- **Gene × Environment** – Some people may be more predisposed to the possible negative cognitive effects of bio-behavioural factors (such as alcohol and poor glycaemic control).
- **Marginal Gains** – Successful cognitive and brain ageing is most probably achieved by optimising a number of factors linked to brain and cognitive measures, which each only account for a small % of the variance.
- **Last Cautions** – These points are largely based on observational and not intervention studies, and also require independent replication.

are in progress, affording greater power, reliably to detect these subtle associations due to longer follow-up periods and a greater number of sampling points. We also continue to expand our information sources on the participants, which now includes whole-genome sequencing on almost all participants, DNA methylation testing on most participants on most waves, gene expression on LBC1936 at 70 and 76, post-mortem brain tissue (Henstridge *et al.* 2015), stem cells, lifetime addresses on LBC1936 to assess environmental exposures, and National Health Service medical records linkage.

Future research should continue to examine predictors of actual cognitive changes rather than simple levels of performance, because the latter are ambiguous with respect to the temporality and direction of causation. At the present time, in order to enhance one's chances of healthy cognitive ageing, the stronger cases may be made for being physically active and fit, keeping one's health in check (and keeping AL low), and avoiding smoking; and perhaps less strong cases may be also made for learning a new language,

increasing one's social network, and eating healthy. Small and manageable improvements across a broad range of behaviours have potential for improving long-term cognitive and brain outcomes.

Supplementary Material

The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291717001489>.

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Declaration of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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