



THE UNIVERSITY *of* EDINBURGH
Edinburgh Medical School

Biomedical Sciences

Title of Assessment: **Case Study**

Name: **Eleanor Conole**

Matriculation Number: **s1876505**

Course Name: **Wellcome Trust 4-year PhD in Translational Neuroscience**

Word count (excluding references): 2,304

CASE STUDY: accelerated cognitive ageing following lacunar stroke and recurrent myocardial infarctions

ELEANOR L.S. CONOLE^{1,2,3*}, SIMON R. COX¹, AND IAN J. DEARY¹

¹Lothian Birth Cohorts group, Department of Psychology, University of Edinburgh, Edinburgh EH8 9JZ, UK

²Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK

³Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh EH16 4SB, UK

*Corresponding author: eleanor.conole@ed.ac.uk

Compiled July 7, 2021

Reported here is a case of an individual participant of the Lothian Birth Cohort 1936 who had a lacunar ischaemic stroke, repeated heart attacks, and was found to have significantly lower total brain volume and cognitive ability relative to the rest of the cohort and a stroke subset. On closer inspection of his MRI, it is clear that the participant had significant small vessel disease pathology, with higher than average white matter hyperintensity burden and evidence of lacunar infarcts.

<http://dx.doi.org/10.1364/ao.XX.XXXXXX>

1. INTRODUCTION

Cognitive impairment and dementia are serious and disabling consequences of stroke. While lacunar strokes are arguably less likely to acutely affect cognition than larger cortical strokes, their association with cerebral small vessel disease (SVD) – the commonest vascular cause of dementia [1] – indicates that they might be symptomatic of a more insidious risk of cognitive decline. To investigate mechanisms of risk cognitive decline following lacunar stroke, in this case report, we review an individual participant of a longitudinal cohort study of ageing - the Lothian Birth Cohort 1936 (LBC1936) – who additionally presented with significant cardiac disease history.

14 2. LOTHIAN BIRTH COHORT

15 LBC1936 is a longitudinal study of ageing comprising 16 individuals born in 1936. Full details of the recruitment 17 procedures and tested protocols have been previously 18 published [2,3]. Participants have taken part in four waves 19 of testing in later life (at mean ages 70, 73, 76 and 79 years). 20 At each wave, subjects were interviewed and tested 21 individually by a trained psychologist and a research nurse 22 during a visit to the Wellcome Trust Clinical Research 23 Facility (<http://www.wtcrf.ed.ac.uk>), Western General 24 Hospital, Edinburgh. This visit included cognitive and 25 other psychological assessments, physical examinations, 26 extensive history taking and blood analyses. From Wave 27 2 onwards, neuroimaging data is also available.

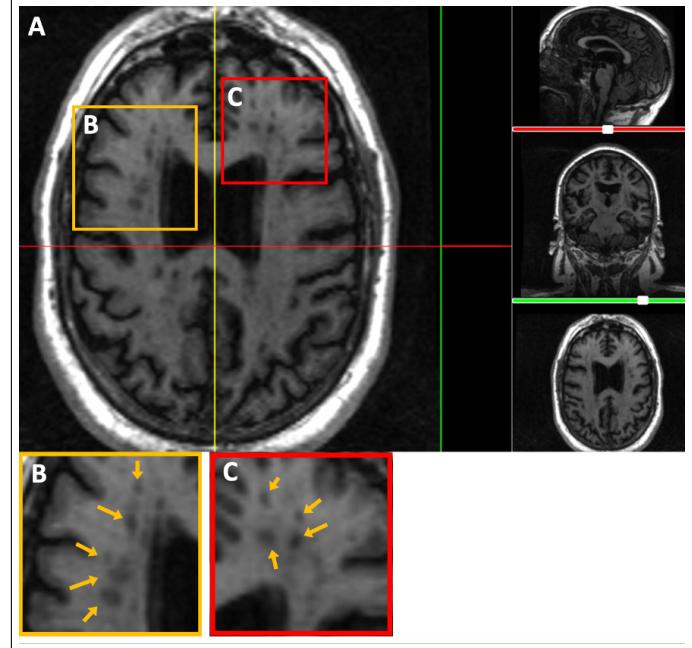


Fig. 1. Lacunar infarcts seen on T1-weighted MRI (arrows) taken at age 73 for LBC1936 Case Study Participant. MRI data, structural T1-(voxel size = 1 × 1 × 1.3mm), were acquired on a 1.5T GE Signa HDx clinical scanner (General Electric, Milwaukee, WI, USA), according to an open-access protocol [3]

23 **A. Life History**

24 The identified participant had 10 years of full-time education, leaving school aged 15. He took statutory retirement aged
 25 48 following 24 years working as a bus driver. He was married until the 4th Wave of the study, following his wife's
 26 passing. The participant was recruited to the LBC1936 study aged 71 years.

