

# THE LANCET

## Healthy Longevity

### **Supplementary appendix**

This appendix formed part of the original submission and has been peer reviewed.  
We post it as supplied by the authors.

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# Association between surgical admissions, cognition, and neurodegeneration in older people: UK Biobank population-based study - Supplementary Material

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## Supplementary methods

Further detail is available in the UK Biobank data showcase at <https://biobank.ndph.ox.ac.uk/showcase/>.

**Table 1 - UK Biobank field references**

Field reference	Label	Comments
eid	Participant identifier	
21003	Age when attended assessment centre	
31	Sex	
53	Date of attending assessment centre	
189 / 22189	Townsend deprivation index	This field was revised during the course of our analysis in favour of indices of multiple deprivation. We retained the original value for our analysis.
2100	Body mass index	
20160	Ever smoked	
4598	Ever depressed for a whole week	
1568	average weekly red wine intake	Used to derive average total weekly units of alcohol
1578	average weekly champagne white wine	
1588	average weekly beer plus cider intake	
1598	average weekly spirits intake	
1608	average weekly fortified wine intake	
4407	average monthly red wine intake	
4418	average monthly champagne plus white wine intake	
4429	average monthly beer plus cider intake	
4440	average monthly spirits intake	
4451	average monthly fortified wine intake	
4462	average monthly intake of other alcoholic drinks	
5364	average weekly intake of other alcohol	
22032	International physical activity questionnaire activity group	
20016	Fluid intelligence score	
20023	Reaction time mean time to correctly identify matches	
20018	Prospective memory result	
4282	Numeric memory maximum digits remembered correctly	
6348	Duration to complete numeric path trail (TMTA)	
6350	Duration to complete alphanumeric path trail (TMTB)	
20197	Paired associate learning number of word pairs correctly associated	
23323	Number of symbol digit matches attempted	Used to derive mean symbol digit matches
23324	Number of symbol digit matches made correctly	Used to derive mean symbol digit matches
25781	Volume of white matter hyperintensities	

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Field reference	Label	Comments
25019	Volume of hippocampus left	
25020	Volume of hippocampus right	
20001	Cancer code self-reported	Used to determine leukaemia, lymphoma, solid tumour
20002	Non cancer code self-reported	Used to derive medical history. 1065 hypertension; 1220 diabetes
41200	Operative procedures main OPCS 4	Used to derive surgeries
41202	Diagnoses main ICD10	Used to derive hospital admissions
41270	Diagnoses (all) ICD10	Used to determine 'ever dementia'
27174	Mean thickness of caudalanteriorcingulate (left hemisphere)	Used to derive average DKT regions
27267	Mean thickness of caudalanteriorcingulate (right hemisphere)	
27175	Mean thickness of caudalmiddlefrontal (left hemisphere)	
27268	Mean thickness of caudalmiddlefrontal (right hemisphere)	
27176	Mean thickness of cuneus (left hemisphere)	
27269	Mean thickness of cuneus (right hemisphere)	
27177	Mean thickness of entorhinal (left hemisphere)	
27270	Mean thickness of entorhinal (right hemisphere)	
27178	Mean thickness of fusiform (left hemisphere)	
27271	Mean thickness of fusiform (right hemisphere)	
27179	Mean thickness of inferiorparietal (left hemisphere)	
27272	Mean thickness of inferiorparietal (right hemisphere)	
27180	Mean thickness of inferiortemporal (left hemisphere)	
27273	Mean thickness of inferiortemporal (right hemisphere)	
27204	Mean thickness of insula (left hemisphere)	
27297	Mean thickness of insula (right hemisphere)	
27181	Mean thickness of isthmuscingulate (left hemisphere)	
27274	Mean thickness of isthmuscingulate (right hemisphere)	
27182	Mean thickness of lateraloccipital (left hemisphere)	
27275	Mean thickness of lateraloccipital (right hemisphere)	
27183	Mean thickness of lateralorbitofrontal (left hemisphere)	
27276	Mean thickness of lateralorbitofrontal (right hemisphere)	
27184	Mean thickness of lingual (left hemisphere)	
27277	Mean thickness of lingual (right hemisphere)	
27185	Mean thickness of medialorbitofrontal (left hemisphere)	
27278	Mean thickness of medialorbitofrontal (right hemisphere)	
27186	Mean thickness of middletemporal (left hemisphere)	
27279	Mean thickness of middletemporal (right hemisphere)	
27188	Mean thickness of paracentral (left hemisphere)	
27281	Mean thickness of paracentral (right hemisphere)	
27187	Mean thickness of parahippocampal (left hemisphere)	
27280	Mean thickness of parahippocampal (right hemisphere)	
27189	Mean thickness of parsopercularis (left hemisphere)	
27282	Mean thickness of parsopercularis (right hemisphere)	
27190	Mean thickness of parsorbitalis (left hemisphere)	
27283	Mean thickness of parsorbitalis (right hemisphere)	
27191	Mean thickness of parstriangularis (left hemisphere)	
27284	Mean thickness of parstriangularis (right hemisphere)	
27192	Mean thickness of pericalcarine (left hemisphere)	
27285	Mean thickness of pericalcarine (right hemisphere)	
27193	Mean thickness of postcentral (left hemisphere)	
27286	Mean thickness of postcentral (right hemisphere)	
27194	Mean thickness of posteriorcingulate (left hemisphere)	
27287	Mean thickness of posteriorcingulate (right hemisphere)	
27195	Mean thickness of precentral (left hemisphere)	
27288	Mean thickness of precentral (right hemisphere)	
27196	Mean thickness of precuneus (left hemisphere)	
27289	Mean thickness of precuneus (right hemisphere)	
27197	Mean thickness of rostralanteriorcingulate (left hemisphere)	
27290	Mean thickness of rostralanteriorcingulate (right hemisphere)	

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Field reference	Label	Comments
27198	Mean thickness of rostralmiddlefrontal (left hemisphere)	
27291	Mean thickness of rostralmiddlefrontal (right hemisphere)	
27199	Mean thickness of superiorfrontal (left hemisphere)	
27292	Mean thickness of superiorfrontal (right hemisphere)	
27200	Mean thickness of superiorparietal (left hemisphere)	
27293	Mean thickness of superiorparietal (right hemisphere)	
27201	Mean thickness of superiortemporal (left hemisphere)	
27294	Mean thickness of superiortemporal (right hemisphere)	
27202	Mean thickness of supramarginal (left hemisphere)	
27295	Mean thickness of supramarginal (right hemisphere)	
27203	Mean thickness of transversetemporal (left hemisphere)	
27296	Mean thickness of transversetemporal (right hemisphere)	

## Cognitive outcomes

Primary cognitive outcomes were reaction time, fluid intelligence, and prospective memory tests collected at Instance-0 (baseline), Instance-2 and Instance-3. As we did not have an *a priori* hypothesis that a specific cognitive domain would be vulnerable to surgery, we analysed each test individually, expecting convergent results across all three tests. All cognitive tests included in this analysis were conducted on supervised kiosks at assessment centres, usually after health questionnaires and prior to interview. All cognitive tests included in this analysis were conducted on supervised kiosks at assessment centres, usually after health questionnaires and prior to interview. The reaction time (Snap) test is a test of simple processing speed, measuring the mean duration in milliseconds until the button is pressed in rounds with correct paired matches. The fluid intelligence raw score is an unweighted sum of correct answers out of 13 language and mathematics questions. The prospective memory (Shape) test is a memory and inhibition test, the results of which we dichotomised as either correct on first attempt or not. Numeric memory raw score is the maximum digits remembered correctly in 12 rounds. Introduced from 2016, TMTA and TMTB raw scores use the duration to complete the pathway in deciseconds. The symbol digit substitution score was the mean number of correct matches. Paired associate learning was the number of word pairs correctly associated of 12 word-pairs.

## Brain imaging outcomes

Brain imaging was performed at UK Biobank assessment centres using a standard Siemens Skyra 3T running VD13A SP4 (as of October 2015), with a standard Siemens 32-channel RF receive head coil in accordance with UK Biobank imaging acquisition protocols.<sup>1,2</sup> Brain imaging data used in this analysis was T1-weighted structural imaging 1x1x1 mm resolution with a 208x256x256 matrix field of view from a 5-minute 3D MPRAGE sagittal scan with in-plane acceleration iPAT=2 and pre-scan normalisation. T2-weighted FLAIR structural imaging had 1.05x1x1 mm resolution, 192x256x256 matrix field of view from a 6-minute 3D SPACE, sagittal scan with in-plane acceleration iPAT=2, partial Fourier = 7/8, fat saturation, elliptical k-space scanning and pre-scan normalization.

We used two primary brain imaging outcomes pre-processed by UK Biobank. Volume of white matter hyperintensities (from T1 and T2 fluid attenuated inversion recovery [FLAIR] images); and the average volume of left and right hippocampi (from T1 structural brain MRI, subcortical volumes [Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Integrated Registration and Segmentation (FIRST) tool,<sup>3</sup>]. These variables were selected due to known associations with dementia and cognition.<sup>4-7</sup> Units were cubic

millimetres as outcome/dependent variables and z-scored using Instance-2 (imaging baseline) means and standard deviations as independent variables.

Secondary brain imaging outcomes were generated by UK Biobank using FreeSurfer image analysis suite<sup>8</sup> from T1 structural volumes with parcellation of the white surface using the Desikan-Killiany-Tourville (DKT31) cortical labelling protocol.<sup>9, 10</sup> We averaged the mean thicknesses of the 31 regions across hemispheres and adjusted type-3 p-values using false discovery rate (FDR) correction for multiple comparisons.

### Primary exposure and risk factors

As previously,<sup>11</sup> two clinicians categorised surgical severity/complexity as minor, intermediate, major, major plus, complex major operation, or excluded (such as diagnostic day procedures), using the National Health Service medical record main procedure code (OPCS-4) and BUPA Schedule of Procedures as at 15 June 2022. Cumulative surgeries were calculated as the sum of eligible procedures dated between eight years prior to baseline Instance-0 date of assessment (~1998) up to date of assessment of the respective instance. Hospital admissions were calculated using ICD10 main diagnosis codes. stroke (I61, I62, I63, I64, I66); and other medical admissions (not stroke).

Age was defined as age at Instance-0 and time as the duration in years from Instance-0 to the relevant assessment date. Risk factors for dementia (as identified by the Lancet Commission<sup>12</sup>) were tested as covariates, including education, alcohol consumption, hypertension, hearing difficulty, smoking, body mass index (BMI), depression, physical activity, and diabetes. We did not attempt to derive air pollution, head injury or social contact, although controlled for stroke hospital admissions. Leukaemia, lymphoma, and solid tumours were also included as covariates consistent with the Charlson index. Deprivation was calculated at Instance-0 using the Townsend deprivation index, based on previous national census data assessing unemployment, non-car ownership, non-home ownership, and overcrowding based on postcode. Data were not imputed, although history of smoking or depression were dichotomised as “yes” or “no/null”. Alcohol consumption was measured using the number of standard alcohol units consumed per week. Physical activity used the International Physical Activity Questionnaire activity group classification and history of hypertension, diabetes and solid tumour were obtained from self-reported medical history collected at interview.

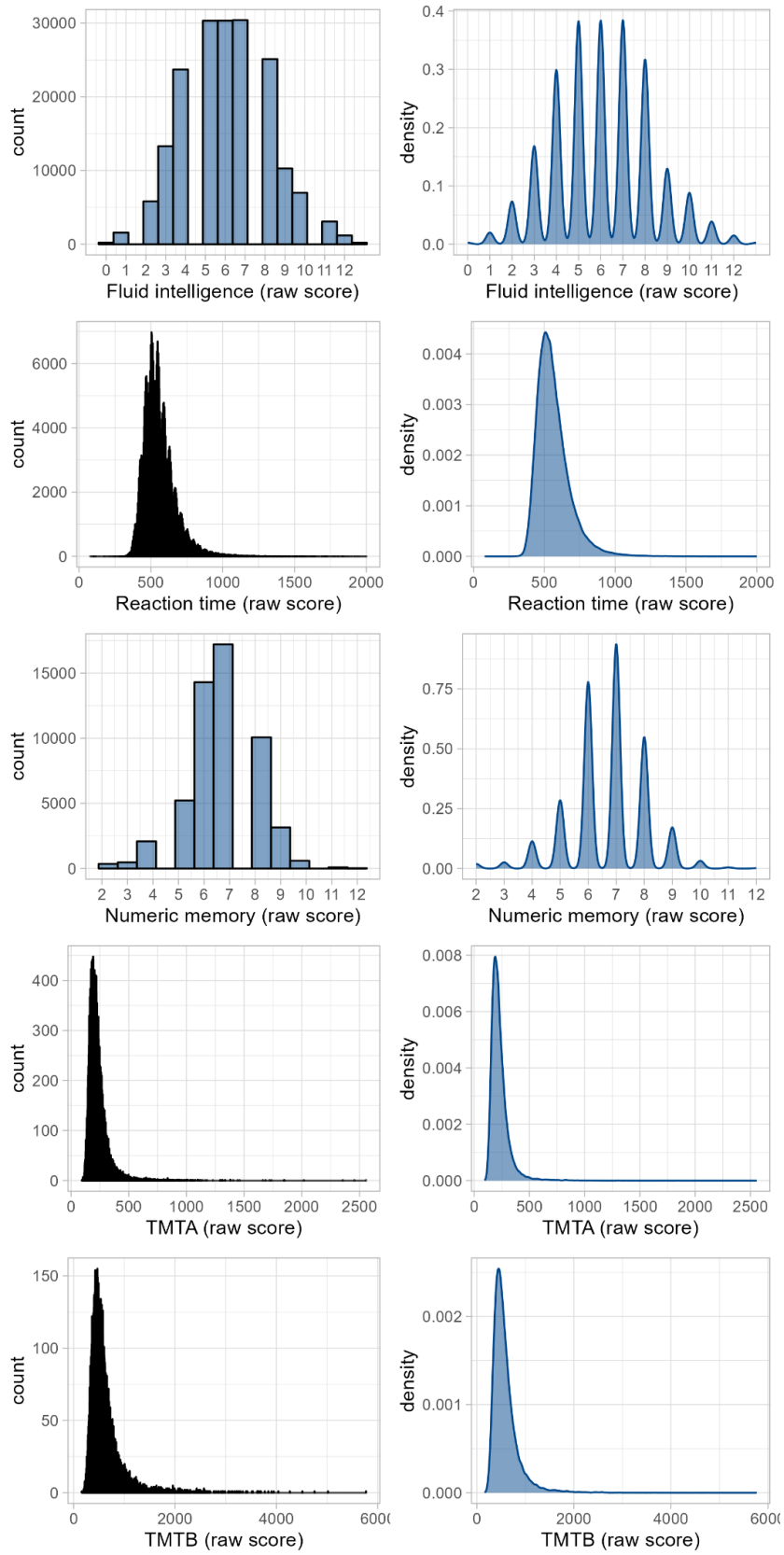
Dementia-ever was defined using International Classification of Diseases version 10 (ICD10) codes. F00, F000, F001, F002, F009, G30, G300, G301, G308, G309, F01, F010, F011, F012, F013, F018, F019, I673, F020, G310, A810, F021, F022, F023, F024, F106, F02,

F028, F03, F051, G311, and G318. Stroke hospital admissions were derived using ICD10 main diagnosis codes. I61, I62, I63, I64, I66. Other medical admissions were derived as 'not stroke'.

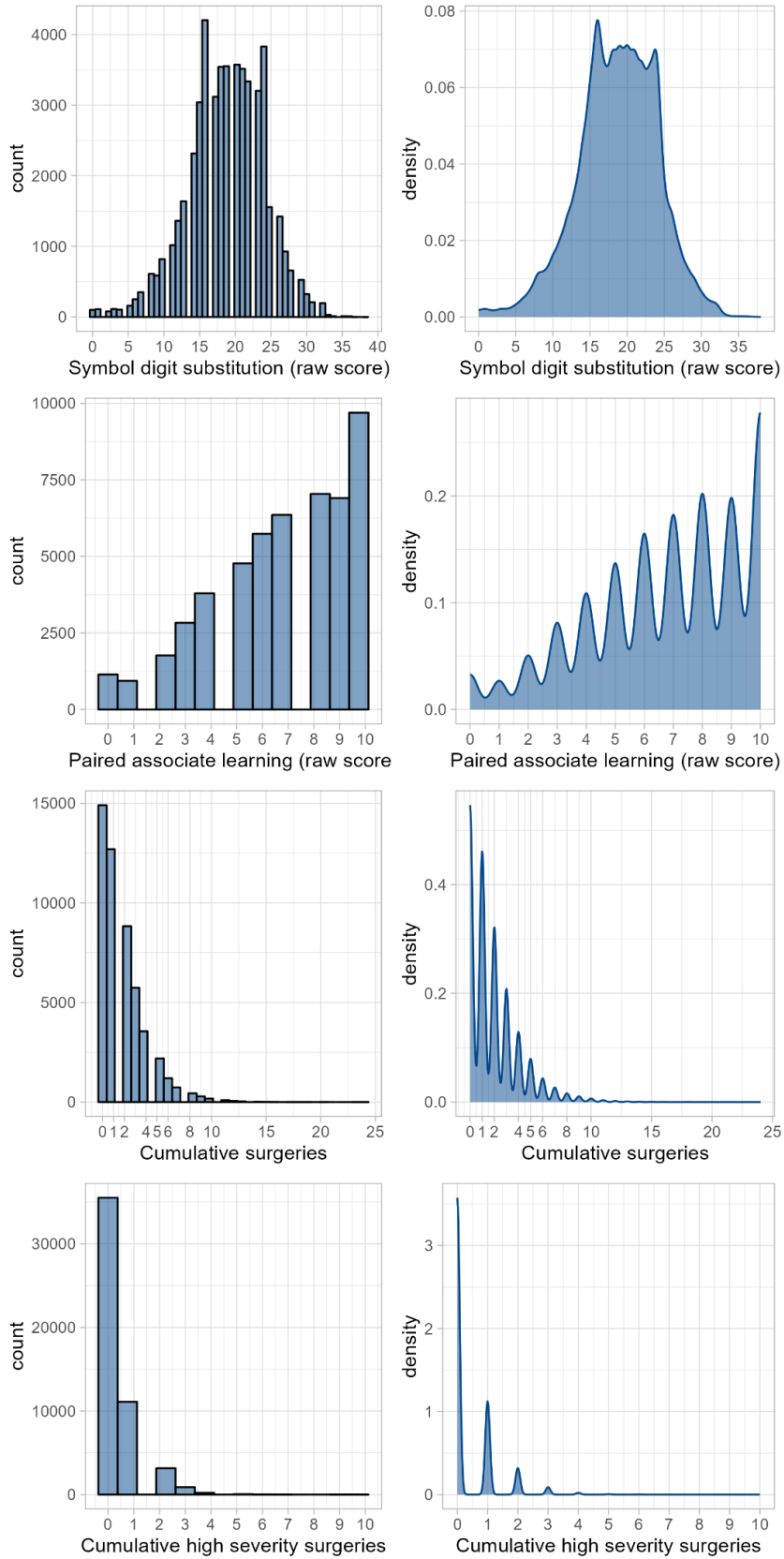
Sensitivity analyses included comparison of these models across stroke/no stroke data subsets, and clinical change in cognition categorised as 1-2 standard deviations from baseline. Exploratory stratification analysis also tested surgeries into one of four groups. 0; 1-2; 3-5; and 6+ surgeries.