27 **B. Death**

28 The participant completed 4 waves of data collection as part of the LBC1936 prior to his death aged 80.7. His last
 29 LBC1936 testing appointment was approximately 3 months prior to his death. The participant's primary cause of death
 30 was myocardial infarction, and secondary causes were listed as complete heart block requiring pacemaker; ventricular
 31 tachycardia; type II diabetes mellitus.

32 **2. BRAIN HEALTH**

33 **A. Stroke history**

34 The participant reported history stroke before his enrolment to the study, but did not provide information on stroke-sub
 35 type. He reported that he had a number of transient ischemic attacks (TIAs) at home (over three), and had '*a bar fitted*
 36 *to stop falling out of bed*'. When interviewed at Wave 2, age 73.7 years, the participant reported that he had frequent
 37 mini-strokes in past but none for past 4 years, until a more serious stroke 5-6 weeks ago, describing to the nurse at the
 38 time of interview that this stroke resulted in '*weakness down one side of my body, my left arm and leg*'.

39 **B. Neuroimaging findings**

40 The participant had evidence of lacunar infarcts on his T1 MRI scan taken at age 73 (see Figure 1) and higher than average
 41 volume of white matter hyperintensities for his age (40ml, LBC1936 mean = 15ml). The participant had notably lower
 42 brain grey matter and white matter volumes, both compared to the average of participants in the cohort and in a subset
 43 of participants who had self-reported history of stroke (Figure 2). In addition to this, the participant had significantly
 44 lower fractional anisotropy in various white matter tracts (Figure 3) compared to the average of the LBC1936 cohort.

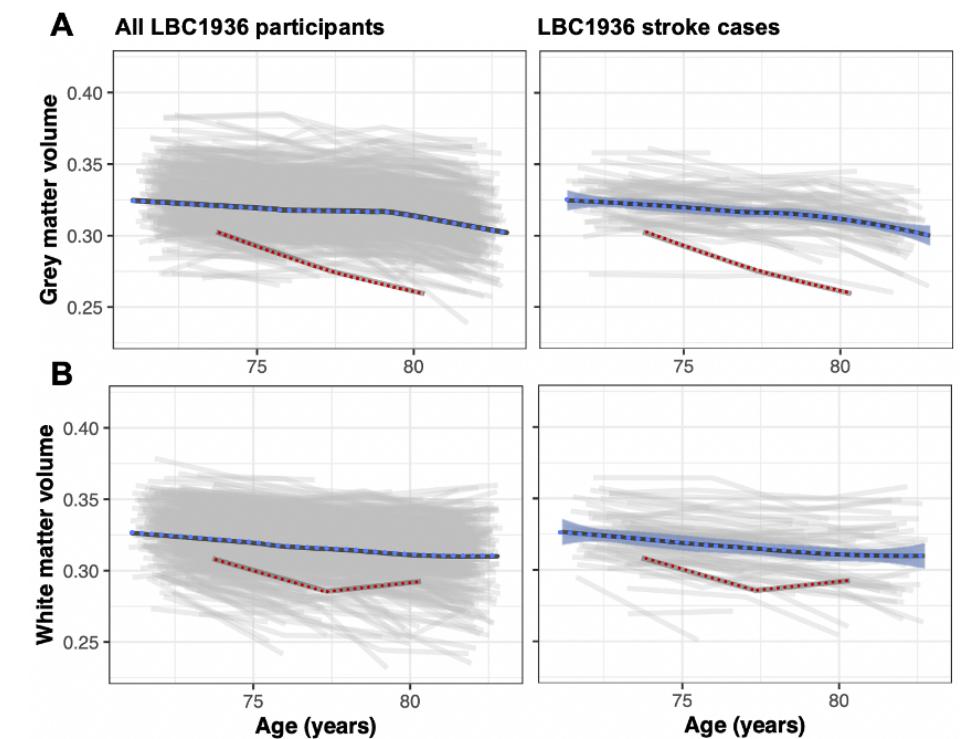
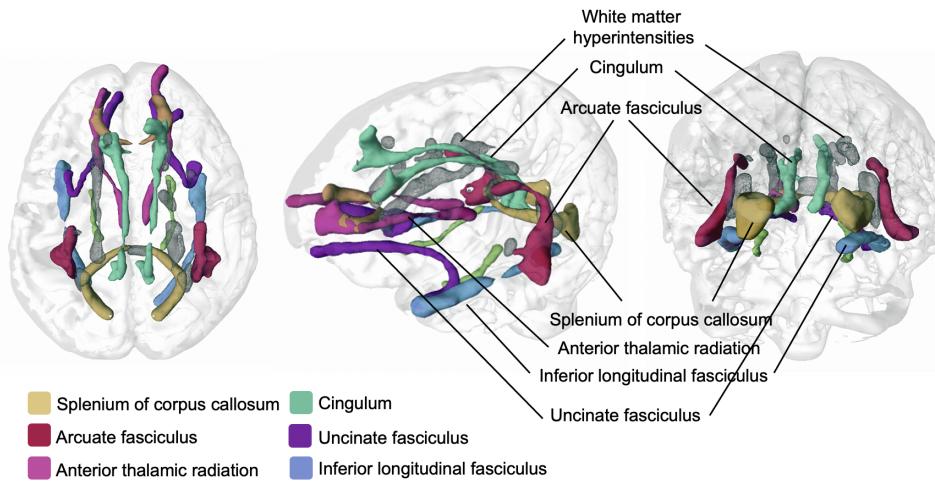


Fig. 2. Age-related decline brain grey and white matter volumes for all participants (right) and a subset of participants with self-reported history of stroke (left). Changes in neuroimaging metrics (y-axis; volume expressed as a ratio of ICV) are shown as age trajectories (x-axis; years) for each participant. Mean brain matter volume score with age plotted as a regression allowing a quadratic term, with 95% confidence intervals, are shown for all participants (blue dotted line) and the individual of interest (red dotted line).

45 **C. Reduced white matter tract integrity****Table 1. Fractional anisotropy values for participant and mean (SD) for LBC1936 cohort.**

WM tract FA	Individual's score	LBC1936 average (SD)
Splenium of corpus callosum	0.388	0.511 (0.066)
Left Arcuate Fasciculus	0.408	0.436 (0.039)
Right Arcuate Fasciculus	0.393	0.415 (0.039)
Left Anterior Thalamic Radiation	0.302	0.324 (0.032)
Right Anterior Thalamic Radiation	0.310	0.335 (0.035)
Left Rostral Cingulum	0.400	0.437 (0.058)
Right Rostral Cingulum	0.369	0.41 (0.047)
Left Ventral Cingulum	0.281	0.276 (0.035)
Right Ventral Cingulum	0.267	0.284 (0.043)
Left Uncinate fasciculus	0.301	0.325 (0.034)
Right Uncinate fasciculus	0.304	0.32 (0.031)
Left Inf. Longitudinal Fasciculus	0.289	0.386 (0.051)
Right Inf. Longitudinal Fasciculus	0.299	0.377 (0.048)

**Fig. 3.** illustration of the respective white matter tracts measured using probabilistic neighbourhood tractography the Case Study participant, with individual white matter tracts illustrated in relative colours. White matter hyperintensities are outlined in grey.46 **D. Cognition**

47 The participant had a below average age11IQ and age70I1Q score and age 70, at Wave 1 of the study, had lower than
 48 average scorings on a variety of cognitive tests compared to the rest of the study sample (see Figure2B). The participant
 49 did not participate in cognitive testing at subsequent waves due to partial blindness from cataracts. While we cannot
 50 compare the participant's cognitive trajectory, we can examine the participant's scores cross-sectionally at Wave 1 and the
 51 participant's MMSE score across all four waves of testing (see Table2). The mini-mental state examination (MMSE) is a
 52 30-point questionnaire that is typically used to measure cognitive impairment and screen for dementia, where a score of
 53 <24 points is indicative of cognitive impairment [3]. At enrolment, the participant had a healthy score of 29, however
 54 by wave 3 of the study, age 77, the participant's cognition had deteriorated to a below average score of 18, crossing the
 55 threshold for mild cognitive impairment.