**Figure 1 Histograms and density plots**



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**Table 2. Model selection**

Characteristic	LMER. Outcome ~ surgeries + age + sex + (1 participant)			LMER. Outcome ~ surgeries + baseline age + time in years + sex + (1 participant)			LMER. Outcome ~ surgeries + baseline age + baseline age <sup>2</sup> + time in years + sex + (1 participant)			GAM. Outcome ~ surgeries + s(age, bs = "cr") + sex + s(participant, bs = "re")		
	Mean change per surgery	95% CI	p-value	Mean change per surgery	95% CI	p-value	Mean change per surgery	95% CI	p-value	Mean change per surgery	95% CI	p-value
Cumulative Surgeries	2.761	2.551, 2.972		1.986	1.771, 2.202		1.957	1.742, 2.173		2.172	1.960, 2.383	
Age each timepoint	4.195	4.159, 4.231										
Baseline age				3.950	3.912, 3.989		0.880	0.325, 1.435	0.0019			
Baseline age <sup>2</sup>							27.853	22.831, 32.875				
Time				5.357	5.281, 5.434		5.373	5.296, 5.449				
Female sex (Ref = Male)	18.388	17.768, 19.009		18.430	17.809, 19.051		18.545	17.924, 19.166		18.740	18.146, 19.333	
s(Age)												
s(participant id)												0.6450
No. observations	544520			544520			544520			544520		
BIC	6,660,960			6,659,853			<b>6,659,744</b>			6,675,376		

All p<0.0001 unless indicated.

**Table 3. Expanded demographics table by cognitive outcomes**

Characteristic	All data			Reaction time			Fluid intelligence			Prospective memory			Numeric memory			TMTA		TMTB		SDST		Paired associate learning	
	0 N = 492802 1	2 N = 71873 <sup>1</sup>	3 N = 6324 <sup>1</sup>	0 N = 487271 1	2 N = 65366 <sup>1</sup>	3 N = 5681 <sup>1</sup>	0 N = 162964 1	2 N = 64700 <sup>1</sup>	3 N = 5658 <sup>1</sup>	0 N = 168755 1	2 N = 65694 <sup>1</sup>	3 N = 5781 <sup>1</sup>	0 N = 50934 1	2 N = 43124 <sup>1</sup>	3 N = 5091 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 52743 <sup>1</sup>	3 N = 5680 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>
Age, mean (SD), y	56 (8)	65 (8)	65 (7)	56 (8)	65 (8)	65 (7)	57 (8)	65 (8)	65 (7)	57 (8)	65 (8)	65 (7)	56 (8)	65 (8)	64 (7)	66 (8)	65 (7)	66 (8)	65 (7)	65 (8)	65 (7)	66 (8)	65 (7)
Sex, female	268,733 (55%)	37,118 (52%)	3,256 (51%)	265,840 (55%)	33,618 (51%)	2,929 (52%)	89,017 (55%)	33,311 (51%)	2,925 (52%)	92,059 (55%)	33,786 (51%)	2,969 (51%)	27,773 (55%)	22,201 (51%)	2,622 (52%)	27,389 (51%)	2,969 (51%)	27,389 (51%)	2,969 (51%)	27,117 (51%)	2,931 (52%)	27,389 (51%)	2,969 (51%)
Ethnic background																							
Asian	11,296 (2.3%)	1,038 (1.4%)	79 (1.2%)	10,495 (2.2%)	885 (1.4%)	72 (1.3%)	5,184 (3.2%)	849 (1.3%)	66 (1.2%)	6,486 (3.8%)	896 (1.4%)	73 (1.3%)	1,629 (3.2%)	552 (1.3%)	68 (1.3%)	710 (1.3%)	73 (1.3%)	710 (1.3%)	73 (1.3%)	700 (1.3%)	72 (1.3%)	710 (1.3%)	73 (1.3%)
Black	7,914 (1.6%)	516 (0.7%)	38 (0.6%)	7,455 (1.5%)	413 (0.6%)	34 (0.6%)	3,909 (2.4%)	404 (0.6%)	33 (0.6%)	4,505 (2.7%)	417 (0.6%)	35 (0.6%)	440 (0.9%)	267 (0.6%)	34 (0.7%)	346 (0.6%)	35 (0.6%)	346 (0.6%)	35 (0.6%)	336 (0.6%)	34 (0.6%)	346 (0.6%)	35 (0.6%)
White	463,474 (94%)	69,322 (96%)	6,144 (97%)	460,416 (94%)	63,191 (97%)	5,516 (97%)	150,172 (92%)	62,589 (97%)	5,500 (97%)	153,524 (91%)	63,501 (97%)	5,614 (97%)	48,073 (94%)	41,764 (97%)	4,935 (97%)	51,471 (97%)	5,614 (97%)	51,471 (97%)	5,614 (97%)	50,985 (97%)	5,515 (97%)	51,471 (97%)	5,614 (97%)
Do not know/Prefer not to answer	1,832 (0.4%)	193 (0.3%)	13 (0.2%)	1,746 (0.4%)	172 (0.3%)	12 (0.2%)	643 (0.4%)	170 (0.3%)	12 (0.2%)	789 (0.5%)	172 (0.3%)	12 (0.2%)	175 (0.3%)	98 (0.2%)	10 (0.2%)	134 (0.3%)	12 (0.2%)	134 (0.3%)	12 (0.2%)	134 (0.3%)	12 (0.2%)	134 (0.3%)	12 (0.2%)
Other	7,417 (1.5%)	776 (1.1%)	48 (0.8%)	7,121 (1.5%)	683 (1.0%)	45 (0.8%)	3,056 (1.9%)	666 (1.0%)	45 (0.8%)	3,451 (2.0%)	686 (1.0%)	45 (0.8%)	617 (1.2%)	431 (1.0%)	42 (0.8%)	578 (1.1%)	45 (0.8%)	578 (1.1%)	45 (0.8%)	570 (1.1%)	45 (0.8%)	578 (1.1%)	45 (0.8%)
Missing	869 (0.2%)	28 (<0.1%)	2 (<0.1%)	38 (<0.1%)	22 (<0.1%)	2 (<0.1%)	0 (0%)	22 (<0.1%)	2 (<0.1%)	0 (0%)	22 (<0.1%)	2 (<0.1%)	0 (0%)	12 (<0.1%)	2 (<0.1%)	18 (<0.1%)	2 (<0.1%)	18 (<0.1%)	2 (<0.1%)	18 (<0.1%)	2 (<0.1%)	18 (<0.1%)	2 (<0.1%)
Townsend Deprivation Index at Instance-0, mean (SD)	-1.30 (3.09)	-1.85 (2.75)	-1.92 (2.66)	-1.33 (3.07)	-1.87 (2.74)	-1.91 (2.67)	-1.17 (2.91)	-1.88 (2.73)	-1.91 (2.66)	-1.11 (2.95)	-1.87 (2.74)	-1.91 (2.67)	-1.46 (2.80)	-1.88 (2.74)	-1.94 (2.66)	-1.86 (2.75)	-1.91 (2.67)	-1.86 (2.75)	-1.91 (2.67)	-1.86 (2.75)	-1.91 (2.66)	-1.86 (2.75)	-1.91 (2.67)
Education																							
Secondary <12 years	134,863 (27%)	16,308 (23%)	1,453 (23%)	133,910 (27%)	15,179 (23%)	1,371 (24%)	46,019 (28%)	14,959 (23%)	1,364 (24%)	47,296 (28%)	15,250 (23%)	1,398 (24%)	14,907 (29%)	9,713 (23%)	1,223 (24%)	12,193 (23%)	1,398 (24%)	12,193 (23%)	1,398 (24%)	12,069 (23%)	1,370 (24%)	12,193 (23%)	1,398 (24%)
Secondary 12 years	35,836 (7.3%)	5,712 (7.9%)	523 (8.3%)	35,638 (7.3%)	5,441 (8.3%)	496 (8.7%)	12,406 (7.6%)	5,410 (8.4%)	494 (8.7%)	12,673 (7.5%)	5,466 (8.3%)	505 (8.7%)	3,590 (7.0%)	3,526 (8.2%)	453 (8.9%)	4,455 (8.4%)	505 (8.7%)	4,455 (8.4%)	505 (8.7%)	4,423 (8.4%)	496 (8.7%)	4,455 (8.4%)	505 (8.7%)
Tertiary >12 years	230,355 (47%)	42,735 (59%)	3,707 (59%)	229,180 (47%)	40,363 (62%)	3,533 (62%)	80,181 (49%)	40,142 (62%)	3,524 (62%)	81,599 (48%)	40,560 (62%)	3,595 (62%)	23,770 (47%)	27,037 (63%)	3,175 (62%)	33,078 (62%)	3,595 (62%)	33,078 (62%)	3,595 (62%)	32,842 (62%)	3,538 (62%)	33,078 (62%)	3,595 (62%)
None of the above	82,002 (17%)	4,637 (6.5%)	292 (4.6%)	80,005 (16%)	3,991 (6.1%)	264 (4.6%)	22,918 (14%)	3,812 (5.9%)	260 (4.6%)	25,305 (15%)	4,024 (6.1%)	266 (4.6%)	8,125 (16%)	2,579 (6.0%)	225 (4.4%)	3,183 (6.0%)	266 (4.6%)	3,183 (6.0%)	266 (4.6%)	3,073 (5.8%)	260 (4.6%)	3,183 (6.0%)	266 (4.6%)
Prefer not to answer	5,279 (1.1%)	297 (0.4%)	17 (0.3%)	4,966 (1.0%)	241 (0.4%)	13 (0.2%)	1,440 (0.9%)	227 (0.4%)	12 (0.2%)	1,882 (1.1%)	241 (0.4%)	13 (0.2%)	542 (1.1%)	151 (0.4%)	12 (0.2%)	198 (0.4%)	13 (0.2%)	198 (0.4%)	13 (0.2%)	189 (0.4%)	12 (0.2%)	198 (0.4%)	13 (0.2%)

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Characteristic	All data			Reaction time			Fluid intelligence			Prospective memory			Numeric memory			TMTA		TMTB		SDST		Paired associate learning	
	0 N = 492802 1	2 N = 71873 <sup>1</sup>	3 N = 6324 <sup>1</sup>	0 N = 487271 1	2 N = 65366 <sup>1</sup>	3 N = 5681 <sup>1</sup>	0 N = 162964 1	2 N = 64700 <sup>1</sup>	3 N = 5658 <sup>1</sup>	0 N = 168755 1	2 N = 65694 <sup>1</sup>	3 N = 5781 <sup>1</sup>	0 N = 50934 1	2 N = 43124 <sup>1</sup>	3 N = 5091 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 52743 <sup>1</sup>	3 N = 5680 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>
Missing	4,467 (0.9%)	2,184 (3.0%)	332 (5.2%)	3,572 (0.7%)	151 (0.2%)	4 (<0.1%)	0 (0%)	150 (0.2%)	4 (<0.1%)	0 (0%)	153 (0.2%)	4 (<0.1%)	0 (0%)	118 (0.3%)	3 (<0.1%)	150 (0.3%)	4 (<0.1%)	150 (0.3%)	4 (<0.1%)	147 (0.3%)	4 (<0.1%)	150 (0.3%)	4 (<0.1%)
BMI, kg/m <sup>2</sup> mean (SD)	27.4 (4.8)	26.7 (4.5)	26.4 (4.4)	27.4 (4.8)	26.6 (4.5)	26.4 (4.4)	27.4 (4.8)	26.6 (4.5)	26.4 (4.4)	27.4 (4.8)	26.6 (4.5)	26.4 (4.4)	27.4 (4.8)	26.6 (4.5)	26.4 (4.4)	26.6 (4.5)	26.4 (4.4)	26.6 (4.5)	26.4 (4.4)	26.6 (4.5)	26.4 (4.4)	26.6 (4.5)	26.4 (4.4)
Ever smoked	292,623 (59%)	43,628 (61%)	3,805 (60%)	290,412 (60%)	39,630 (61%)	3,398 (60%)	97,542 (60%)	39,234 (61%)	3,386 (60%)	100,180 (59%)	39,828 (61%)	3,465 (60%)	30,244 (59%)	25,998 (60%)	3,049 (60%)	32,179 (60%)	3,465 (60%)	32,179 (60%)	3,465 (60%)	31,866 (60%)	3,400 (60%)	32,179 (60%)	3,465 (60%)
Hearing difficulty	118,962 (24%)	27,858 (39%)	2,627 (42%)	117,911 (24%)	25,414 (39%)	2,374 (42%)	42,158 (26%)	25,156 (39%)	2,365 (42%)	43,506 (26%)	25,567 (39%)	2,415 (42%)	13,178 (26%)	16,949 (39%)	2,099 (41%)	21,006 (39%)	2,415 (42%)	21,006 (39%)	2,415 (42%)	20,785 (39%)	2,367 (42%)	21,006 (39%)	2,415 (42%)
Ever depression	87,982 (18%)	38,520 (54%)	3,918 (62%)	87,119 (18%)	35,662 (55%)	3,535 (62%)	85,171 (52%)	35,334 (55%)	3,529 (62%)	87,579 (52%)	35,837 (55%)	3,610 (62%)	26,516 (52%)	23,512 (55%)	3,192 (63%)	28,744 (54%)	3,610 (62%)	28,744 (54%)	3,610 (62%)	28,477 (54%)	3,540 (62%)	28,744 (54%)	3,610 (62%)
Weekly alcohol intake, standard units, mean (SD)	15 (18)	13 (15)	13 (15)	15 (18)	14 (15)	14 (16)	15 (17)	14 (15)	14 (15)	14 (17)	14 (15)	14 (16)	15 (17)	14 (15)	14 (15)	14 (15)	14 (16)	14 (15)	14 (16)	14 (15)	14 (16)	14 (15)	14 (16)
IPAQ physical activity at Instance-0																							
Low	70,318 (14%)	10,929 (15%)	931 (15%)	69,730 (14%)	10,041 (15%)	839 (15%)	22,186 (14%)	9,969 (15%)	838 (15%)	22,823 (14%)	10,078 (15%)	850 (15%)	6,531 (13%)	6,581 (15%)	769 (15%)	8,112 (15%)	850 (15%)	8,112 (15%)	850 (15%)	8,063 (15%)	839 (15%)	8,112 (15%)	850 (15%)
Moderate	153,857 (31%)	25,001 (35%)	2,202 (35%)	152,913 (31%)	22,878 (35%)	1,985 (35%)	52,150 (32%)	22,698 (35%)	1,976 (35%)	53,312 (32%)	22,992 (35%)	2,020 (35%)	15,660 (31%)	15,324 (36%)	1,751 (34%)	18,820 (35%)	2,020 (35%)	18,820 (35%)	2,020 (35%)	18,675 (35%)	1,983 (35%)	18,820 (35%)	2,020 (35%)
High	154,546 (31%)	23,927 (33%)	2,222 (35%)	153,474 (31%)	21,740 (33%)	2,001 (35%)	54,558 (33%)	21,496 (33%)	1,996 (35%)	55,831 (33%)	21,841 (33%)	2,035 (35%)	17,637 (35%)	14,230 (33%)	1,789 (35%)	17,703 (33%)	2,035 (35%)	17,703 (33%)	2,035 (35%)	17,531 (33%)	2,004 (35%)	17,703 (33%)	2,035 (35%)
Missing	114,081 (23%)	12,016 (17%)	969 (15%)	111,154 (23%)	10,707 (16%)	856 (15%)	34,070 (21%)	10,537 (16%)	848 (15%)	36,789 (22%)	10,783 (16%)	876 (15%)	11,106 (22%)	6,989 (16%)	782 (15%)	8,622 (16%)	876 (15%)	8,622 (16%)	876 (15%)	8,474 (16%)	854 (15%)	8,622 (16%)	876 (15%)
Hypertension	133,789 (27%)	19,458 (27%)	1,655 (26%)	132,139 (27%)	17,573 (27%)	1,486 (26%)	43,759 (27%)	17,339 (27%)	1,476 (26%)	45,767 (27%)	17,685 (27%)	1,515 (26%)	13,593 (27%)	11,577 (27%)	1,317 (26%)	14,134 (27%)	1,515 (26%)	14,134 (27%)	1,515 (26%)	13,950 (26%)	1,482 (26%)	14,134 (27%)	1,515 (26%)
Myocardial infarction ever	11,685 (2.4%)	1,461 (2.0%)	132 (2.1%)	11,475 (2.4%)	1,293 (2.0%)	118 (2.1%)	3,617 (2.2%)	1,268 (2.0%)	118 (2.1%)	3,835 (2.3%)	1,301 (2.0%)	123 (2.1%)	1,255 (2.5%)	881 (2.0%)	111 (2.2%)	1,041 (2.0%)	123 (2.1%)	1,041 (2.0%)	123 (2.1%)	1,023 (1.9%)	117 (2.1%)	1,041 (2.0%)	123 (2.1%)
Stroke ever	6,773 (1.4%)	871 (1.2%)	82 (1.3%)	6,621 (1.4%)	746 (1.1%)	71 (1.2%)	2,005 (1.2%)	736 (1.1%)	70 (1.2%)	2,168 (1.3%)	751 (1.1%)	73 (1.3%)	621 (1.2%)	481 (1.1%)	61 (1.2%)	585 (1.1%)	73 (1.3%)	585 (1.1%)	73 (1.3%)	576 (1.1%)	71 (1.3%)	585 (1.1%)	73 (1.3%)
Diabetes ever	22,107 (4.5%)	2,807 (3.9%)	251 (4.0%)	21,595 (4.4%)	2,486 (3.8%)	228 (4.0%)	7,524 (4.6%)	2,444 (3.8%)	223 (3.9%)	8,150 (4.8%)	2,505 (3.8%)	235 (4.1%)	2,155 (4.2%)	1,638 (3.8%)	204 (4.0%)	1,954 (3.7%)	235 (4.1%)	1,954 (3.7%)	235 (4.1%)	1,927 (3.7%)	230 (4.0%)	1,954 (3.7%)	235 (4.1%)
Lymphoma ever	1,966 (0.4%)	341 (0.5%)	25 (0.4%)	1,951 (0.4%)	314 (0.5%)	22 (0.4%)	643 (0.4%)	306 (0.5%)	22 (0.4%)	668 (0.4%)	316 (0.5%)	23 (0.4%)	172 (0.3%)	210 (0.5%)	21 (0.4%)	257 (0.5%)	23 (0.4%)	257 (0.5%)	23 (0.4%)	256 (0.5%)	22 (0.4%)	257 (0.5%)	23 (0.4%)