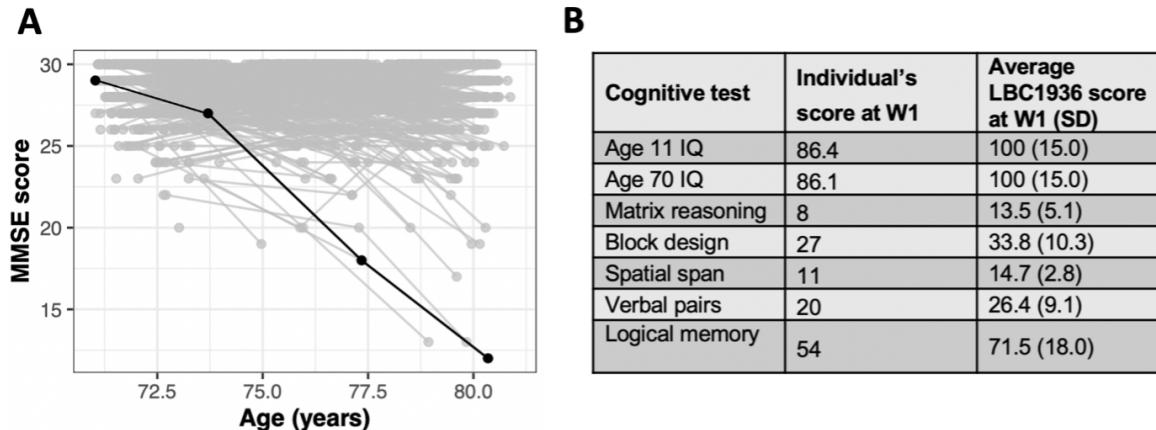


Fig. 4. Decline in cognitive function. (A) Average ageing trajectories for LBC1936 MMSE scores; each point on the graph shows the data for one individual at each wave of the study. Individuals who returned for follow-up waves have their points connected with a grey line. The black line is the study participant. (B) Cross-sectional comparison of case study participant's cognitive test scores with the LBC1936 average at Wave 2 of the study.

56 3. HEALTH

57 A. Cardiac health

58 The participant had significant cardiac history and had suffered two heart attacks in 1984 and 2000 by the time of
 59 enrolment to the study age 71 years. Following the second heart attack, he had a quadruple bypass on his left ventricle in
 60 2000, and at his last ECG recording he had slight abnormal heart rhythm and irregularity. At the next wave of the study,
 61 the participant had developed angina for which he took glyceryl trinitrate and had developed pernicious anaemia. By
 62 Wave 3 of the study, the participant had had a 3rd myocardial infarction (MI). By Wave 4, the participant had had no
 63 further MIs and his angina was under control; he reported that he had not used his glyceryl trinitrate spray for the last 18
 64 months.

65 B. Physical health and lifestyle

66 At the time of enrolment to the LBC1936 study, age 70, the participant was classified as clinically obese with a BMI of
 67 36.43kgm². This increased to 38.29 kgm² by age 73 years, which crossed into the category of morbidly obese (Figure
 68 5B). It is likely that physical inactivity contributed to this increase in weight as at the medical interview at Wave 2, the
 69 participant reported a significant reduction in his mobility owing to pains in his calves, resulting in an inability to walk
 70 long distances. The participant also complained of his right leg swelling after a vein was removed for his bypass surgery.
 71 Over the subsequent waves of testing at 77 and 80 years, the participant had lost weight, with his BMI decreasing to
 72 30.12 kgm² by Wave 4 of the study.

73 The participant was a current smoker at the time of enrolment, self-reporting that he smoked 45 cigarettes per day,
 74 by wave 3, this had increased to 100 cigarettes per day. The patient was taking aspirin (300 mg/day), atorvastatin
 75 (40 mg/day), an ACE inhibitor (perindopril, 5 mg/day), and a non-thiazide diuretic (indapamide, 1.5 mg/day). He
 76 intermittently took glyceryl trinitrate spray for angina following his heart-surgery in 2000.

77 The participant's physical health measures showed a decline over the four waves of testing. Measures of cardiovascular
 78 fitness (lung function tests, 6m walk time) and physical strength (grip strength) were used to monitor LBC1936 participants
 79 physical health with age. The participant's grip strength measures are presented in Figure 5C. At Wave 1 the participant's
 80 grip strength of 24kg was below the LBC1936 average for his age and sex (mean = 29.6kg, SD=10.2). An improvement in
 81 grip strength was seen between Wave 1 and Wave 2 of the study which could be credited to a learning effect, however
 82 this then steadily declined to well below average for his age and sex (18kg) by the last wave of testing. At Wave 3 of
 83 the study, at the age of 77.35, the participant self-reported that he had a diagnosis of rheumatoid arthritis and where he
 84 complained at the medical interview of slight arthritic tendencies in his hands, which may explain this sharp decline in
 85 this particular test of physical functioning.

86 The participant's lung function, as measured by FEV1/FVC ratio and PEF shows a similar slight improvement but
 87 then subsequent decline across the period of follow-up (Figure 5D and 5E). At Wave 1 the individual FEV1/FVC ratio
 88 was as to be expected for his age and sex (participant: 77.7%; LBC1936 mean: 78%), his FER showed slight improvement
 89 at Wave 3 of testing, but this rapidly dropped well below a value that is considered diagnostic for Chronic Obstructive

90 Pulmonary Disease (<70%) (16) by his final attendance. The participant's peak expiratory flow (PEF) was below average
 91 at Wave 1 (participant: 250L/min; LBC1936 mean = 272L/min). Again, this improved slightly only to then decline acutely
 92 by the final wave of testing.

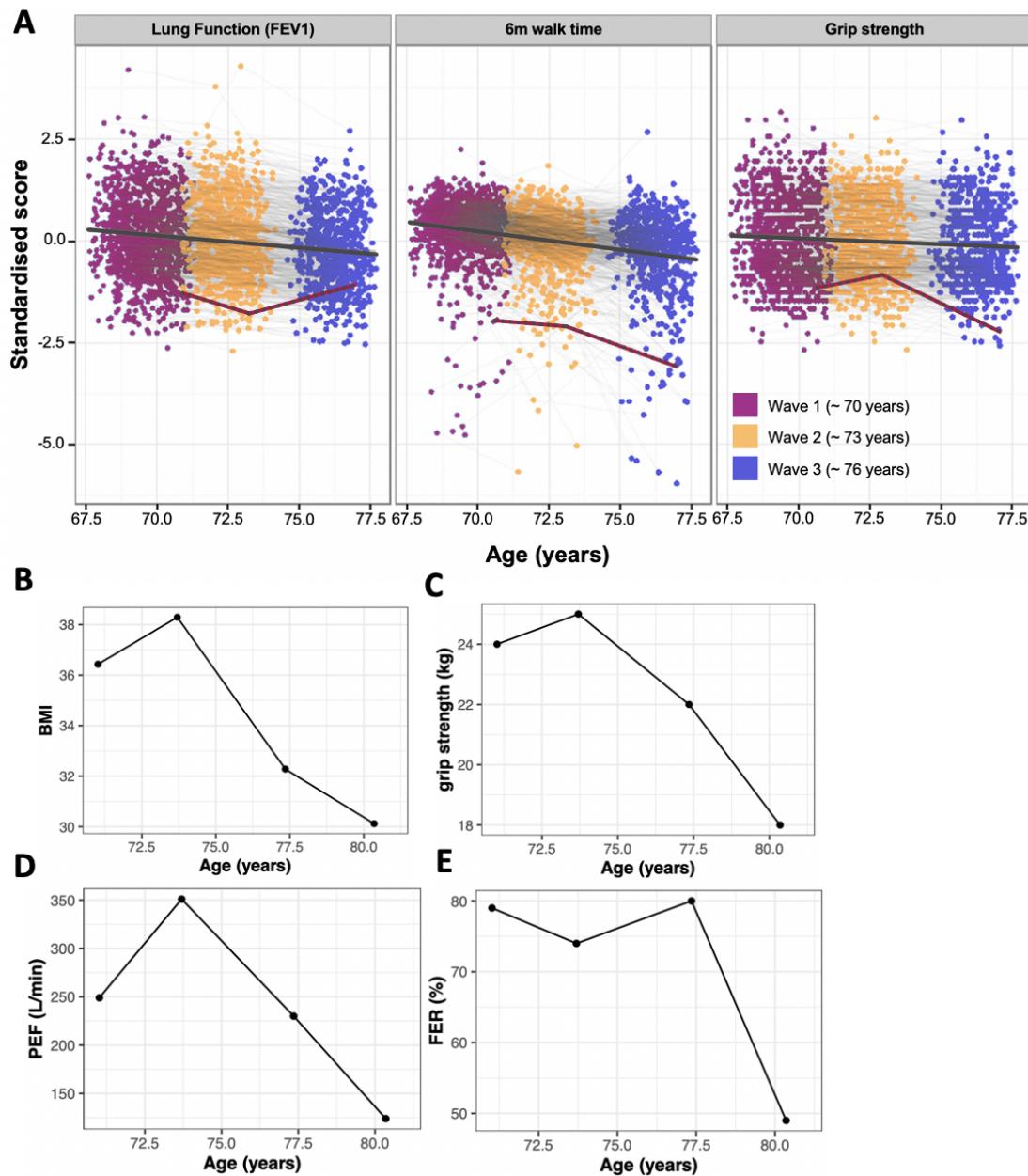


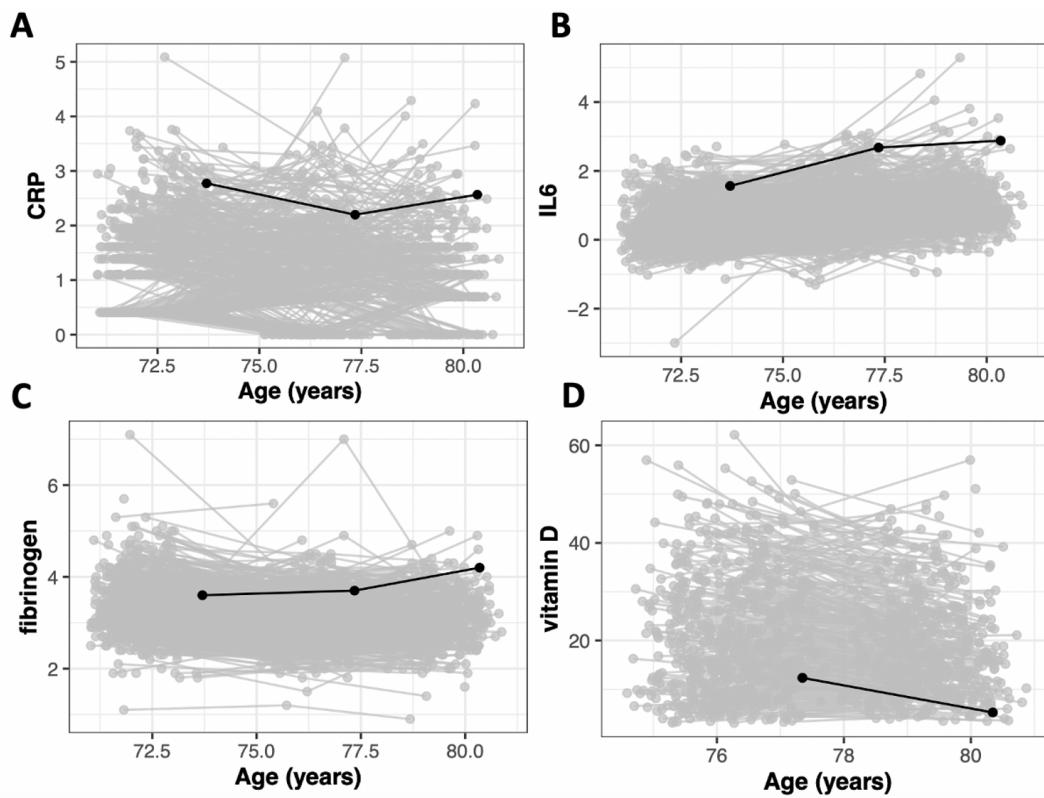
Fig. 5. Age-related change in three measures of physical fitness. (A) Average ageing trajectories for LBC1936; each point on the graph shows the data for one individual at the first (pink), second (yellow), and third (purple) follow-up waves. Individuals who returned for follow-up waves have their points connected with a grey line. The mean change across all three waves is illustrated by the grey line, whereas the change in the case study participant is illustrated in red dotted line. Note that all variables are standardised so that higher scores indicate higher levels of physical fitness. (B) Participant's BMI (kg/m^2) at all four Waves of testing. (C) Average Grip strength (kg) (for left and right hand) was measured using a North Coast Hydraulic Hand Dynamometer, JAMAR. (D) Peak expiratory flow (PEF). (E) Forced Expiratory Ratio (%), calculated as forced expiratory volume in one-second (FEV1)/ Forced vital capacity (FVC). Both lung function tests were measured using a Micro Medical Spirometer, each the best of three.

93 **C. Other conditions**

94 The participant was deaf with hearing aids and had cataracts and subsequent corrective surgery in both eyes by wave
 95 3 of the study. By wave 4 of the study the participant was registered partially blind. The participant additionally had
 96 hypertension and diabetes mellitus.

97 **D. Inflammation**

98 At the time of MRI scan wave 2, initial pertinent laboratory investigations revealed high inflammatory markers, two of
 which (IL6 and fibrinogen) increased as the participant ages as summarised in Figure 6.