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Characteristic	All data			Reaction time			Fluid intelligence			Prospective memory			Numeric memory			TMTA		TMTB		SDST		Paired associate learning	
	0 N = 492802 <sub>1</sub>	2 N = 71873 <sup>1</sup>	3 N = 6324 <sup>1</sup>	0 N = 487271 <sub>1</sub>	2 N = 65366 <sup>1</sup>	3 N = 5681 <sup>1</sup>	0 N = 162964 <sub>1</sub>	2 N = 64700 <sup>1</sup>	3 N = 5658 <sup>1</sup>	0 N = 168755 <sub>1</sub>	2 N = 65694 <sup>1</sup>	3 N = 5781 <sup>1</sup>	0 N = 50934 <sub>1</sub>	2 N = 43124 <sup>1</sup>	3 N = 5091 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 52743 <sup>1</sup>	3 N = 5680 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>
Solid tumour ever	41,813 (8.5%)	8,684 (12%)	740 (12%)	41,441 (8.5%)	7,928 (12%)	657 (12%)	13,844 (8.5%)	7,820 (12%)	656 (12%)	14,253 (8.4%)	7,964 (12%)	677 (12%)	4,217 (8.3%)	5,141 (12%)	598 (12%)	6,581 (12%)	677 (12%)	6,581 (12%)	677 (12%)	6,518 (12%)	658 (12%)	6,581 (12%)	677 (12%)
Cumulative Surgeries, mean (SD)	0.84 (1.30)	1.87 (2.09)	1.89 (2.01)	0.84 (1.30)	1.83 (2.06)	1.86 (2.01)	0.86 (1.32)	1.83 (2.05)	1.86 (2.01)	0.87 (1.33)	1.83 (2.06)	1.86 (2.01)	0.87 (1.32)	1.85 (2.04)	1.82 (1.98)	1.92 (2.11)	1.86 (2.01)	1.92 (2.11)	1.86 (2.01)	1.91 (2.10)	1.86 (2.01)	1.92 (2.11)	1.86 (2.01)
Cumulative Surgeries																							
0	273,564 (56%)	21,369 (30%)	1,760 (28%)	270,821 (56%)	19,860 (30%)	1,606 (28%)	89,556 (55%)	19,711 (30%)	1,603 (28%)	92,358 (55%)	19,948 (30%)	1,635 (28%)	27,695 (54%)	12,841 (30%)	1,468 (29%)	15,350 (29%)	1,635 (28%)	15,350 (29%)	1,635 (28%)	15,219 (29%)	1,606 (28%)	15,350 (29%)	1,635 (28%)
1-2	171,644 (35%)	30,165 (42%)	2,726 (43%)	169,618 (35%)	27,521 (42%)	2,461 (43%)	57,190 (35%)	27,230 (42%)	2,449 (43%)	59,337 (35%)	27,655 (42%)	2,500 (43%)	18,153 (36%)	18,259 (42%)	2,222 (44%)	22,397 (42%)	2,500 (43%)	22,397 (42%)	2,500 (43%)	22,212 (42%)	2,458 (43%)	22,397 (42%)	2,500 (43%)
3-5	41,813 (8.5%)	15,882 (22%)	1,481 (23%)	41,175 (8.5%)	14,139 (22%)	1,298 (23%)	14,223 (8.7%)	13,970 (22%)	1,290 (23%)	14,940 (8.9%)	14,224 (22%)	1,325 (23%)	4,469 (8.8%)	9,508 (22%)	1,138 (22%)	12,095 (23%)	1,325 (23%)	12,095 (23%)	1,325 (23%)	11,944 (23%)	1,299 (23%)	12,095 (23%)	1,325 (23%)
6+	5,781 (1.2%)	4,457 (6.2%)	357 (5.6%)	5,657 (1.2%)	3,846 (5.9%)	316 (5.6%)	1,995 (1.2%)	3,789 (5.9%)	316 (5.6%)	2,120 (1.3%)	3,867 (5.9%)	321 (5.6%)	617 (1.2%)	2,516 (5.8%)	263 (5.2%)	3,415 (6.4%)	321 (5.6%)	3,415 (6.4%)	321 (5.6%)	3,368 (6.4%)	317 (5.6%)	3,415 (6.4%)	321 (5.6%)
Reaction time, milliseconds, mean(SD)	559 (117)	601 (112)	594 (108)	559 (117)	601 (112)	594 (108)	567 (121)	601 (112)	594 (106)	568 (123)	601 (112)	594 (108)	567 (124)	603 (113)	592 (108)	605 (114)	594 (108)	605 (114)	594 (108)	604 (113)	594 (106)	605 (114)	594 (108)
Fluid intelligence, correct, mean (SD)	5.99 (2.16)	6.48 (2.07)	6.74 (2.02)	6.00 (2.15)	6.49 (2.07)	6.74 (2.02)	5.99 (2.16)	6.48 (2.07)	6.74 (2.02)	5.99 (2.16)	6.48 (2.07)	6.74 (2.02)	6.01 (2.12)	6.45 (2.04)	6.77 (2.01)	6.40 (2.05)	6.74 (2.02)	6.40 (2.05)	6.74 (2.02)	6.41 (2.05)	6.74 (2.02)	6.40 (2.05)	6.74 (2.02)
Prospective memory, correct on first attempt	129,271 (77%)	53,693 (82%)	4,973 (86%)	128,925 (77%)	53,527 (82%)	4,921 (87%)	126,007 (77%)	53,086 (82%)	4,906 (87%)	129,271 (77%)	53,693 (82%)	4,973 (86%)	38,865 (76%)	34,665 (80%)	4,391 (86%)	42,602 (80%)	4,973 (86%)	42,602 (80%)	4,973 (86%)	42,329 (80%)	4,919 (87%)	42,602 (80%)	4,973 (86%)
Numeric memory, maximum correct, mean (SD)	6.49 (1.82)	6.62 (1.55)	6.67 (1.76)	6.50 (1.79)	6.65 (1.49)	6.80 (1.49)	6.55 (1.73)	6.66 (1.46)	6.82 (1.41)	6.49 (1.82)	6.62 (1.55)	6.67 (1.76)	6.49 (1.82)	6.62 (1.55)	6.67 (1.76)	6.62 (1.55)	6.67 (1.76)	6.62 (1.55)	6.67 (1.76)	6.66 (1.47)	6.80 (1.48)	6.62 (1.55)	6.67 (1.76)
TMTA at Instance-2, deciseconds, mean (SD)		230 (90)	218 (89)		230 (90)	221 (86)		230 (89)	221 (86)		230 (90)	218 (89)		228 (92)	216 (90)	230 (90)	218 (89)	230 (90)	218 (89)	231 (88)	221 (86)	230 (90)	218 (89)
TMTB at Instance-2, deciseconds, mean (SD)		570 (294)	528 (261)		571 (292)	535 (255)		571 (291)	535 (253)		570 (294)	528 (261)		564 (291)	521 (255)	570 (294)	528 (261)	570 (294)	528 (261)	572 (290)	537 (254)	570 (294)	528 (261)
SDST at Instance-2, matches, mean (SD)		18.6 (5.3)	19.7 (5.3)		18.6 (5.3)	19.7 (5.3)		18.6 (5.3)	19.7 (5.3)		18.6 (5.3)	19.7 (5.3)		18.7 (5.3)	19.8 (5.3)	18.6 (5.3)	19.7 (5.3)	18.6 (5.3)	19.7 (5.3)	18.6 (5.3)	19.7 (5.3)	18.6 (5.3)	19.7 (5.3)

Characteristic	All data			Reaction time			Fluid intelligence			Prospective memory			Numeric memory			TMTA		TMTB		SDST		Paired associate learning	
	0 N = 492802 1	2 N = 71873 <sup>1</sup>	3 N = 6324 <sup>1</sup>	0 N = 487271 1	2 N = 65366 <sup>1</sup>	3 N = 5681 <sup>1</sup>	0 N = 162964 1	2 N = 64700 <sup>1</sup>	3 N = 5658 <sup>1</sup>	0 N = 168755 1	2 N = 65694 <sup>1</sup>	3 N = 5781 <sup>1</sup>	0 N = 50934 1	2 N = 43124 <sup>1</sup>	3 N = 5091 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>	2 N = 52743 <sup>1</sup>	3 N = 5680 <sup>1</sup>	2 N = 53257 <sup>1</sup>	3 N = 5781 <sup>1</sup>
Paired associate learning at Instance-2, matches, mean (SD)		6.73 (2.66)	7.11 (2.59)		6.74 (2.65)	7.15 (2.55)		6.76 (2.63)	7.17 (2.53)		6.73 (2.66)	7.11 (2.59)		6.77 (2.66)	7.16 (2.59)	6.73 (2.66)	7.11 (2.59)	6.73 (2.66)	7.11 (2.59)	6.77 (2.62)	7.17 (2.53)	6.73 (2.66)	7.11 (2.59)
Vol white matter hyperintensities, cubic millimetres, mean (SD)		5,216 (6,877)	5,176 (6,553)		5,069 (6,677)	5,039 (6,404)		5,054 (6,652)	5,028 (6,360)		5,084 (6,699)	5,074 (6,446)		5,450 (7,045)	5,074 (6,446)	5,478 (7,066)	5,074 (6,446)	5,478 (7,066)	5,074 (6,446)	5,439 (7,027)	5,011 (6,337)	5,478 (7,066)	5,074 (6,446)
Vol avg hippocampus, cubic millimetres, mean (SD)		3,818 (447)	3,814 (439)		3,827 (445)	3,820 (436)		3,828 (444)	3,821 (434)		3,826 (445)	3,819 (435)		3,815 (450)	3,819 (435)	3,814 (450)	3,819 (435)	3,814 (450)	3,819 (435)	3,816 (450)	3,821 (434)	3,814 (450)	3,819 (435)

Data are presented as no. of patients (% within group), unless otherwise stated.

TMTA = trail making test A (numeric); TMTB = trail making test B (alphanumeric); SDST = symbol digit substitution; IPAQ = International Physical Activity Questionnaire activity groups.

**Table 4. I-0 participants returning at I-2**

Characteristic	I-2, N = 71,873 <sup>1</sup>	No I-2, N = 420,929 <sup>1</sup>	p-value <sup>2</sup>
Age	55 (49, 61)	58 (50, 63)	<0.0001
Sex Female	37,118 (52%)	231,615 (55%)	<0.0001
Ethnic background			<0.0001
Asian	1,038 (1.4%)	10,258 (2.4%)	
Black	516 (0.7%)	7,398 (1.8%)	
Do not know/Prefer not to answer	193 (0.3%)	1,639 (0.4%)	
Other	776 (1.1%)	6,641 (1.6%)	
White	69,322 (96%)	394,152 (94%)	
Townsend Deprivation Index	-2.58 (-3.88, -0.40)	-2.05 (-3.59, 0.70)	<0.0001
Education			<0.0001
None of the above	4,822 (6.8%)	77,180 (18%)	
Prefer not to answer	250 (0.4%)	5,029 (1.2%)	
Secondary <12 years	16,727 (24%)	118,136 (28%)	
Secondary 12 years	5,782 (8.1%)	30,054 (7.2%)	
Tertiary >12 years	43,406 (61%)	186,949 (45%)	
BMI	26.1 (23.7, 28.9)	26.9 (24.2, 30.1)	<0.0001
Ever smoked	41,237 (57%)	251,386 (60%)	<0.0001
Hearing difficulty	16,270 (23%)	102,692 (24%)	<0.0001
Ever depression	12,279 (17%)	75,703 (18%)	<0.0001
Average weekly alcohol units	12 (3, 24)	10 (0, 21)	<0.0001
IPAQ physical activity			<0.0001
High	23,927 (33%)	130,619 (31%)	
Low	10,929 (15%)	59,389 (14%)	
Missing	12,016 (17%)	102,065 (24%)	
Moderate	25,001 (35%)	128,856 (31%)	
Hypertension	19,458 (27%)	114,331 (27%)	0.6207
Myocardial infarction	1,461 (2.0%)	10,224 (2.4%)	<0.0001
Stroke	871 (1.2%)	5,902 (1.4%)	0.0001
Diabetes	2,807 (3.9%)	19,300 (4.6%)	<0.0001
Lymphoma	341 (0.5%)	1,625 (0.4%)	0.0005
Solid tumour	8,684 (12%)	33,129 (7.9%)	<0.0001
Cumulative Surgeries, mean (SD)	0.63 (1.03)	0.88 (1.34)	<0.0001
Cumulative Surgeries factored			<0.0001
0	44,497 (62%)	229,067 (54%)	



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Characteristic	I-2, N = 71,873 <sup>1</sup>	No I-2, N = 420,929 <sup>1</sup>	p-value <sup>2</sup>
1-2	23,224 (32%)	148,420 (35%)	
3-5	3,861 (5.4%)	37,952 (9.0%)	
6+	291 (0.4%)	5,490 (1.3%)	
Reaction time, milliseconds	520 (469, 586)	539 (481, 614)	<0.0001
Fluid intelligence, correct	7 (5, 8)	6 (4, 7)	<0.0001
Prospective memory, correct-first-attempt	20,374 (86%)	108,897 (75%)	<0.0001
Numeric memory, maximum correct	7 (6, 8)	7 (6, 7)	<0.0001

<sup>1</sup>Median (IQR); n (%)

<sup>2</sup>Wilcoxon rank sum test; Pearson's Chi-squared test

## Foundation models. cognitive outcomes ~ surgeries variables

Table 5. Foundation models cognitive outcomes ~ cumulative surgeries

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	1.957	1.742, 2.173		-0.114	-0.121, -0.107		0.927	0.919, 0.935		-0.052	-0.060, -0.044		1.681	1.320, 2.043		8.562	7.426, 9.698		-0.193	-0.214, -0.173		-0.099	-0.110, -0.088	
Time in years	5.373	5.296, 5.449		0.023	0.021, 0.026		1.071	1.066, 1.077		-0.008	0.011, -0.005		-0.233	0.451, -0.015	0.0363	-0.378	0.918, 0.163	0.1711	0.038	0.027, 0.049		0.023	0.017, 0.029	
Baseline age	0.880	0.325, 1.435	0.0019	0.251	0.233, 0.270		1.173	1.147, 1.199		0.068	0.048, 0.088		-8.204	9.620, -6.789		-	28.867, -19.923		0.152	0.070, 0.234	0.0003	0.102	0.059, 0.146	
Baseline age <sup>2</sup> normalised	27.853	22.831, 32.875		-2.368	-2.533, -2.202		0.187	0.153, 0.228		-0.784	0.965, -0.604		108.206	95.160, 121.251		336.585	295.328, 377.843		-4.168	4.921, -3.414		-1.513	-1.913, -1.113	
Sex Female	18.545	17.924, 19.166		-0.249	0.270, -0.229		0.918	0.896, 0.942		-0.235	0.258, -0.212		-4.550	6.039, -3.061		-0.851	5.537, 3.836	0.7220	0.099	0.012, 0.185	0.0248	0.811	0.765, 0.856	
No. Obs.	544,520			182,490			189,725			54,211			50,374			49,128			50,393			50,968		
Log-likelihood	-3,329,819			-391,363			-97,375			-91,012			-294,020			-341,047			-149,552			-119,523		
AIC	6,659,655			782,741			194,765			182,040			588,057			682,109			299,121			239,062		
BIC	6,659,744			782,822			194,836			182,111			588,127			682,180			299,191			239,133		
Residual df	544,512			182,482			189,718			54,203			50,366			49,120			50,385			50,960		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3. All p<0.0001 unless indicated.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup> normalised/1000 + time + female sex + (1|participant).

**Table 6. Foundation models cognitive outcomes ~ surgery factored**

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per category	95% CI <sup>1</sup>	p-value	Mean change per category	95% CI <sup>1</sup>	p-value	log(OR) <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per category	95% CI <sup>1</sup>	p-value	Mean change per category	95% CI <sup>1</sup>	p-value	Mean change per category	95% CI <sup>1</sup>	p-value	Mean change per category	95% CI <sup>1</sup>	p-value	Mean change per category	95% CI <sup>1</sup>	p-value
Cumulative Surgeries factored																								
1-2	2.528	1.886, 3.170		-0.224	-0.245, -0.203		0.886	0.862, 0.910		-0.087	0.111, -0.063		3.859	2.080, 5.638		17.077	11.547, 22.606		-0.448	-0.550, -0.346		-0.209	-0.264, -0.155	
3-5	7.632	6.598, 8.665		-0.455	-0.488, -0.422		0.732	0.702, 0.763		-0.208	0.246, -0.169		7.614	5.525, 9.702		34.617	28.096, 41.138		-0.822	-0.942, -0.702		-0.417	-0.481, -0.353	
6+	12.456	10.188, 14.724		-0.665	-0.737, -0.593		0.641	0.584, 0.703		-0.270	0.357, -0.184		11.602	8.294, 14.911		65.452	55.082, 75.822		-1.416	-1.607, -1.226		-0.726	-0.827, -0.625	
Time in years	5.390	5.313, 5.466		0.023	0.020, 0.025		1.071	1.066, 1.076		-0.009	0.012, -0.005		-0.236	-0.454, -0.018	0.0340	-0.381	-0.922, 0.160	0.1676	0.039	0.028, 0.050		0.023	0.018, 0.029	
Baseline age	0.874	0.319, 1.429	0.0020	0.252	0.233, 0.270		1.173	1.147, 1.199		0.068	0.048, 0.088		-8.228	9.644, -6.813		-24.446	28.919, -19.973		0.155	0.073, 0.236	0.0002	0.103	0.060, 0.147	
Baseline age <sup>2</sup> normalised	27.935	22.913, 32.958		-2.369	-2.535, -2.203		0.187	0.153, 0.228		-0.784	0.965, -0.604		108.444	95.397, 121.490		337.170	295.907, 378.433		-4.195	-4.949, -3.441		-1.526	-1.926, -1.126	
Sex Female	18.540	17.919, 19.162		-0.247	-0.268, -0.227		0.919	0.896, 0.942		-0.235	0.258, -0.212		-4.580	6.070, -3.090		-0.971	5.659, 3.717	0.6848	0.102	0.016, 0.188	0.0200	0.812	0.766, 0.858	
No. Obs.	544,520			182,490			189,725			54,211			50,374			49,128			50,393			50,968		
Log-likelihood	-3,329,830			-391,356			-97,381			-91,024			-294,020			-341,047			-149,567			-119,540		
AIC	6,659,681			782,732			194,780			182,067			588,060			682,114			299,155			239,099		
BIC	6,659,793			782,833			194,871			182,156			588,148			682,202			299,243			239,187		
Residual df	544,510			182,480			189,716			54,201			50,364			49,118			50,383			50,958		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup> normalised/1000 + time + female sex + (1|participant). All p<0.0001 unless indicated.

**Table 7. Foundation models cognitive outcome ~ high complexity surgeries**

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Cumulative Major+Major++CMO Surgeries	2.970	2.429, 3.511		-0.155	-0.172, -0.137		0.893	0.874, 0.912		-0.068	0.088, -0.048		3.086	2.090, 4.083		14.355	11.232, 17.477		-0.301	0.358, -0.243		-0.184	0.214, -0.153	
Time in years	5.512	5.437, 5.586		0.014	0.012, 0.017		1.065	1.060, 1.070		-0.012	0.016, -0.009		-0.220	0.439, -0.002	0.0477	-0.285	0.826, 0.255	0.3008	0.036	0.025, 0.047		0.023	0.017, 0.028	
Baseline age	0.875	0.320, 1.431	0.0020	0.252	0.234, 0.271		1.173	1.147, 1.199		0.068	0.048, 0.087		-8.234	9.650, -6.817		-24.598	29.077, -20.119		0.157	0.075, 0.239	0.0002	0.104	0.060, 0.147	
Baseline age <sup>2</sup> normalised	28.119	23.095, 33.144		-2.390	2.557, -2.224		0.185	0.152, 0.226		-0.790	0.971, -0.609		108.690	95.636, 121.743		339.694	298.371, 381.017		-4.247	5.002, -3.491		-1.540	1.941, -1.139	
Sex Female	18.491	17.869, 19.113		-0.247	0.268, -0.227		0.920	0.898, 0.944		-0.235	0.258, -0.211		-4.772	6.265, -3.278		-1.862	6.566, 2.842	0.4379	0.119	0.033, 0.206	0.0069	0.824	0.778, 0.870	
No. Obs.	544,520			182,490			189,725			54,211			50,374			49,128			50,393			50,968		
Log-likelihood	-3,329,919			-391,716			-97,490			-91,069			-294,042			-341,114			-149,664			-119,606		
AIC	6,659,854			783,448			194,995			182,154			588,101			682,244			299,343			239,228		
BIC	6,659,943			783,529			195,066			182,225			588,172			682,314			299,414			239,299		
Residual df	544,512			182,482			189,718			54,203			50,366			49,120			50,385			50,960		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3. All p<0.0001 unless indicated.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup> normalised/1000 + time + female sex + (1|participant).

Fully adjusted models. cognitive outcomes ~ surgeries variables

Table 8· Fully adjusted models cognitive outcome ~ cumulative surgeries

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	0.273	0.022, 0.523	0.0327	-0.057	-0.064, -0.049		0.957	0.947, 0.967		-0.025	-0.034, -0.016		0.686	0.275, 1.097	0.0011	4.351	3.081, 5.622		-0.094	-0.117, -0.070		-0.050	-0.062, -0.038	
Cumulative Stroke Admissions	41.812	33.057, 50.567		-0.348	-0.674, -0.021	0.0371	0.609	0.407, 0.911	0.0157	-0.289	-0.669, 0.091	0.01363	21.900	1.154, 44.954	0.0626	81.094	10.554, 151.634	0.0242	-1.985	3.271, -0.698	0.0025	-0.452	1.135, 0.231	0.1949
Cumulative Other Medical Admissions	3.892	3.265, 4.518		-0.093	-0.113, -0.074		0.905	0.882, 0.929		-0.058	-0.081, -0.035		2.423	1.551, 3.295	0.0000	7.376	4.674, 10.078		-0.188	-0.238, -0.139		-0.065	-0.091, -0.039	
Time in years	5.150	5.055, 5.244		0.013	0.010, 0.016		1.055	1.049, 1.061		-0.014	-0.017, -0.010		-0.236	-0.454, -0.019	0.0333	-0.430	-0.972, 0.111	0.1191	0.039	0.028, 0.050		0.022	0.016, 0.028	
Baseline age	2.572	2.021, 3.123		0.157	0.140, 0.174		1.114	1.088, 1.140		0.040	0.021, 0.060		-7.452	-8.861, -6.043		-21.294	-25.674, -16.915		0.090	0.010, 0.170	0.0280	0.077	0.035, 0.119	0.0004
Baseline age <sup>2</sup> normalised	11.307	6.316, 16.297		-1.388	-1.540, -1.235		0.312	0.253, 0.384		-0.470	-0.646, -0.293		99.792	86.806, 112.779		300.895	260.481, 341.309		-3.512	4.253, -2.772		-1.209	1.597, -0.821	
Sex Female	15.280	14.626, 15.933		-0.171	-0.191, -0.151		0.975	0.949, 1.003	0.0793	-0.205	-0.229, -0.181		-5.330	-6.897, -3.763		-0.818	-5.666, 4.031	0.7410	0.122	0.032, 0.211	0.0077	0.789	0.742, 0.836	
Deprivation	3.247	3.142, 3.352		-0.073	-0.077, -0.070		0.924	0.919, 0.928		-0.021	-0.025, -0.017		1.074	0.802, 1.345		4.616	3.776, 5.457		-0.105	-0.121, -0.090		-0.022	-0.030, -0.014	
Education																								
None of the above	22.607	21.675, 23.540		-2.003	-2.033, -1.973		0.402	0.387, 0.417		-0.703	-0.738, -0.668		30.579	27.314, 33.843		188.046	177.772, 198.320		-2.554	2.740, -2.368		-1.812	1.909, -1.715	
Prefer not to answer	34.267	31.208, 37.327		-2.124	-2.224, -2.024		0.340	0.304, 0.379		-0.718	-0.834, -0.601		37.126	24.624, 49.628		223.092	183.810, 262.374		-2.441	3.150, -1.733		-2.256	2.621, -1.891	
Secondary <12 years	8.178	7.453, 8.903		-0.993	-1.015, -0.971		0.757	0.734, 0.781		-0.240	-0.266, -0.214		8.391	6.579, 10.203		60.486	54.926, 66.047		-0.947	-1.050, -0.844		-0.905	0.959, -0.850	
Secondary ≥12 years	3.368	2.196, 4.540		-0.163	-0.198, -0.127		1.080	1.023, 1.139	0.0055	0.032	-0.012, 0.075	0.1528	0.311	-2.382, 3.004	0.8210	17.119	8.910, 25.329		-0.193	-0.345, -0.041	0.0130	-0.233	-0.313, -0.152	

Association between surgical admissions, cognition, and neurodegeneration in older people: UK Biobank population-based study – Supplementary Material

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
BMI	-1.542	-1.988, -1.096		-0.031	0.045, -0.017		0.984	0.965, 1.003	0.0943	-0.035	0.051, -0.018		-1.641	2.836, -0.446	0.7140	2.171	1.498, 5.840	0.2461	0.039	0.029, 0.107	0.2626	-0.114	-0.150, -0.078	
BMI <sup>2</sup> norm	20.768	13.427, 28.109		0.503	0.279, 0.727		1.440	1.051, 1.973	0.0232	0.397	0.128, 0.667	0.0038	25.206	4.851, 45.560	0.0152	35.021	97.440, 27.399	0.2715	-1.412	2.569, -0.256	0.0167	1.401	0.793, 2.010	
Ever smoked	-3.901	4.535, -3.268		0.157	0.137, 0.176		1.228	1.195, 1.261		0.093	0.070, 0.116		0.454	1.077, 1.984	0.5610	-3.610	8.343, 1.122	0.1349	-0.027	0.114, 0.061	0.5489	0.123	0.078, 0.169	
Ever depression	7.641	6.9108, 8.371		0.059	0.040, 0.077		1.135	1.106, 1.165		0.034	0.012, 0.057	0.0027	0.484	1.015, 1.982	0.5270	-1.316	5.925, 3.293	0.5756	-0.113	0.198, -0.028	0.0093	0.187	0.142, 0.231	
Average weekly alcohol units scaled	-4.589	4.904, -4.273		0.137	0.127, 0.146		1.139	1.122, 1.155		0.054	0.043, 0.065		-1.682	2.444, -0.919		-3.457	5.792, -1.122	0.0037	0.127	0.084, 0.170		0.097	0.075, 0.120	
IPAQ physical activity																								
Moderate	2.930	2.161, 3.699		0.306	0.283, 0.330		1.139	1.102, 1.177		0.131	0.104, 0.159		-4.827	6.608, -3.047		19.489	25.003, 13.976		0.383	0.281, 0.484		0.164	0.111, 0.218	
Low	3.601	2.621, 4.582		0.325	0.294, 0.355		1.145	1.097, 1.196		0.164	0.128, 0.201		-6.359	8.643, -4.075		32.084	39.144, 25.024		0.557	0.426, 0.687		0.207	0.139, 0.276	
Missing	6.745	5.880, 7.609		-0.140	0.167, -0.113		0.815	0.787, 0.845		-0.066	0.098, -0.035		1.152	1.105, 3.409		2.239	4.767, 9.245	0.5311	-0.246	0.375, -0.117	0.0002	-0.166	0.234, -0.099	
Hypertension	3.933	3.196, 4.669		-0.097	0.119, -0.074		0.922	0.894, 0.951		-0.035	0.063, -0.008	0.0102	3.341	1.571, 5.111		10.601	5.110, 16.091	0.0002	-0.286	0.387, -0.185		-0.109	0.162, -0.056	0.0001
Diabetes	11.930	10.386, 13.474		-0.191	0.237, -0.144		0.812	0.766, 0.861		-0.115	0.174, -0.057	0.0001	13.794	9.806, 17.781		33.989	21.537, 46.440		-0.812	1.039, -0.585		-0.188	0.308, -0.069	0.0019
Solid tumour	-2.306	3.425, -1.187		0.133	0.098, 0.167		1.180	1.125, 1.237		0.078	0.036, 0.119	0.0002	-1.743	4.062, 0.576		-6.189	13.381, 1.004	0.0917	0.045	0.088, 0.177	0.5083	0.048	0.021, 0.117	0.1756
Cumulative Surgeries * Cumulative Other Medical Admissions	-0.234	0.357, -0.111		0.009	0.005, 0.012		1.012	1.007, 1.017		0.008	0.004, 0.012	0.0004												
Time in years * Deprivation	-0.119	0.145, -0.092		0.001	0.000, 0.002	0.0150	1.003	1.001, 1.005	0.0008															

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
No. Obs.	544,520			182,490			189,725			54,211			50,374			49,128			50,393			50,968		
Log-likelihood	-3,324,271			-376,926			-93,180			-89,571			-293,634			-339,940			-148,648			-118,009		
AIC	6,648,598			753,909			186,414			179,197			587,321			679,933			297,348			236,070		
BIC	6,648,912			754,192			186,688			179,437			587,550			680,162			297,577			236,300		
Residual df	544,492			182,462			189,698			54,184			50,348			49,102			50,367			50,942		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3. All p<0.0001 unless indicated.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup> normalised/1000 + time + female sex + (1|participant).

<sup>3</sup>Fully adjusted models were cognitive outcome ~ surgeries + cumulative stroke admissions + cumulative other medical admissions + age + age<sup>2</sup> normalised + time\*deprivation + female sex + education + body mass index + body mass index<sup>2</sup> normalised + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalised by variable<sup>2</sup> / 1000. Interaction for surgeries\*other medical admissions and time\*deprivation included in reaction time, fluid intelligence and prospective memory fully adjusted models. Linear smoothing uses the formula,  $y \sim x + I(x^2)$ . Cumulative surgical procedures calculated from 8 years prior to baseline (instance 0).

Foundation models. cognitive outcomes ~ brain imaging variables

Table 9. Foundation models cognitive outcomes ~ volume of white matter hyperintensities

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value
Volume of white matter hyperintensities	0.0008	0.0006, 0.0009		-1.11e-05	-1.42e-05, -8.06e-06		1	1, 1		-8.73e-06	-1.12e-05, -6.24e-06		0.0003	0.0002, 0.0005		0.0013	0.0009, 0.0017		-4.82e-07	-6.44e-07, -3.2e-07		-1.67e-05	-2.08e-05, -1.26e-05	
Baseline age	3.022	1.135, 4.909	0.0017	0.217	0.180, 0.254		1.180	1.126, 1.238		0.102	0.071, 0.133		-6.799	-8.514, -5.085		8.014	-13.402, -2.625	0.0036	0.006	0.004, 0.008		0.114	0.062, 0.165	
Baseline age <sup>2</sup> norm	9.851	-7.524, 27.226	0.2665	-2.173	-2.513, -1.832		0.152	0.099, 0.234		-1.172	-1.457, -0.887		91.968	76.148, 107.788		155.760	106.072, 205.448		0.071	-0.090, -0.053		-1.598	-2.077, -1.120	
Time in years	1.471	0.522, 2.419	0.0024	0.017	0.000, 0.034	0.0437	1.069	1.035, 1.105	0.0001	-0.009	-0.025, 0.007	0.2824	-1.157	-2.066, -0.248	0.0126	-4.318	-7.020, -1.617	0.0017	-	-0.001, 0.001	0.9183	0.042	0.018, 0.067	0.0008
Sex Female	23.199	21.213, 25.185		-0.299	-0.338, -0.260		0.996	0.947, 1.048	0.8799	-0.233	-0.266, -0.200		-4.969	-6.782, -3.157		-5.595	-11.292, -0.102	0.0543	-0.007	-0.009, -0.004		0.763	0.709, 0.818	
No. Obs.	46,246			45,745			46,577			37,108			36,434			36,434			36,005			36,434		
Log-likelihood	-280,177																							
AIC	560,370			192,752			41,076			137,734			427,864			510,056			-63,891			170,825		
BIC	560,440			192,822			41,137			137,802			427,932			510,124			-63,823			170,893		
Residual df	46,238			45,737			46,570			37,100			36,426			36,426			35,997			36,426		

<sup>1</sup>CI = confidence interval; OR = odds ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All p<0.0001 unless indicated.

<sup>2</sup>All available raw data were used across instances 0, 2, 3. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All minimally adjusted linear mixed effects models were adjusted for cognitive outcome ~ imaging variable + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not justified/not used in imaging models.