99 **Fig. 6.** Age-related changes in inflammatory profiles. Average ageing trajectories for LBC1936 inflammatory protein levels; each point on the graph shows the data for one individual at each wave of the study. Individuals who returned for follow-up waves have their points connected with a grey line. The black line is the study participant (A) C-Reactive Protein; log(CRP) (B) Interleukin 6 levels, note y-axis displays log(IL6) scores (C)fibrinogen (D) vitamin D.

100 **4. DISCUSSION**

101 In this case report, we present an LBC1936 participant who experienced sharp cognitive and physical decline in the
 102 waves of testing prior to his death. We reflect on the presentation of lacunar infarcts on his MRI, physical and lifestyle
 103 factors that may have influenced cognitive functioning in order to understand his accelerated ageing trajectory.

104 The participant's exact history of stroke was unclear as information about his medical history was gleaned off self-
 105 report, and what he chose to disclose at the time of interview at each wave of the study. Over the 10 years that the
 106 participant took part in the study, he mentioned frequent TIAs (a regular enough occurrence that a bar was fitted to stop
 107 him falling out of bed) and a more serious stroke 5 weeks prior to his imaging assessment at Wave 2 (age 73.7 years). On
 108 this occasion, it is most likely that he suffered from lacunar stroke. This is suspected from his comments of '*I had weakness*
 109 *down one side of my body, my left arm and leg*', a description consistent with *pure motor hemiparesis*, and the presentation of
 110 lacunar infarcts on his MRI – functional and structural hallmarks of lacunar stroke [4].