**Table 10. Foundation models cognitive outcomes ~ volume of average hippocampus**

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value
vol hippocampus avg	-0.017	-0.019, -0.014		0.0005	0.0005, 0.0006		1	1, 1		0.0003	0.0002, 0.0003		-0.011	-0.014, -0.009		-0.032	-0.039, -0.025		7.95e-06	5.41e-06, 1.05e-05		0.0003	0.0003, 0.0004	
Baseline age	3.620	1.766, 5.474	0.0001	0.197	0.161, 0.234		1.174	1.119, 1.231		0.094	0.063, 0.125		-6.581	-8.284, -4.878		-7.593	-12.966, -2.220	0.0056	0.006	0.004, 0.008		0.110	0.058, 0.161	
Baseline age <sup>2</sup> normalized	3.550	-13.515, 20.615	0.6834	-1.939	-2.273, -1.605		0.163	0.106, 0.250		-1.084	-1.367, -0.801		88.906	73.205, 104.607		150.207	100.678, 199.736		-0.070	-0.088, -0.051		-1.559	-2.034, -1.083	
Time in years	1.386	0.450, 2.322	0.0037	0.023	0.007, 0.040	0.0051	1.072	1.037, 1.108		-0.006	-0.022, 0.010	0.4691	-1.255	-2.161, -0.350	0.0066	-4.764	-7.465, -2.062	0.0005	0.000	-0.001, 0.001	0.8549	0.046	0.022, 0.071	0.0002
Sex Female	18.963	16.938, 20.988		-0.176	-0.215, -0.136		1.082	1.027, 1.140	0.0030	-0.170	-0.204, -0.137		-7.819	-9.683, -5.955		-14.096	-19.979, -8.214		-0.004	-0.007, -0.002	0.0001	0.850	0.793, 0.906	
No. Obs.	47,556			47,027			46,577			37,551			36,822			36,822			36,387			36,822		
AIC	576,127			197,908			41,011			139,266			432,326			515,706			-64,478			172,670		
BIC	576,197			197,978			41,072			139,334			432,394			515,774			-64,410			172,738		
Residual df	47,548			47,019			46,570			37,543			36,814			36,814			36,379			36,814		

<sup>1</sup>CI = confidence interval; OR = odds ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All p<0.0001 unless indicated.

<sup>2</sup>All available raw data were used across instances 0, 2, 3. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All minimally adjusted linear mixed effects models were adjusted for cognitive outcome ~ imaging variable + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not justified/not used in imaging models.

Fully adjusted models. cognitive outcomes ~ brain imaging primary outcomes

Table 11· Fully adjusted models. cognitive outcomes ~ white matter hyperintensities

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value
Volume of white matter hyperintensities	0.0007	0.0006, 0.0009		-8.16e-06	-1.11e-05, -5.18e-06		1	1, 1		-6.16e-06	-8.68e-06, -3.63e-06		0.0003	0.0001, 0.0004		0.0012	0.0007, 0.0016		-3.53e-07	-5.2e-07, -1.85e-07		-1.15e-05	-1.56e-05, -7.36e-06	
Cumulative Stroke Admissions	-1.401	-37.700, -34.899	0.9397	-1.086	-1.750, -0.422	0.0014	0.445	0.205, 0.966	0.0406	-0.285	-0.860, 0.291	0.3320	1.758	30.557, 34.074	0.9151	82.166	16.293, 180.625	0.1019	-0.018	-0.056, 0.019	0.3351	-0.319	-1.246, 0.607	0.4997
Cumulative Other Medical Admissions	2.475	1.315, 3.635	0.0000	-0.106	0.128, -0.085	0.0000	0.903	0.879, 0.927	0.0000	-0.027	-0.046, 0.009	0.0038	2.593	1.553, 3.634	0.0000	8.488	5.275, 11.702	0.0000	-0.003	0.004, -0.002	0.0000	-0.089	-0.120, -0.059	0.0000
Baseline age	3.602	1.694, 5.511	0.0002	0.171	0.136, 0.207	0.0000	1.163	1.108, 1.222	0.0000	0.084	0.053, 0.115	0.0000	-6.104	7.850, -4.359	0.0000	-5.819	11.215, -0.424	0.0345	0.006	0.003, 0.008	0.0000	0.086	0.035, 0.138	0.0010
Baseline age <sup>2</sup> normalised	3.330	-14.257, 20.916	0.7106	-1.667	-1.993, -1.341	0.0000	0.182	0.117, 0.284	0.0000	-0.972	-1.258, -0.686	0.0000	84.110	67.997, 100.224	0.0000	130.505	80.720, 180.290	0.0000	-0.063	0.082, -0.044	0.0000	-1.288	-1.761, -0.815	0.0000
Time in years	1.530	0.578, 2.481	0.0016	0.023	0.006, 0.040	0.0065	1.062	1.028, 1.099	0.0004	-0.007	-0.023, 0.009	0.3781	-1.284	2.198, -0.369	0.0060	-4.493	7.186, -1.799	0.0011	0.000	0.001, 0.001	0.8081	0.042	0.018, 0.067	0.0007
Sex Female	22.648	20.526, 24.771	0.0000	-0.264	0.304, -0.225	0.0000	1.008	0.954, 1.065	0.7790	-0.214	-0.249, 0.179	0.0000	-5.400	7.349, -3.451	0.0000	-5.328	11.354, 0.697	0.0830	-0.007	0.009, -0.004	0.0000	0.750	0.693, 0.808	0.0000
Deprivation	1.169	0.797, 1.540	0.0000	-0.028	-0.035, 0.021	0.0000	0.967	0.958, 0.976	0.0000	-0.012	-0.018, 0.006	0.0001	0.831	0.493, 1.169	0.0000	3.376	2.330, 4.421	0.0000	-0.001	-0.001, 0.000	0.0109	-0.021	-0.031, -0.011	0.0000
Education	NA		NA	NA		NA	NA		NA		NA	NA	NA		NA		NA	NA		NA	NA		NA	NA
Prefer not to answer	23.724	5.506, 41.941	0.0107	0.093	0.249, 0.434	0.5939	1.005	0.684, 1.478	0.9790	0.171	-0.130, 0.473	0.2652	-4.029	21.081, 13.022	0.6432	-38.960	91.125, 13.205	0.1432	0.002	0.018, 0.022	0.8544	-0.590	-1.082, -0.098	0.0188

Association between surgical admissions, cognition, and neurodegeneration in older people: UK Biobank population-based study – Supplementary Material

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value
Secondary <12 years	-9.979	-14.592, -5.365	0.0000	0.962	0.875, 1.048	0.0000	1.696	1.535, 1.874	0.0000	0.499	0.422, 0.576	0.0000	-20.669	-25.040, -16.298	0.0000	-83.773	-97.201, -70.344	0.0000	0.025	0.020, 0.030	0.0000	0.828	0.701, 0.955	0.0000
Secondary 12 years	-15.635	-21.029, -10.241	0.0000	1.732	1.632, 1.833	0.0000	2.606	2.284, 2.973	0.0000	0.867	0.778, 0.957	0.0000	-29.584	-34.651, -24.518	0.0000	-120.435	-136.001, -104.869	0.0000	0.033	0.027, 0.039	0.0000	1.546	1.399, 1.693	0.0000
Tertiary >12 years	-21.723	-26.075, -17.370	0.0000	2.039	1.957, 2.120	0.0000	2.363	2.153, 2.595	0.0000	0.827	0.754, 0.899	0.0000	-28.669	-32.787, -24.552	0.0000	-135.043	-147.700, -122.386	0.0000	0.035	0.030, 0.039	0.0000	1.746	1.626, 1.866	0.0000
BMI	0.701	-1.043, 2.445	0.4306	-0.050	-0.082, 0.018	0.0023	0.965	0.920, 1.011	0.1351	-0.038	-0.067, 0.009	0.0108	-0.798	-2.429, 0.833	0.3377	3.394	1.634, 8.421	0.1858	-0.000	-0.002, 0.001	0.6564	-0.122	-0.169, 0.074	0.0000
BMI <sup>2</sup> norm	-12.655	-42.668, 17.358	0.4085	0.695	0.141, 1.249	0.0139	1.797	0.793, 4.073	0.1601	0.370	-0.130, 0.869	0.1472	9.992	18.178, 38.163	0.4869	-46.336	133.146, 40.474	0.2955	-0.004	-0.036, 0.029	0.8350	1.522	0.699, 2.345	0.0003
Ever smoked	-0.580	-2.647, 1.487	0.5823	0.039	0.000, 0.077	0.0476	1.045	0.990, 1.103	0.1096	0.053	0.019, 0.087	0.0021	0.292	1.603, 2.187	0.7629	-0.448	6.304, 5.409	0.8809	0.000	-0.002, 0.003	0.7700	0.134	0.078, 0.189	0.0000
Ever depression	-1.725	-3.745, 0.294	0.0940	0.035	0.002, 0.073	0.0628	1.148	1.089, 1.210	0.0000	-0.006	-0.039, 0.027	0.7355	1.243	0.621, 3.106	0.1911	1.148	4.598, 6.894	0.6953	0.000	0.002, 0.002	0.9230	0.157	0.103, 0.212	0.0000
average total weekly units alcohol scaled	-0.705	-1.081, 0.330	0.0002	0.033	0.026, 0.039	0.0000	1.011	1.001, 1.022	0.0303	0.028	0.022, 0.034	0.0000	-0.463	-0.812, 0.113	0.0094	-1.251	2.326, 0.176	0.0225	0.001	0.000, 0.001	0.0026	0.034	0.023, 0.044	0.0000
IPAQ physical activity	NA		NA	NA		NA	NA		NA	NA	NA	NA	NA		NA	NA		NA	NA	NA	NA	NA		NA
Low	0.307	-2.781, 3.394	0.8456	0.394	0.336, 0.451	0.0000	1.256	1.155, 1.365	0.0000	0.200	0.150, 0.251	0.0000	-6.926	9.772, 4.080	0.0000	-26.135	34.936, 17.334	0.0000	0.004	0.001, 0.008	0.0112	0.243	0.159, 0.326	0.0000
Missing	3.697	0.669, 6.724	0.0167	-0.001	-0.057, 0.055	0.9739	0.918	0.852, 0.989	0.0245	-0.041	-0.090, 0.009	0.1095	-4.707	7.497, 1.917	0.0009	-11.922	20.547, 3.297	0.0067	-0.003	-0.006, 0.000	0.0784	-0.115	-0.197, 0.033	0.0058

Association between surgical admissions, cognition, and neurodegeneration in older people: UK Biobank population-based study – Supplementary Material

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value
Moderate	1.710	-0.700, 4.121	0.1643	0.301	0.257, 0.346	0.0000	1.122	1.053, 1.194	0.0003	0.127	0.087, 0.166	0.0000	-5.918	8.124, -3.712	0.0000	-13.764	20.587, -6.942	0.0001	0.004	0.001, 0.007	0.0021	0.195	0.130, 0.260	0.0000
Hypertension	1.001	-1.406, 3.409	0.4148	-0.046	0.091, -0.001	0.0439	1.029	0.968, 1.094	0.3581	-0.047	0.087, -0.008	0.0188	1.404	0.819, 3.627	0.2158	2.288	4.581, 9.158	0.5138	-0.003	0.006, -0.001	0.0164	-0.079	0.144, -0.014	0.0173
Diabetes	9.993	4.621, 15.366	0.0003	-0.096	0.196, 0.004	0.0591	0.901	0.791, 1.025	0.1122	-0.183	0.272, -0.094	0.0001	10.963	5.964, 15.963	0.0000	14.713	0.746, 30.172	0.0621	-0.012	0.018, -0.006	0.0001	-0.267	0.414, -0.120	0.0004
Solid tumour	-0.829	-3.960, 2.301	0.6036	0.009	0.049, 0.067	0.7646	1.043	0.964, 1.128	0.2997	-0.008	0.059, 0.043	0.7492	-0.694	-3.546, 2.158	0.6334	-2.038	10.856, 6.780	0.6505	-0.002	0.005, 0.001	0.2205	-0.011	0.095, 0.073	0.7920
No. Obs.	44,854			44,367			45,180			35,731			35,061			35,061			34,644			35,061		
AIC	542,887			182,212			38,931			131,560			411,413			489,429			-61,380			162,446		
BIC	543,113			182,438			39,149			131,781			411,634			489,649			-61,160			162,666		
Residual df	44,828			44,341			45,155			35,705			35,035			35,035			34,618			35,035		

<sup>1</sup>CI = confidence interval; OR = odds ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All p<0.0001 unless indicated.

<sup>2</sup>All available raw data were used across instances 0, 2, 3. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All minimally adjusted linear mixed effects models were adjusted for cognitive outcome ~ imaging variable + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not justified/not used in imaging models.

Table 12- Fully adjusted models cognitive outcomes ~ average volume of hippocampus

Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value
Volume average hippocampus	-0.015	-0.017, -0.012		0.0004	0.000364, 0.000452		1.00	1, 1		0.0002	0.00017, 0.000249		-0.009	-0.012, -0.008		-0.025	-0.032, -0.018		6.25e-06	3.67e-06, 8.84e-06		0.0002	0.0002, 0.0003	
Cumulative Stroke Admissions	-1.476	-36.634, 33.682	0.9344	-1.030	-1.674, -0.387	0.0017	0.424	0.196, 0.915	0.0287	-0.271	-0.845, 0.304	0.3556	1.539	30.731, 33.809	0.9255	84.256	14.474, 182.985	0.0944	-0.019	-0.056, 0.019	0.3262	-0.337	-1.264, 0.589	0.4755
Cumulative Other Medical Admissions	2.477	1.336, 3.618	0.0000	-0.103	-0.125, -0.082	0.0000	0.903	0.879, 0.927	0.0000	-0.031	-0.050, -0.013	0.0008	2.519	1.487, 3.551	0.0000	8.153	4.952, 11.355	0.0000	-0.003	-0.004, -0.002	0.0000	-0.087	-0.117, -0.057	0.0000
Baseline age	4.101	2.225, 5.977	0.0000	0.156	0.121, 0.191	0.0000	1.158	1.103, 1.216	0.0000	0.076	0.046, 0.107	0.0000	-5.970	-7.704, -4.237	0.0000	-5.357	-10.739, -0.024	0.0510	0.005	0.003, 0.007	0.0000	0.086	0.035, 0.137	0.0010
Baseline age <sup>2</sup> normalised	-1.904	-19.180, 15.372	0.8290	-1.485	-1.805, -1.164	0.0000	0.191	0.123, 0.299	0.0000	-0.889	-1.174, -0.605	0.0000	81.982	65.985, 97.978	0.0000	124.955	75.320, 174.590	0.0000	-0.061	-0.080, -0.042	0.0000	-1.279	-1.749, -0.809	0.0000
Time in years	1.473	0.533, 2.412	0.0021	0.027	0.011, 0.044	0.0011	1.064	1.029, 1.100	0.0003	-0.005	-0.021, 0.011	0.5607	-1.363	-2.274, -0.451	0.0034	-4.847	-7.540, -2.154	0.0004	0.000	0.001, 0.001	0.7592	0.045	0.021, 0.070	0.0003
Sex Female	18.756	16.594, 20.918	0.0000	-0.165	-0.205, -0.125	0.0000	1.083	1.023, 1.146	0.0059	-0.164	-0.200, -0.129	0.0000	-7.906	-9.909, -5.903	0.0000	-12.221	-18.440, -6.003	0.0001	-0.005	-0.007, -0.003	0.0000	0.810	0.751, 0.869	0.0000
Deprivation	1.100	0.734, 1.465	0.0000	-0.026	-0.033, -0.020	0.0000	0.968	0.959, 0.977	0.0000	-0.012	-0.018, -0.006	0.0001	0.795	0.459, 1.131	0.0000	3.402	2.359, 4.445	0.0000	-0.001	-0.001, 0.000	0.0127	-0.020	-0.030, -0.010	0.0001
Education	NA		NA	NA		NA	NA		NA		NA	NA	NA		NA		NA	NA		NA		NA		NA
Prefer not to answer	19.589	2.106, 37.072	0.0281	0.081	-0.247, 0.408	0.6285	0.989	0.672, 1.455	0.9546	0.112	-0.181, 0.405	0.4529	-6.230	-22.804, 10.344	0.4613	-52.015	-102.934, -1.097	0.0453	-0.004	-0.023, 0.016	0.7186	-0.568	-1.047, -0.089	0.0201

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Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches		
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value
Secondary <12 years	-9.839	-14.383, -5.295	0.0000	0.954	0.869, 1.039	0.0000	1.680	1.520, 1.856	0.0000	0.497	0.420, 0.574	0.0000	-20.018	-24.359, -15.677	0.0000	-86.553	-99.946, -73.160	0.0000	0.025	0.020, 0.030	0.0000	0.850	0.723, 0.976	0.0000
Secondary 12 years	-15.522	-20.835, -10.208	0.0000	1.716	1.617, 1.815	0.0000	2.558	2.242, 2.918	0.0000	0.861	0.771, 0.950	0.0000	-28.802	-33.836, -23.768	0.0000	-122.564	-138.095, -107.034	0.0000	0.033	0.027, 0.039	0.0000	1.553	1.407, 1.700	0.0000
Tertiary >12 years	-20.916	-25.207, -16.626	0.0000	2.012	1.931, 2.092	0.0000	2.307	2.101, 2.533	0.0000	0.813	0.741, 0.886	0.0000	-27.693	-31.785, -23.601	0.0000	-136.895	-149.525, -124.264	0.0000	0.034	0.029, 0.039	0.0000	1.751	1.632, 1.870	0.0000
BMI	0.846	0.829, 2.521	0.3222	-0.057	-0.088, -0.026	0.0003	0.961	0.917, 1.008	0.1030	-0.051	-0.079, -0.023	0.0004	-0.932	-2.514, 0.650	0.2481	3.681	1.222, 8.583	0.1412	-0.001	-0.003, 0.001	0.2933	-0.131	-0.177, -0.084	0.0000
BMI <sup>2</sup> norm	-12.929	-41.662, 15.804	0.3778	0.790	0.260, 1.320	0.0035	1.854	0.817, 4.205	0.1397	0.588	0.105, 1.071	0.0171	13.395	13.831, 40.621	0.3349	-48.281	-132.643, 36.081	0.2620	0.006	0.026, 0.038	0.7127	1.651	0.853, 2.449	0.0001
Ever smoked	-0.394	2.430, 1.642	0.7046	0.039	0.002, 0.077	0.0405	1.045	0.990, 1.103	0.1100	0.053	0.020, 0.087	0.0017	0.544	1.339, 2.427	0.5714	0.337	5.507, 6.181	0.9100	0.000	0.002, 0.003	0.7501	0.131	0.076, 0.186	0.0000
Ever depression	-1.381	3.369, 0.607	0.1734	0.033	-0.004, 0.070	0.0779	1.145	1.086, 1.207	0.0000	-0.006	-0.039, 0.027	0.7085	1.277	0.575, 3.129	0.1765	1.535	4.198, 7.268	0.5997	-0.000	0.002, 0.002	0.8132	0.154	0.100, 0.208	0.0000
average total weekly units alcohol scaled	-0.845	1.214, 0.476	0.0000	0.035	0.028, 0.042	0.0000	1.012	1.002, 1.023	0.0172	0.029	0.023, 0.035	0.0000	-0.509	0.856, 0.162	0.0040	-1.304	2.377, -0.232	0.0172	0.001	0.000, 0.001	0.0028	0.035	0.025, 0.045	0.0000
IPAQ physical activity	NA		NA	NA		NA	NA		NA	NA		NA		NA	NA		NA	NA		NA	NA		NA	NA
Low	-0.280	3.318, 2.759	0.8568	0.391	0.334, 0.447	0.0000	1.260	1.159, 1.370	0.0000	0.201	0.151, 0.251	0.0000	-7.143	9.971, 4.315	0.0000	-26.548	35.330, 17.767	0.0000	0.004	0.001, 0.007	0.0141	0.248	0.165, 0.331	0.0000

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Characteristic	Reaction time, milliseconds			Fluid intelligence, correct			Prospective memory, correct-first-time (logistic)			Numeric memory, maximum correct			TMTA, deciseconds			TMTB, deciseconds			SDST, matches			Paired associate learning, matches						
	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value	Mean change per cubic millimetre	95% CI <sup>1</sup>	p-value				
Missing	3.888	0.907 6.869	0.0106	0.002	-0.054, 0.057	0.9562	0.922	0.856, 0.994	0.0332	-	0.037	-0.086, 0.013	0.1452	-	7.354 1.806	0.0012	-	11.831	20.444, 3.219	0.0071	-	0.003	0.006, 0.000	0.0699	-	0.115	0.196 0.033	0.0059
Moderate	1.754	- 0.621 4.129	0.1478	0.305	0.261, 0.349	0.0000	1.125	1.057, 1.198	0.0002	0.132	0.093, 0.171	0.0000	-	6.030	8.222 3.838	0.0000	-	14.698	21.506, 7.890	0.0000	0.004	0.002, 0.007	0.0016	0.201	0.137 0.266	0.0000		
Hypertension	1.426	- 0.930 3.782	0.2355	-	-0.093, -0.006	0.0266	1.010	0.951, 1.074	0.7376	-	0.053	-0.092, -0.014	0.0075	1.673	0.523 3.868	0.1354	2.889	3.925, 9.703	0.4059	-	0.004	-	0.007, 0.001	0.0028	-	0.092	0.157 0.028	0.0051
Diabetes	9.585	4.334 14.836	0.0003	-	-0.164, 0.031	0.1826	0.917	0.806, 1.044	0.1897	-	0.166	-0.253, -0.078	0.0002	11.150	6.201 16.099	0.0000	16.122	0.756, 31.489	0.0398	-	0.010	0.016, 0.005	0.0004	-	0.248	0.393 0.102	0.0009	
Solid tumour	-	3.619 2.552	0.7347	0.007	-0.050, 0.065	0.8013	1.037	0.959, 1.123	0.3622	-	0.006	-0.057, 0.044	0.8132	-	3.419 2.254	0.6874	-	9.735, 7.877	0.8362	-	0.002	0.006, 0.001	0.1982	-	0.017	0.100 0.067	0.6973	
No. Obs.	46,149			45,634			45,180			36,159			35,435			35,435			35,012			35,435						
AIC	558,473			187,272			38,888			133,046			415,712			494,855			-	61,941			164,208					
BIC	558,700			187,499			39,106			133,267			415,932			495,076			-	61,721			164,428					
Residual df	46,123			45,608			45,155			36,133			35,409			35,409			34,986			35,409						

<sup>1</sup>CI = confidence interval; OR = odds ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All p<0.0001 unless indicated.

<sup>2</sup>All available raw data were used across instances 0, 2, 3. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All minimally adjusted linear mixed effects models were adjusted for cognitive outcome ~ imaging variable + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not justified/not used in imaging models.

## Foundation models. brain imaging outcomes ~ surgeries variables

**Table 13. Foundation models brain imaging ~ cumulative surgeries**

Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	175.172	144.877, 205.466		-8.524	-10.425, -6.622	
Time in years	52.555	43.118, 61.993		-5.584	-6.014, -5.153	
Baseline age	-922.493	-1035.858, -809.127		56.638	49.412, 63.864	
Baseline age <sup>2</sup> normalised	11390.402	10350.931, 12429.874		-686.486	-752.731, -620.242	
Sex Female	-508.869	-628.707, -389.031		223.409	-231.060, -215.758	
No. Obs.	47,686			49,217		
Log-likelihood	-482,811			-362,154		
AIC	965,638			724,323		
BIC	965,708			724,394		
Residual df	47,678			49,209		

<sup>1</sup>CI = Confidence Interval. All p<0.0001 unless indicated.

Imaging outcomes are in units of cubic millimetres. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All available data were used across instances 0, 2, 3. All minimally adjusted linear mixed effects models were brain imaging outcome ~ surgeries variable(s) + age + normalized age<sup>2</sup> + female sex (1|participant). All fully adjusted linear mixed effects models were brain imaging outcome ~ surgeries variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not significant/used in imaging models.



**Table 14. Foundation models brain imaging ~ surgery factored**

Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
Cumulative Surgeries factored						
1-2	246.219	112.378, 380.061		-6.206	-14.326, 1.913	0.1341
3-5	542.223	378.429, 706.017		-28.674	-38.759, -18.588	
6+	1453.631	1176.119, 1731.143		-58.959	-76.010, -41.908	
Time in years	53.195	43.759, 62.630		-5.628	-6.059, -5.198	
Baseline age	-924.706	-1038.085, -811.326		56.751	49.525, 63.978	
Baseline age <sup>2</sup> normalised	11418.443	10378.910, 12457.977		-688.025	-754.270, -621.779	
Sex Female	-508.485	-628.360, -388.611		-223.541	-231.194, -215.888	
No. Obs.	47,686			49,217		
Log-likelihood	-482,802			-362,152		
AIC	965,624			724,325		
BIC	965,712			724,413		
Residual df	47,676			49,207		

<sup>1</sup>CI = Confidence Interval. All p<0.0001 unless indicated.

Imaging outcomes are in units of cubic millimetres. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All available data were used across instances 0, 2, 3. All minimally adjusted linear mixed effects models were: brain imaging outcome ~ surgeries variable(s) + age + normalized age<sup>2</sup> + female sex (1|participant). All fully adjusted linear mixed effects models were: brain imaging outcome ~ surgeries variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not significant/used in imaging models.

**Table 15. Foundation models brain imaging ~ high complexity cumulative surgeries**

Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
Cumulative Major+Major++CMO Surgeries	414.538	330.815, 498.262		-22.163	-27.400, -16.927	
Time in years	54.607	45.183, 64.032		-5.672	-6.101, -5.243	
Baseline age	-921.803	-1035.215, -808.390		56.586	49.359, 63.813	
Baseline age <sup>2</sup> normalised	11396.624	10356.692, 12436.557		-686.403	-752.660, -620.147	
Sex Female	-536.675	-656.861, -416.489		-221.843	-229.514, -214.172	
No. Obs.	47,686			49,217		
Log-likelihood	-482,827			-362,157		
AIC	965,670			724,330		
BIC	965,740			724,400		
Residual df	47,678			49,209		

<sup>1</sup>CI = Confidence Interval. All p<0.0001 unless indicated.

Imaging outcomes are in units of cubic millimetres. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All available data were used across instances 0, 2, 3. All minimally adjusted linear mixed effects models were brain imaging outcome ~ surgeries variable(s) + age + normalized age<sup>2</sup> + female sex (1|participant). All fully adjusted linear mixed effects models were brain imaging outcome ~ surgeries variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not significant/used in imaging models.

## Fully adjusted models. primary brain imaging outcomes ~ surgeries variables

Table 16. Fully adjusted models. primary brain imaging outcomes ~ cumulative surgeries

Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	100.022	66.173, 133.871		-5.763	-7.892, -3.635	
Cumulative Stroke Admissions	6271.288	4320.191, 8222.385		-161.291	-277.374, -45.208	0.0065
Cumulative Other Medical Admissions	148.509	75.389, 221.629	0.0001	-8.660	-13.249, -4.070	0.0002
Time in years	53.759	44.298, 63.220		-5.661	-6.095, -5.227	
Baseline age	-943.036	-1055.488, -830.585		56.207	48.994, 63.420	
Baseline age <sup>2</sup> normalised	11459.545	10428.027, 12491.062		-679.031	-745.180, -612.881	
Sex Female	-248.620	-374.122, -123.119	0.0001	-230.410	-238.448, -222.371	
Deprivation	3.081	-18.859, 25.022	0.7831	-4.024	-5.432, -2.616	
Education						
None of the above	-65.030	-309.989, 179.930	0.6028	-63.121	-78.311, -47.930	
Prefer not to answer	512.760	-443.607, 1469.127	0.2933	-35.366	-91.446, 20.714	0.2164
Secondary <12 years	-33.432	-172.725, 105.861	0.6381	-42.271	-50.844, -33.698	
Secondary 12 years	212.806	6.494, 419.117	0.0432	-28.289	-40.695, -15.883	
BMI	-66.647	-168.068, 34.775	0.1978	12.089	5.887, 18.290	0.0001
BMI <sup>2</sup> normalised	2729.575	985.317, 4473.834	0.0022	-197.713	-303.993, -91.433	0.0003
Ever smoked	153.177	31.306, 275.048	0.0138	-4.569	-12.336, 3.198	0.2489
Ever depression	-120.204	-237.549, -2.860	0.0447	14.184	6.874, 21.493	0.0001
Average weekly alcohol units (scaled)	64.299	5.607, 122.991	0.0318	-10.233	-13.810, -6.656	

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Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
IPAQ physical activity						
Moderate	77.386	-65.567, 220.339	0.2887	-7.812	-17.002, 1.378	0.0957
Low	60.143	-123.355, 243.641	0.5206	-11.354	-23.137, 0.429	0.0589
Missing	233.796	55.298, 412.294	0.0103	-23.489	-34.960, -12.019	0.0001
Hypertension	1521.798	1380.399, 1663.198		-21.555	-30.618, -12.493	
Diabetes	877.029	561.274, 1192.784		-91.574	-111.677, -71.470	
Solid tumour	16.439	-172.458, 205.336	0.8646	10.747	-1.393, 22.886	0.0827
No. Obs.	47,686			49,217		
Log-likelihood	-482,225			-361,899		
AIC	964,501			723,850		
BIC	964,729			724,079		
Residual df	47,660			49,191		

<sup>1</sup>CI = Confidence Interval. All p<0.0001 unless indicated.

Imaging outcomes are in units of cubic millimetres. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All available data were used across instances 0, 2, 3. All minimally adjusted linear mixed effects models were: brain imaging outcome ~ surgeries variable(s) + age + normalized age<sup>2</sup> + female sex (1|participant). All fully adjusted linear mixed effects models were: brain imaging outcome ~ surgeries variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not significant/used in imaging models.

**Table 17. Fully adjusted models. primary brain imaging outcomes ~ surgery factored**

Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
Cumulative Surgeries factored						
1-2	145.862	12.237, 279.487	0.0324	-2.777	-10.939, 5.385	0.5049
3-5	262.272	92.945, 431.600	0.0024	-19.288	-29.766, -8.809	0.0003
6+	902.681	604.109, 1201.253		-36.960	-55.376, -18.544	0.0001
Cumulative Stroke Admissions	6263.470	4312.466, 8214.475		-160.243	-276.336, -44.151	0.0068
Cumulative Other Medical Admissions	155.660	83.497, 227.823		-9.610	-14.134, -5.086	
Time in years	54.136	44.676, 63.595		-5.690	-6.124, -5.256	
Baseline age	-943.435	-1055.893, -830.978		56.199	48.985, 63.412	
Baseline age <sup>2</sup> normalised	11467.268	10435.715, 12498.822		-679.208	-745.359, -613.056	
Sex Female	-248.456	-373.979, -122.932	0.0001	-230.510	-238.550, -222.470	
Deprivation	3.521	-18.420, 25.462	0.7531	-4.044	-5.452, -2.636	
Education						
None of the above	-64.289	-309.227, 180.649	0.6069	-63.528	-78.719, -48.338	
Prefer not to answer	520.179	-436.197, 1476.555	0.2864	-35.693	-91.777, 20.392	0.2123
Secondary <12 years	-32.437	-171.739, 106.866	0.6481	-42.481	-51.055, -33.907	
Secondary 12 years	211.143	4.833, 417.453	0.0449	-28.265	-40.673, -15.858	
BMI	-66.393	-167.827, 35.041	0.1995	12.064	5.861, 18.267	0.0001
BMI <sup>2</sup> norm	2728.401	983.996, 4472.806	0.0022	-197.495	-303.789, -91.201	0.0003
Ever smoked	155.599	33.727, 277.471	0.0123	-4.716	-12.483, 3.051	0.2340
Ever depression	-119.630	-236.984, -2.276	0.0457	14.062	6.751, 21.372	0.0002
Average weekly alcohol units (scaled)	63.847	5.153, 122.540	0.0330	-10.192	-13.770, -6.615	

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Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
IPAQ physical activity						
Moderate	76.407	-66.545, 219.359	0.2948	-7.688	-16.878, 1.503	0.1011
Low	59.910	-123.596, 243.416	0.5222	-11.293	-23.077, 0.490	0.0603
Missing	235.557	57.049, 414.064	0.0097	-23.506	-34.978, -12.035	0.0001
Hypertension	1525.066	1383.662, 1666.469		-21.693	-30.756, -12.630	
Diabetes	878.026	562.260, 1193.791		-91.784	-111.888, -71.680	
Solid tumour	29.064	-159.307, 217.436	0.7623	9.534	-2.571, 21.639	0.1227
No. Obs.	47,686			49,217		
Log-likelihood	-482,211			-361,894		
AIC	964,478			723,845		
BIC	964,723			724,091		
Residual df	47,658			49,189		

<sup>1</sup>CI = Confidence Interval. All p<0.0001 unless indicated.

Imaging outcomes are in units of cubic millimetres. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All available data were used across instances 0, 2, 3. All minimally adjusted linear mixed effects models were brain imaging outcome ~ surgeries variable(s) + age + normalized age<sup>2</sup> + female sex (1|participant). All fully adjusted linear mixed effects models were brain imaging outcome ~ surgeries variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not significant/used in imaging models.

**Table 18. Fully adjusted models. primary brain imaging outcomes ~ high complexity cumulative surgeries**

Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
Cumulative Major+Major++CMO Surgeries	247.728	161.696, 333.760		-17.047	-22.456, -11.639	
Cumulative Stroke Admissions	6275.433	4324.255, 8226.610		-162.270	-278.341, -46.199	0.0061
Cumulative Other Medical Admissions	191.533	122.771, 260.295		-10.618	-14.943, -6.294	
Time in years	54.549	45.100, 63.998		-5.693	-6.125, -5.260	
Baseline age	-938.123	-1050.580, -825.666		55.917	48.705, 63.130	
Baseline age <sup>2</sup> normalised	11413.837	10382.136, 12445.537		-676.082	-742.235, -609.928	
Sex Female	-268.782	-394.601, -142.963		-228.969	-237.026, -220.912	
Deprivation	3.158	-18.782, 25.099	0.7778	-4.016	-5.423, -2.608	
Education						
None of the above	-39.272	-283.956, 205.411	0.7531	-64.384	-79.559, -49.210	
Prefer not to answer	550.994	-405.309, 1507.296	0.2588	-37.170	-93.237, 18.896	0.1938
Secondary <12 years	-21.884	-161.056, 117.287	0.7579	-42.837	-51.402, -34.273	
Secondary 12 years	217.526	11.211, 423.840	0.0388	-28.624	-41.028, -16.219	
BMI	-68.473	-169.902, 32.956	0.1858	12.250	6.049, 18.452	0.0001
BMI2 norm	2757.292	1012.988, 4501.597	0.0019	-199.965	-306.236, -93.693	0.0002
Ever smoked	157.897	36.045, 279.749	0.0111	-4.807	-12.572, 2.958	0.2250
Ever depression	-113.053	-230.333, 4.228	0.0589	13.848	6.543, 21.153	0.0002
Average weekly alcohol units (scaled)	62.441	3.764, 121.118	0.0370	-10.176	-13.751, -6.600	
IPAQ physical activity						
Moderate	71.663	-71.269, 214.596	0.3258	-7.479	-16.667, 1.709	0.1106

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Characteristic	Volume of total white matter hyperintensities			Average hippocampal volume		
	Mean volume	95% CI <sup>1</sup>	p-value	Mean volume	95% CI <sup>1</sup>	p-value
Low	55.519	-127.976, 239.014	0.5532	-11.058	-22.839, 0.724	0.0658
Missing	234.088	55.591, 412.585	0.0102	-23.442	-34.911, -11.972	0.0001
Hypertension	1524.418	1383.041, 1665.794		-21.619	-30.679, -12.559	
Diabetes	875.978	560.220, 1191.736		-91.402	-111.504, -71.300	
Solid tumour	68.574	-117.626, 254.775	0.4704	8.420	-3.552, 20.392	0.1681
No. Obs.	47,686			49,217		
Log-likelihood	-482,225			-361,893		
AIC	964,501			723,839		
BIC	964,729			724,067		
Residual df	47,660			49,191		

<sup>1</sup>CI = Confidence Interval. All p<0.0001 unless indicated.