111 On closer inspection of his MRI at age 73, it is clear that the participant had some small-vessel disease aetiology, with
 112 presentation of characteristic hypointense lacunar infarcts on his T1 MRI scan (see figure 1) and higher than average
 113 volume of white matter hyperintensities for his age (40ml, LBC1936 mean = 15ml). Lacunar infarcts are characterised as
 114 small (<15mm in diameter) subcortical clots that result from the presumed occlusion of individual arteries in the brain

[5]. They are estimated to account for 25% of ischaemic strokes, a figure similar to infarcts due to atherosclerosis [6], but notably do not always present as an acute stroke (owing to the small brain area often affected). Lacunar infarcts have been observed in neurology for decades – indeed, there are records of them as early as the 19th century by French neuropathologists (who provided the term '*lacune*', Latin for '*lake*', from the small holes of empty fluid that they observed in stroke victims' brains at autopsy). Since the seminal work of C Miller Fisher [7], a Canadian neuropathologist who reported the association between small vessel disease and stroke, they are now widely recognised in clinical practice as a stroke subtype, considered both hallmarks of, and risk for, lacunar ischaemic stroke [5].

The participant described at least three separate occasions of 'mini-strokes', most likely transient ischaemic attacks (TIAs), preceding his most stroke. This is fitting with his MRI scan, given that preceding TIAs occur in about 25% of cases of lacunar stroke and remain a high recurrence following stroke [8]. It is hypothesised that most lacunar infarcts are the main neuroimaging presentation of a more widespread diffuse aberration of the brain's small cerebral arterioles, which can also manifest functionally as cognitive decline [9]. This is in line with this particular case, as while the participant had no dementia diagnosis his MMSE score was significantly past the threshold suggestive of cognitive impairment at his last two attendances to the study. Lacunar ischaemic stroke also appears to be more closely associated with white matter hyperintensities (WMHs) than cortical ischaemic stroke [8]. WMHs present as bright white regions on T2-weighted and FLAIR MRI images and are mostly considered to reflect an underlying form of SVD [10]. The participant also had significantly reduced white matter integrity, which reduced tract FA in multiple white matter tracts, again aligning with suspected SVD which affects the brain globally rather than focally.

The participant's extensive cardiovascular history is of interest to this case as they relate to this participant's risk of stroke and subsequent cognitive consequences following stroke. The participant had three heart attacks and died of a fourth heart attack, age 80.7, 3 months after their last attendance to the study. The cause of death of this patient is not uncommon given his profile; in people who have had a stroke, the long term risk of dying by cardiac disease is 2-fold that of age-matched controls [4]. Indeed, the relationship between stroke and cardiovascular health is well established [3,6,11] and risk factors for lacunar infarcts such as the ones observed here include increasing age, male gender, hypertension, diabetes, smoking, high BMI, previous TIA, and previous heart disease history, all of which the current participant had. In addition to this, it has been proposed that vascular-mediated inflammation in particular is a key risk for accelerated cognitive ageing – both in terms of small vessel disease progression and diffuse white matter loss [10,12–14] – and this participant had elevated blood-circulating levels of inflammatory markers of CRP, IL6 and fibrinogen, which increased with advancing age.

144 **A. Lessons and future interventions**

145 A scoring system based on data from the Framingham Heart Study has been developed to estimate risk of CHD following stroke [15], where a relative risk score is ascribed based on age, sex, total blood cholesterol level, high-density lipoprotein cholesterol level, blood pressure, diabetes incidence, and whether the patient smokes cigarettes. A retrospective scoring from data collected on the participant at age 73 puts this participant into the highest risk category for mortality by cardiac event by this metric and an updated measure as the participant had all relevant risk factors [4].

150 The participant was taking antiplatelet agents (aspirin) and an ACE-inhibitor (perindopril, 5 mg / day), which have been shown to lower the risk of MI and stroke. However, there is no evidence that cessation of smoking happened; indeed the participant's self-reported cigarette intake increased between study waves. It is possible that secondary intervention could have assisted the participant to stop smoking. The provision of counselling, drug replacement therapy (e.g nicotine replacement), and group-based smoking cessation programmes could have helped in this instance and are recommended for future treatment management. A similar holistic approach could have been applied to increase the participant's physical activity levels and weight management, though there were further medical complications (leg weakness after stroke; calf-pain following vein-removal) that may have foiled this effort.

158 We are unable to assess whether the cognitive impairment could be explained by other factors such as depression [18] or fatigue. The participant had lower than average scores across most tests of physical fitness, and these declined acutely towards the end of his participation in the study. Physical function in older age has been shown to be indicative of overall health and has also been found to be consistently associated with cognition [17–20].

162 Future research should focus on healthy patients who present with first occasion lacunar stroke, with frequent neuroimaging follow-up, subtype the stroke by evaluation of MRI-DWI, control for confounding factors including 163 differences in VRFs, and premorbid cognitive impairment, depression, and imaging biomarkers of SVD (e.g WMHs, 164 perivascular spaces [12]) to tease apart the relative contributions to an accelerated cognitive ageing trajectory for 165 patients following lacunar stroke.