Imaging outcomes are in units of cubic millimetres. Total volume of white matter hyperintensities were generated from T1 and T2 FLAIR brain images. Hippocampal left/right volumes were generated from subcortical (FIRST) T1 structural brain images. All available data were used across instances 0, 2, 3. All minimally adjusted linear mixed effects models were: brain imaging outcome ~ surgeries variable(s) + age + normalized age<sup>2</sup> + female sex (1|participant). All fully adjusted linear mixed effects models were: brain imaging outcome ~ surgeries variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. All fully adjusted linear mixed effects models adjusted for cognitive outcome ~ imaging variable(s) + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalized + time + female sex + deprivation + education + body mass index (BMI) + normalized BMI<sup>2</sup> + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalized by variable<sup>2</sup> / 1000. Interaction terms were not significant/used in imaging models.



**Table 19. Models. secondary (DKT) brain imaging outcomes ~ cumulative surgeries**

Dependent variable	Foundation								Fully adjusted							
	Cumulative surgeries				Cumulative high complexity surgeries				Cumulative surgeries				Cumulative high complexity surgeries			
	Mean volume /surgery	95% CI	Type 3 p-value	p-value (FDR)	Mean volume /surgery	95% CI	Type 3 p-value	p-value (FDR)	Mean volume /surgery	95% CI	Type 3 p-value	p-value (FDR)	Mean volume surgery	95% CI	Type 3 p-value	p-value (FDR)
1. Average mean thickness caudal anterior cingulate	-0.0017	-0.003, -0.001	0.0038	0.0061	-0.0047	-0.008, -0.002	0.0035	0.0090	-0.0008	-0.002, 0.000	0.2060	0.4090	-0.0034	-0.007, -0.000	0.0461	0.1590
2. Average mean thickness caudal middle frontal	-0.0005	-0.001, 0.000	0.1370	0.1610	-0.0004	-0.002, 0.001	0.6570	0.7270	0.0002	-0.001, 0.001	0.5320	0.7850	0.0004	-0.001, 0.002	0.6670	0.9600
3. Average mean thickness cuneus	0.0011	0.000, 0.002	0.0004	0.0008	0.0013	-0.000, 0.003	0.1310	0.1850	0.0007	0.000, 0.001	0.0391	0.1730	-0.0004	-0.002, 0.001	0.6810	0.9600
4. Average mean thickness entorhinal	-0.0026	-0.004, -0.001	0.0001	0.0002	-0.0083	-0.012, -0.005			-0.0013	-0.003, 0.000	0.0907	0.2010	<b>-0.0055</b>	<b>-0.009, -0.002</b>	<b>0.0042</b>	<b>0.0365</b>
5. Average mean thickness fusiform	-0.0014	-0.002, -0.001	0.0000		-0.0041	-0.006, -0.002			-0.0006	-0.001, 0.000	0.0636	0.1970	<b>-0.0027</b>	<b>-0.004, -0.001</b>	<b>0.0017</b>	<b>0.0268</b>
6. Average mean thickness inferior parietal	-0.0005	-0.001, 0.000	0.0624	0.0806	-0.0011	-0.003, 0.000	0.1680	0.2260	-0.0002	-0.001, 0.000	0.4920	0.7630	-0.0008	-0.002, 0.001	0.3050	0.5910
7. Average mean thickness inferior temporal	-0.0012	-0.002, -0.001		0.0001	-0.0035	-0.005, -0.002		0.0001	-0.0006	-0.001, 0.000	0.0567	0.1970	<b>-0.0023</b>	<b>-0.004, -0.001</b>	<b>0.0059</b>	<b>0.0368</b>
8. Average mean thickness insula	-0.0031	-0.004, -0.002			-0.0057	-0.008, -0.004			<b>-0.0012</b>	<b>-0.002, -0.000</b>	<b>0.0028</b>	<b>0.0431</b>	<b>-0.0021</b>	<b>-0.004, -0.000</b>	<b>0.0425</b>	<b>0.1590</b>
9. Average mean thickness isthmus cingulate	-0.0010	-0.002, -0.000	0.0086	0.0134	-0.0020	-0.004, -0.000	0.0480	0.0930	-0.0008	-0.002, 0.000	0.0778	0.2010	-0.0016	-0.004, 0.001	0.1410	0.3640
10. Average mean thickness lateral occipital	0.0006	0.000, 0.001	0.0302	0.0407	0.0003	-0.001, 0.002	0.7390	0.7900	0.0002	-0.000, 0.001	0.5830	0.7970	-0.0013	-0.003, 0.000	0.1070	0.3020
11. Average mean thickness lateral orbitofrontal	-0.0008	-0.001, -0.000	0.0122	0.0180	-0.0016	-0.003, 0.000	0.0552	0.1010	-0.0001	-0.001, 0.001	0.8260	0.9080	-0.0003	-0.002, 0.001	0.7260	0.9780
12. Average mean thickness lingual	0.0013	0.001, 0.002		0.0001	0.0010	-0.001, 0.003	0.2280	0.2950	0.001	0.000, 0.002	0.0061	0.0625	-0.0004	-0.002, 0.001	0.6270	0.9600
13. Average mean thickness medial orbito frontal	-0.0019	-0.003, -0.001			-0.0041	-0.006, -0.002		0.0001	-0.001	-0.002, -0.000	0.0142	0.0801	-0.002	-0.004, 0.000	0.0566	0.1750
14. Average mean thickness middle temporal	-0.0015	-0.002, -0.001			-0.0042	-0.006, -0.003			-0.0008	-0.002, -0.000	0.0155	0.0801	<b>-0.0029</b>	<b>-0.005, -0.001</b>	<b>0.0009</b>	<b>0.0268</b>
15. Average mean thickness paracentral	-0.0015	-0.002, -0.001	0.0003	0.0007	-0.0025	-0.005, -0.000	0.0323	0.0668	-0.0001	-0.001, 0.001	0.7900	0.9070	-0.0001	-0.003, 0.002	0.9200	0.9780
16. Average mean thickness parahippocampal	-0.0028	-0.004, -0.002			-0.0078	-0.011, -0.005			-0.0012	-0.003, 0.000	0.0593	0.1970	<b>-0.0047</b>	<b>-0.008, -0.001</b>	<b>0.0047</b>	<b>0.0365</b>
17. Average mean thickness parsopercularis	-0.0010	-0.002, -0.000	0.0012	0.0022	-0.0013	-0.003, 0.000	0.1300	0.1850	-0.0001	-0.001, 0.001	0.7160	0.8540	0	-0.002, 0.002	0.9630	0.9780
18. Average mean thickness parsorbitalis	-0.0009	-0.002, -0.000	0.0146	0.0206	-0.0018	-0.004, 0.000	0.0664	0.1140	-0.0002	-0.001, 0.001	0.6320	0.8040	-0.0007	-0.003, 0.001	0.4810	0.7850
19. Average mean thickness parstriangularis	-0.0005	-0.001, 0.000	0.0816	0.1010	-0.0005	-0.002, 0.001	0.5590	0.6620	0	-0.001, 0.001	0.9290	0.9600	0.0002	-0.002, 0.002	0.8270	0.9780
20. Average mean thickness pericalcarine	0.0015	0.001, 0.002			0.0032	0.002, 0.005	0.0001	0.0003	0.0009	0.000, 0.002	0.0117	0.0801	0.0012	-0.000, 0.003	0.1570	0.3740
21. Average mean thickness postcentral	-0.0004	-0.001, 0.000	0.2490	0.2570	-0.0001	-0.002, 0.002	0.8920	0.9220	-0.0002	-0.001, 0.001	0.5910	0.7970	-0.0003	-0.002, 0.002	0.7680	0.9780
22. Average mean thickness posterior cingulate	-0.0013	-0.002, -0.001	0.0002	0.0004	-0.0024	-0.004, -0.000	0.0151	0.0360	-0.0004	-0.001, 0.000	0.3070	0.5290	-0.0008	-0.003, 0.001	0.4590	0.7850
23. Average mean thickness precentral	-0.0021	-0.003, -0.001			-0.0045	-0.007, -0.002		0.0001	-0.0008	-0.002, 0.000	0.0818	0.2010	-0.0025	-0.005, -0.000	0.0271	0.1200
24. Average mean thickness precuneus	-0.0001	-0.001, 0.000	0.7300	0.7300	-0.0005	-0.002, 0.001	0.5770	0.6620	0.0004	-0.000, 0.001	0.2110	0.4090	-0.0001	-0.002, 0.002	0.9420	0.9780
25. Average mean thickness rostral anterior cingulate	-0.0015	-0.002, -0.001	0.0001	0.0003	-0.0033	-0.005, -0.001	0.0018	0.0050	-0.0008	-0.002, 0.000	0.0843	0.2010	-0.0015	-0.004, 0.001	0.1960	0.4340
26. Average mean thickness rostral middle frontal	-0.0003	-0.001, 0.000	0.2180	0.2330	-0.0001	-0.002, 0.001	0.9260	0.9260	-0.0001	-0.001, 0.000	0.6480	0.8040	0	-0.002, 0.002	0.9780	0.9780
27. Average mean thickness superior frontal	-0.0011	-0.002, -0.000	0.0007	0.0013	-0.0020	-0.004, -0.000	0.0212	0.0469	-0.0003	-0.001, 0.000	0.4050	0.6610	-0.0009	-0.003, 0.001	0.3360	0.6130
28. Average mean thickness superior parietal	0.0004	-0.000, 0.001	0.1970	0.2180	0.0009	-0.001, 0.003	0.2710	0.3360	0.0004	-0.000, 0.001	0.2870	0.5230	0.0001	-0.002, 0.002	0.8780	0.9780
29. Average mean thickness superior temporal	-0.0026	-0.003, -0.002			-0.0049	-0.007, -0.003			<b>-0.0012</b>	<b>-0.002, -0.000</b>	<b>0.0018</b>	<b>0.0431</b>	-0.0023	-0.004, -0.000	0.0204	0.1050
30. Average mean thickness supramarginal	-0.0009	-0.002, -0.000	0.0026	0.0044	-0.0015	-0.003, 0.000	0.0756	0.1230	-0.0001	-0.001, 0.001	0.8490	0.9080	-0.0001	-0.002, 0.002	0.8730	0.9780
31. Average mean thickness transverse temporal	-0.0008	-0.002, 0.000	0.1400	0.1610	-0.0023	-0.005, 0.001	0.1140	0.1770	0	-0.001, 0.001	0.9620	0.9620	-0.0016	-0.005, 0.001	0.2890	0.5910

## Sensitivity analyses. stroke and 1SD/2SD cognitive decline

Table 20. Foundation models - reaction time stroke/no stroke datasets

Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	1.957	1.742, 2.173		-2.155	-7.960, 3.650	0.4660	1.942	1.726, 2.157	
Time in years	0.880	0.325, 1.435	0.0019	-5.559	-33.776, 22.659	0.6990	0.902	0.347, 1.456	0.0015
Baseline age	27.853	22.831, 32.875		91.037	-152.989, 335.063	0.4640	27.629	22.607, 32.651	
Baseline age <sup>2</sup> normalised	5.373	5.296, 5.449		3.998	0.532, 7.465	0.0240	5.373	5.297, 5.450	
Sex Female	18.545	17.924, 19.166		32.128	4.326, 59.930	0.0236	18.584	17.963, 19.205	
No. Obs.	544,520			531			543,989		
Log-likelihood	-3,329,819			-3,387			-3,326,300		
AIC <sup>1</sup>	6,659,655			6,789			6,652,617		
BIC <sup>1</sup>	6,659,744			6,824			6,652,706		
Residual df	544,512			523			543,981		

<sup>1</sup>CI = Confidence Interval, AIC = Akaike's Information Criteria, BIC = Bayesian Information Criteria, Age<sup>2</sup> norm. = Quadratic term normalized by variable<sup>2</sup> / 1000. All p<0.0001 unless indicated.

**Table 21. Fully adjusted models - reaction time with stroke/no stroke datasets**

Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	0.273	0.022, 0.523	0.0327	-5.296	-13.255, 2.663	0.1917	0.282	0.032, 0.533	0.0272
Cumulative Stroke Admissions	3.892	3.265, 4.518	0.0000	7.897	-0.299, 16.093	0.0589	3.847	3.217, 4.478	0.0000
Cumulative Other Medical Admissions	41.812	33.057, 50.567	0.0000	52.230	-4.601, 109.062	0.0716	NA		NA
Time in years	2.572	2.021, 3.123	0.0000	-5.674	-33.319, 21.972	0.6869	2.584	2.033, 3.135	0.0000
Baseline age	11.306	6.316, 16.297	0.0000	88.209	-	0.4692	11.195	6.204, 16.186	0.0000
Baseline age <sup>2</sup> normalised	5.150	5.055, 5.244	0.0000	4.801	0.375, 9.227	0.0337	5.149	5.055, 5.244	0.0000
Sex Female	3.247	3.142, 3.352	0.0000	2.279	-1.774, 6.332	0.2699	3.248	3.143, 3.353	0.0000
Deprivation	15.280	14.626, 15.933	0.0000	26.016	-3.222, 55.254	0.0810	15.276	14.622, 15.929	0.0000
Education	NA		NA	NA		NA	NA		NA
None of the above	22.607	21.675, 23.539	0.0000	58.632	24.295, 92.969	0.0009	22.550	21.618, 23.483	0.0000
Prefer not to answer	34.267	31.208, 37.327	0.0000	39.126	-72.097, 150.349	0.4898	34.257	31.197, 37.317	0.0000
Secondary <12 years	8.178	7.453, 8.903	0.0000	-6.570	-39.445, 26.306	0.6948	8.193	7.468, 8.918	0.0000

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Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Secondary 12 years	3.368	2.196, 4.540	0.0000	10.023	-43.093, 63.139	0.7110	3.361	2.189, 4.533	0.0000
BMI	-1.542	-1.988, -1.095	0.0000	7.154	-12.583, 26.891	0.4767	-1.549	-1.995, -1.103	0.0000
BMI <sup>2</sup> norm·	20.768	13.427, 28.109	0.0000	-131.758	-452.109, 188.594	0.4194	20.900	13.558, 28.242	0.0000
Ever smoked	-3.901	-4.535, -3.268	0.0000	-0.528	-29.215, 28.158	0.9711	-3.908	-4.542, -3.275	0.0000
Ever depression	7.641	6.910, 8.371	0.0000	-16.753	-51.063, 17.557	0.3378	7.660	6.929, 8.391	0.0000
Average weekly alcohol units (scaled)	-4.588	-4.904, -4.273	0.0000	-12.778	-26.476, 0.920	0.0674	-4.577	-4.893, -4.261	0.0000
IPAQ physical activity	NA		NA	NA		NA	NA		NA
Moderate	2.930	2.161, 3.699	0.0000	46.938	9.375, 84.500	0.0144	2.900	2.131, 3.669	0.0000
Low	3.601	2.621, 4.582	0.0000	14.048	-25.560, 53.655	0.4862	3.615	2.634, 4.595	0.0000
Missing	6.745	5.880, 7.609	0.0000	33.747	-4.783, 72.278	0.0859	6.733	5.869, 7.597	0.0000
Hypertension	3.933	3.196, 4.669	0.0000	19.141	-7.338, 45.620	0.1561	3.916	3.179, 4.653	0.0000
Diabetes	11.930	10.386, 13.474	0.0000	-12.627	-50.023, 24.768	0.5073	12.005	10.459, 13.550	0.0000

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Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Solid tumour	-2.306	-3.425, -1.187	0.0001	-24.693	-67.162, 17.776	0.2538	-2.285	-3.404, -1.166	0.0001
Cumulative Surgeries * Cumulative Other Medical Admissions	-0.234	-0.357, -0.111	0.0002	-0.333	-1.864, 1.198	0.6695	-0.226	-0.350, -0.102	0.0004
Time in years * Deprivation	-0.118	-0.145, -0.092	0.0000	-0.852	-2.188, 0.485	0.2098	-0.118	-0.144, -0.092	0.0000
No. Obs.	544,520			531			543,989		
Log-likelihood	-3,324,271			-3,296			-3,320,836		
AIC <sup>1</sup>	6,648,598			6,648			6,641,725		
BIC <sup>1</sup>	6,648,912			6,767			6,642,028		
Residual df	544,492			503			543,962		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3. All p<0.0001 unless indicated.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup> normalised/1000 + time + female sex + (1|participant).

<sup>3</sup>Fully adjusted models were cognitive outcome ~ surgeries + cumulative stroke admissions + cumulative other medical admissions + age + age<sup>2</sup> normalised + time\*deprivation + female sex + education + body mass index + body mass index<sup>2</sup> normalised + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalised by variable<sup>2</sup> / 1000. Interaction for surgeries\*other medical admissions and time\*deprivation included in reaction time, fluid intelligence and prospective memory fully adjusted models. Linear smoothing uses the formula,  $y \sim x + I(x^2)$ . Cumulative surgical procedures calculated from 8 years prior to baseline (instance 0).

**Table 22. Foundation models - fluid intelligence and stroke/no stroke datasets**

Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	-0.114	-0.121, -0.107		-0.121	-0.309, 0.068	0.2060	-0.113	-0.120, -0.106	
Time in years	0.251	0.233, 0.270		1.379	0.468, 2.289	0.0034	0.251	0.233, 0.269	
Baseline age	-2.368	-2.533, -2.202		-12.026	-19.875, -4.177	0.0030	-2.363	-2.529, -2.198	
Baseline age <sup>2</sup> normalised	0.023	0.021, 0.026		0.125	-0.026, 0.276	0.1040	0.023	0.021, 0.026	
Sex Female	-0.249	-0.270, -0.229		-0.806	-1.654, 0.042	0.0624	-0.249	-0.270, -0.229	
Log-likelihood	182,490			126			182,364		
AIC <sup>1</sup>	-391,363			-280			-391,079		
BIC <sup>1</sup>	782,741			577			782,173		
Residual df	782,822			599			782,254		
No. Obs.	182,482			118			182,356		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3. All p<0.0001 unless indicated.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup> normalised/1000 + time + female sex + (1|participant).

<sup>3</sup>Fully adjusted models were cognitive outcome ~ surgeries + cumulative stroke admissions + cumulative other medical admissions + age + age<sup>2</sup> normalised + time\*deprivation + female sex + education + body mass index + body mass index<sup>2</sup> normalised + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalised by variable<sup>2</sup> / 1000. Interaction for surgeries\*other medical admissions and time\*deprivation included in reaction time, fluid intelligence and prospective memory fully adjusted models. Linear smoothing uses the formula,  $y \sim x + I(x^2)$ . Cumulative surgical procedures calculated from 8 years prior to baseline (instance 0).

**Table 23. Fully adjusted models - fluid intelligence with stroke/no stroke datasets**

Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI1	p-value	Mean change per surgery	95% CI1	p-value	Mean change per surgery	95% CI1	p-value
Cumulative Surgeries	-0.057	-0.064, -0.049		0.167	-0.097, 0.432	<b>0.2120</b>	-0.057	-0.065, -0.050	
Cumulative Stroke Admissions	-0.093	-0.113, -0.074		0.182	-0.054, 0.419	0.1290	-0.095	-0.114, -0.076	
Cumulative Other Medical Admissions	-0.348	-0.674, -0.021	0.0371	-0.911	-3.036, 1.215	0.3970			
Time in years	0.157	0.140, 0.174		0.949	0.029, 1.869	0.0433	0.156	0.140, 0.173	
Baseline age	-1.388	-1.540, -1.235		-8.294	-16.259, -0.328	0.0415	-1.385	-1.538, -1.233	
Baseline age <sup>2</sup> normalised	0.013	0.010, 0.016		-0.039	-0.191, 0.114	0.6090	0.013	0.010, 0.016	
Sex Female	-0.073	-0.077, -0.070		-0.064	-0.192, 0.063	0.3210	-0.073	-0.077, -0.070	
Deprivation	-0.171	-0.191, -0.151		-0.823	-1.717, 0.071	0.0707	-0.170	-0.190, -0.150	
Education (Ref = Tertiary)									
None of the above	-2.003	-2.033, -1.973		-2.163	-3.290, -1.036	0.0002	-2.003	-2.032, -1.973	
Prefer not to answer	-2.124	-2.224, -2.024		-0.461	-3.508, 2.585	0.7640	-2.125	-2.225, -2.025	
Secondary <12 years	-0.993	-1.015, -0.971		-1.254	-2.183, -0.324	0.0088	-0.993	-1.015, -0.971	
Secondary 12 years	-0.163	-0.198, -0.127		0.643	-1.174, 2.460	0.4840	-0.163	-0.198, -0.128	

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Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI1	p-value	Mean change per surgery	95% CI1	p-value	Mean change per surgery	95% CI1	p-value
BMI	-0.031	-0.045, -0.017		0.297	-0.246, 0.841	0.2800	-0.031	-0.045, -0.018	
BMI <sup>2</sup> norm	0.503	0.279, 0.727		-4.721	-13.218, 3.776	0.2730	0.506	0.281, 0.730	
Ever smoked	0.157	0.137, 0.176		0.314	-0.505, 1.134	0.4480	0.156	0.137, 0.176	
Ever depression	0.059	0.040, 0.077		0.113	-0.635, 0.861	0.7650	0.059	0.040, 0.077	
Average weekly alcohol units (scaled)	0.137	0.127, 0.146		-0.060	-0.475, 0.356	0.7770	0.137	0.127, 0.146	
IPAQ physical activity (Ref = High)									
Moderate	0.306	0.283, 0.330		0.828	-0.284, 1.939	0.1430	0.306	0.283, 0.329	
Low	0.325	0.294, 0.355		1.148	-0.056, 2.351	0.0613	0.325	0.294, 0.355	
Missing	-0.140	-0.167, -0.113		0.572	-0.481, 1.625	0.2840	-0.140	-0.167, -0.114	
Hypertension	-0.097	-0.119, -0.074		-0.227	-1.063, 0.608	0.5900	-0.097	-0.120, -0.074	
Diabetes	-0.191	-0.237, -0.144		-1.617	-2.654, -0.580	0.0026	-0.187	-0.234, -0.141	
Solid tumour	0.133	0.098, 0.167		0.497	-0.813, 1.808	0.4530	0.132	0.097, 0.166	
Cumulative Surgeries * Cumulative Other Medical Admissions	0.009	0.005, 0.012		-0.081	-0.147, -0.016	0.0155	0.009	0.005, 0.012	



Characteristic	Original model			Stroke admissions			No stroke admissions		
	Mean change per surgery	95% CI1	p-value	Mean change per surgery	95% CI1	p-value	Mean change per surgery	95% CI1	p-value
Time in years * Deprivation	0.001	0.000, 0.002	0.0150	-0.016	-0.067, 0.034	0.5140	0.001	0.000, 0.002	0.0133
No. Obs.	182,490			126			182,364		
Log-likelihood	-376,926			-260			-376,662		
AIC <sup>1</sup>	753,909			575			753,379		
BIC <sup>1</sup>	754,192			655			753,652		
Residual df	182,462			98			182,337		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3. All p<0.0001 unless indicated.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup>normalised/1000 + time + female sex + (1|participant).

<sup>3</sup>Fully adjusted models were cognitive outcome ~ surgeries + cumulative stroke admissions + cumulative other medical admissions + age + age<sup>2</sup>normalised + time\*deprivation + female sex + education + body mass index + body mass index<sup>2</sup> normalised + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalised by variable<sup>2</sup> / 1000. Interaction for surgeries\*other medical admissions and time\*deprivation included in reaction time, fluid intelligence and prospective memory fully adjusted models. Linear smoothing uses the formula,  $y \sim x + I(x^2)$ . Cumulative surgical procedures calculated from 8 years prior to baseline (instance 0).

**Table 24. Foundation models cognition ~ cumulative surgeries from baseline**

Characteristic	Original Reaction time, milliseconds			Subset reaction time, milliseconds			Original Fluid intelligence, correct			Subset fluid intelligence, correct		
	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value	Mean change per surgery	95% CI <sup>1</sup>	p-value
Cumulative Surgeries (from baseline – 8 y)	1.957	1.742, 2.173					-0.114	-0.121, -0.107				
Cumulative Surgeries (from baseline)				1.039	0.542, 1.536					-0.050	-0.065, -0.034	
Time in years	5.373	5.296, 5.449		5.465	5.372, 5.558		0.023	0.021, 0.026		0.016	0.013, 0.019	
Baseline age	0.880	0.325, 1.435	0.0019	0.806	0.250, 1.361	0.0045	0.251	0.233, 0.270		0.256	0.237, 0.274	
Baseline age <sup>2</sup> normalised	27.853	22.831, 32.875		28.964	23.942, 33.987		-2.368	-2.533, -2.202		-2.434	-2.600, -2.267	
Sex Female	18.545	17.924, 19.166		18.661	18.040, 19.283		-0.249	-0.270, -0.229		-0.256	-0.277, -0.236	
No. Obs.	544,520			544,520			182,490			182,490		
Log-likelihood	-3,329,819			-3,329,968			-391,363			-391,847		
AIC	6,659,655			6,659,953			782,741			783,711		
BIC	6,659,744			6,660,043			782,222			783,792		
Residual df	544,512			544,512			182,482			182,482		

<sup>1</sup>CI = Confidence Interval; OR = Odds Ratio; TMTA = trail making test A; TMTB = trail making test B; SDST = symbol digit substitution. All available data were used across instances 0, 2, 3. All p<0.0001 unless indicated.

<sup>2</sup>All models were linear mixed effects models of all available data. Foundation models were minimally adjusted. cognitive outcome ~ surgeries + age + age<sup>2</sup>normalised/1000 + time + female sex + (1|participant).

<sup>3</sup>Fully adjusted models were cognitive outcome ~ surgeries + cumulative stroke admissions + cumulative other medical admissions + age + age<sup>2</sup>normalised + time\*deprivation + female sex + education + body mass index + body mass index<sup>2</sup> normalised + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant).

Quadratic terms normalised by  $\text{variable}^2 / 1000$ . Interaction for surgeries\*other medical admissions and time\*deprivation included in reaction time, fluid intelligence and prospective memory fully adjusted models. Linear smoothing uses the formula,  $y \sim x + l(x^2)$ . Cumulative surgical procedures calculated from 8 years prior to baseline (instance 0).

## Cognitive decline models

### Reaction time

**Table 25. Foundation models. Reaction time 1SD/2SD cognitive decline ~ cumulative surgeries I-2 – I-0 & I-3-I-2**

Primary outcome. reaction time	Cognitive Decline 1SD			Cognitive Decline 2SD		
Characteristic	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
Cumulative Surgeries	1.019	1.010, 1.029		1.025	1.007, 1.042	0.0048
Time in years	1.032	1.029, 1.034		1.046	1.041, 1.051	
Baseline age	1.093	1.085, 1.101		1.110	1.094, 1.127	
Sex Female	1.161	1.119, 1.206		1.193	1.109, 1.284	
No. Obs.	63,467			63,467		
Log-likelihood	-34,041			-12,130		
AIC	68,094			24,272		
BIC	68,148			24,326		
Residual df	63,461			63,461		

<sup>1</sup>OR = Odds Ratio, CI = Confidence Interval. All p<0.0001 unless indicated.

**Table 26. Foundation models. Reaction time 1SD/2SD cognitive decline ~ cumulative surgeries as a factor I-2 – I-0 & I-3-I-2**

Primary outcome. reaction time	Cognitive Decline 1SD			Cognitive Decline 2SD		
Characteristic	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
Cumulative Surgeries factored						
1-2	1.023	0.978, 1.070	0.3200	1.031	0.942, 1.128	0.5074
3-5	1.080	1.025, 1.139	0.0040	1.099	0.992, 1.218	0.0719
6+	1.164	1.072, 1.264	0.0003	1.162	0.995, 1.357	0.0572
Time in years	1.032	1.029, 1.034		1.046	1.041, 1.052	
Baseline age	1.093	1.085, 1.101		1.110	1.094, 1.127	
Sex Female	1.161	1.119, 1.205		1.193	1.109, 1.283	
No. Obs.	63,467			63,467		
Log-likelihood	-34,040			-12,131		
AIC	68,097			24,278		
BIC	68,169			24,351		
Residual df	63,459			63,459		

<sup>1</sup>OR = Odds Ratio, CI = Confidence Interval. All p<0.0001 unless indicated.

**Table 27. Foundation models. Reaction time 1SD/2SD cognitive decline ~ high complexity surgeries I-2 – I-0 & I-3-I-2**

Primary outcome. reaction time	Cognitive Decline 1SD			Cognitive Decline 2SD		
Characteristic	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
Cumulative Major+Major++CMO Surgeries	1.053	1.027, 1.079		1.058	1.010, 1.107	0.0166
Time in years	1.032	1.029, 1.034		1.046	1.041, 1.052	
Baseline age	1.093	1.085, 1.102		1.111	1.094, 1.127	
Sex Female	1.156	1.114, 1.201		1.187	1.103, 1.278	
No. Obs.	63,467			63,467		
Log-likelihood	-34,041			-12,131		
AIC	68,094			24,274		
BIC	68,148			24,328		
Residual df	63,461			63,461		

<sup>1</sup>OR = Odds Ratio, CI = Confidence Interval. All p<0.0001 unless indicated.

**Table 28. Foundation models. Reaction time 1SD/2SD cognitive decline ~ surgical admissions (binary) I-2 – I-0 & I-3-I-2**

Characteristic	Primary outcome. reaction time			Cognitive Decline 1SD			Cognitive Decline 2SD		
	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
Surgical admissions	1.051	1.009, 1.095	0.0178	1.063	0.979, 1.154	0.1465			
Time in years	1.032	1.030, 1.035		1.047	1.042, 1.052				
Baseline age	1.094	1.086, 1.103		1.112	1.096, 1.128				
Sex Female	1.161	1.119, 1.206		1.192	1.108, 1.283				
No. Obs.	63,467			63,467					
Log-likelihood	-34,046			-12,133					
AIC	68,105			24,278					
BIC	68,159			24,332					
Residual df	63,461			63,461					

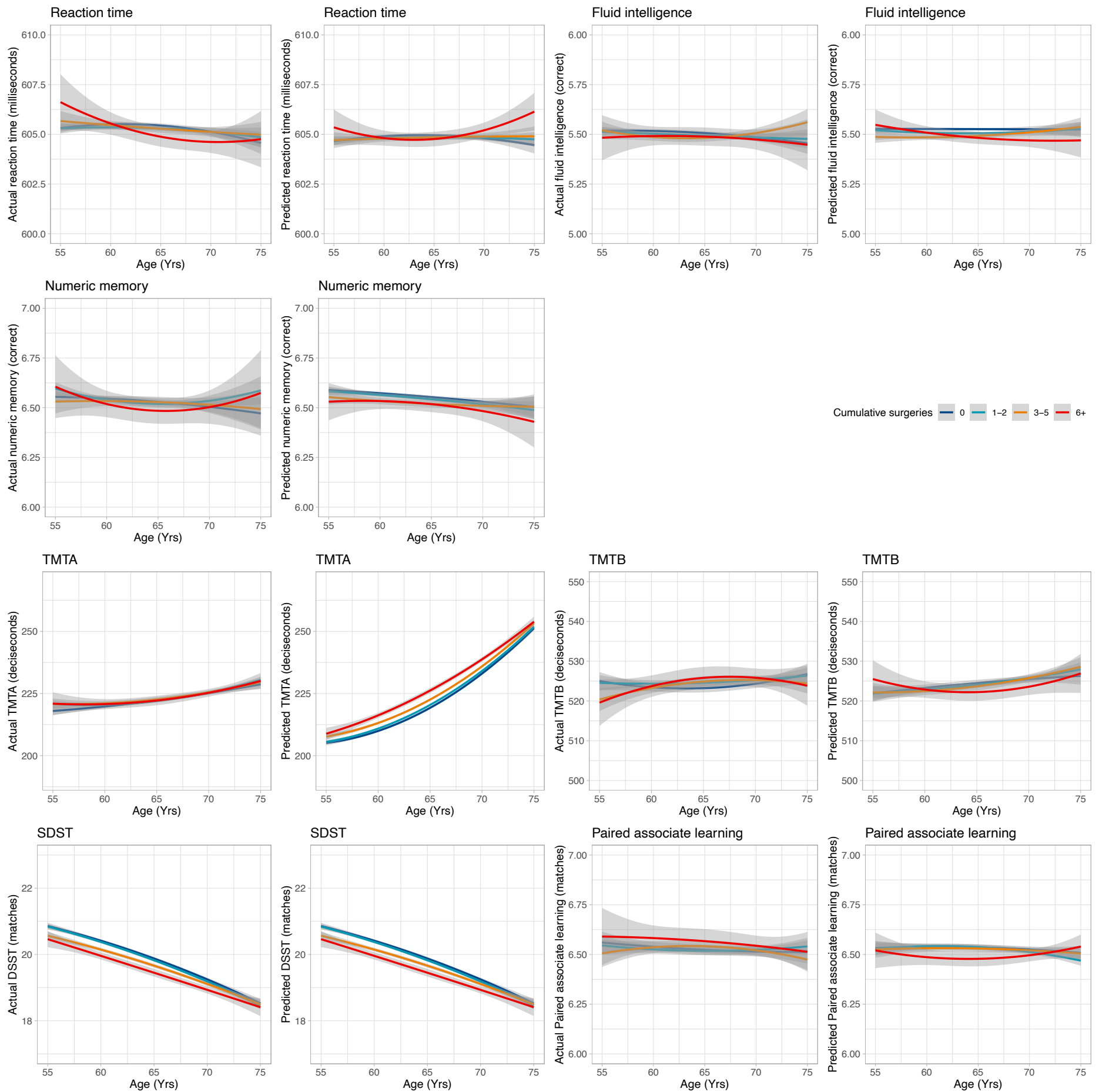
<sup>1</sup>OR = Odds Ratio, CI = Confidence Interval. All p<0.0001 unless indicated.

**Table 29. Foundation models. Reaction time 1SD/2SD cognitive decline ~ high complexity surgical admissions (binary) I-2 – I-0 & I-3-I-2**

Characteristic	Primary outcome. reaction time			Cognitive Decline 1SD			Cognitive Decline 2SD		
	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
Major surgical admissions	1.061	1.019, 1.106	0.0042	1.029	0.951, 1.114	0.4652			
Time in years	1.032	1.029, 1.035		1.047	1.042, 1.052				
Baseline age	1.094	1.086, 1.102		1.112	1.096, 1.129				
Sex Female	1.158	1.116, 1.202		1.191	1.107, 1.282				
No. Obs.	63,467			63,467					
Log-likelihood	-34,045			-12,134					
AIC	68,102			24,279					
BIC	68,157			24,334					
Residual df	63,461			63,461					

<sup>1</sup>OR = Odds Ratio, CI = Confidence Interval. All p<0.0001 unless indicated.

**Figure 2. Plots of actual and predicted values for fully adjusted models: association of cumulative surgeries at a specific age for all cognitive outcomes.**



TMTA = Trail making test A; TMTB = Trail making test B; SDST = Symbol digit substitution test. Reaction time, fluid intelligence and numeric memory include Instance-0, Instance-2, and Instance-3 data. TMTA, TMTB, SDST and paired associate learning include Instance-2 and Instance-3 data. All linear mixed effects models fully adjusted for cognitive outcome ~ cumulative surgeries + cumulative stroke admissions + cumulative other medical admissions + baseline age + baseline age<sup>2</sup> normalised + time\*deprivation + female sex + education + body mass index + body mass index<sup>2</sup> normalised + smoking + depression + alcohol consumption + physical activity + hypertension + diabetes + solid tumour + (1|participant). Quadratic terms normalised by variable<sup>2</sup> / 1000. Interaction for surgeries\*other medical admissions included in reaction time and fluid intelligence fully adjusted models. Linear smoothing uses the formula,  $y \sim x + I(x^2)$ .

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