167 5. CONCLUSION:

168 Retrospective scoring via two independent risk measures placed this participant in the highest risk category for cardiac
 169 disease. In the case of this participant it is likely that prior to death the participant had some degree of small vessel
 170 disease. The changes in cognition seen through a declining performance on the MMSE test, and accelerated brain-ageing
 171 trajectory relative to the rest of the cohort, may be a direct result from a variety of cellular mechanisms related to his
 172 recurrent TIAs and lacunar strokes. These include, but are not limited to, small vessel endothelial damage, subtle increase
 173 in blood-brain barrier permeability, and leakage of substances toxic to the brain into the perivascular tissue [8]. It is likely
 174 that a variety of vascular risk factors including his weight, hypertension, high levels of circulating inflammatory protein
 175 levels such as CRP and IL6, severe smoking habit and cardiovascular disease history contributed to his propensity of SVD
 176 which may underly his accelerated ageing trajectory.

177 6. REFERENCES

1. Makin SDJ, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. *J Neurol Neurosurg Psychiatry* 2013;84(8):893.
2. Taylor AM, Pattie A, Deary IJ. Cohort profile update: the Lothian Birth Cohorts of 1921 and 1936. *International journal of epidemiology* 2018;47(4):1042–1042r.
3. Wardlaw JM, Bastin ME, Valdés Hernández MC, et al. Brain aging, cognition in youth and old age and vascular disease in the Lothian Birth Cohort 1936: rationale, design and methodology of the imaging protocol. *International Journal of Stroke* 2011;6(6):547–559.
4. Adams RJ, Chimowitz MI, Alpert JS, et al. Coronary Risk Evaluation in Patients With Transient Ischemic Attack and Ischemic Stroke. *Circulation* 2003;108(10):1278–1290.
5. Norrving B. Lacunar infarcts: no black holes in the brain are benign. *Pract Neurol* 2008;8(4):222.
6. Donnan G. Subcortical stroke. Oxford Medical Publications; 2002.
7. Caplan LR, Mohr JP, Ackerman RH. In Memoriam: Charles Miller Fisher, MD (1913-2012). *Archives of Neurology* 2012;69(9):1208–1209.
8. Wardlaw JM. What causes lacunar stroke? *J Neurol Neurosurg Psychiatry* 2005;76(5):617.
9. Wardlaw J, Sandercock P, Dennis M, Starr J. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? *Stroke* 2003;34(3):806–812.
10. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *The Lancet Neurology* 2019;18(7):684–696.
11. Schmidt Reinholt, Schmidt Helena, Pichler Martin, et al. C-Reactive Protein, Carotid Atherosclerosis, and Cerebral Small-Vessel Disease. *Stroke* 2006;37(12):2910–2916.
12. Aribisala BS, Wiseman S, Morris Z, et al. Circulating inflammatory markers are associated with magnetic resonance imaging-visible perivascular spaces but not directly with white matter hyperintensities. *Stroke* 2014;45(2):605–607.
13. Rouhl RPW, Damoiseaux JGMC, Lodder J, et al. Vascular inflammation in cerebral small vessel disease. *Neurobiology of Aging* 2012;33(8):1800–1806.
14. Fornage M, Chiang YA, O'Meara ES, et al. Biomarkers of inflammation and MRI-defined small vessel disease of the brain: the Cardiovascular Health Study. *Stroke* 2008;39(7):1952–1959.
15. Grundy SM, Pasternak R, Greenland P, et al. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Journal of the American College of Cardiology* 1999;34(4):1348–1359.
16. Grool AM, van der Graaf Y, Mali WP, Geerlings MI. Location of cerebrovascular and degenerative changes, depressive symptoms and cognitive functioning in later life: the SMART-Medea study. *Journal of Neurology, Neurosurgery Psychiatry* 2011;82(10):1093–1100.
17. Sternäng O, Reynolds CA, Finkel D, et al. Grip Strength and Cognitive Abilities: Associations in Old Age. *J Gerontol B Psychol Sci Soc Sci* 2016;71(5):841–848.
18. Chou M-Y, Nishita Y, Nakagawa T, et al. Role of gait speed and grip strength in predicting 10-year cognitive decline among community-dwelling older people. *BMC Geriatrics* 2019;19(1):186.
19. Clouston SA, Brewster P, Kuh D, et al. The dynamic relationship between physical function and cognition in longitudinal aging cohorts. *Epidemiologic reviews* 2013;35(1):33–50.
20. Zammit AR, Robitaille A, Piccinin AM, et al. Associations Between Aging-Related Changes in Grip Strength and Cognitive Function in Older Adults: A Systematic Review. *J Gerontol A Biol Sci Med Sci* 2019;74(4):519–527.