

**Supplementary Figures and Tables to ““Brain age” relates to early life factors  
but not to accelerated brain aging”.**

**Supplementary Table 1** (List of cortical Features)

**Supplementary Table 2** (List of subcortical Features)

**Supplementary Table 3** (Sample demographics)

**Supplementary Table 4** (Contact Information Lifebrain)

**Supplementary Table 5** (Data acquisition parameters)

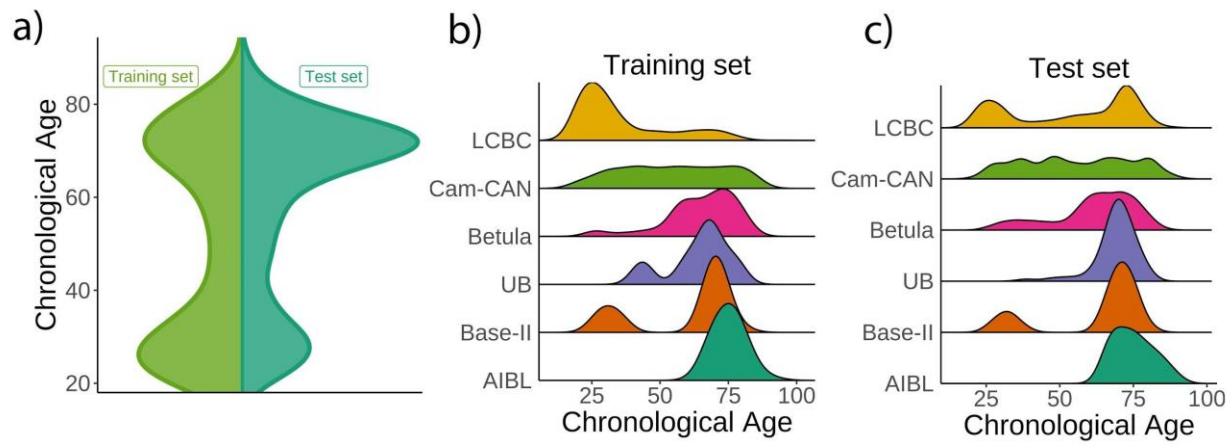
**Supplementary Fig. 1** (Lifebrain demographics)

**Supplementary Fig.2** (Equivalence tests)

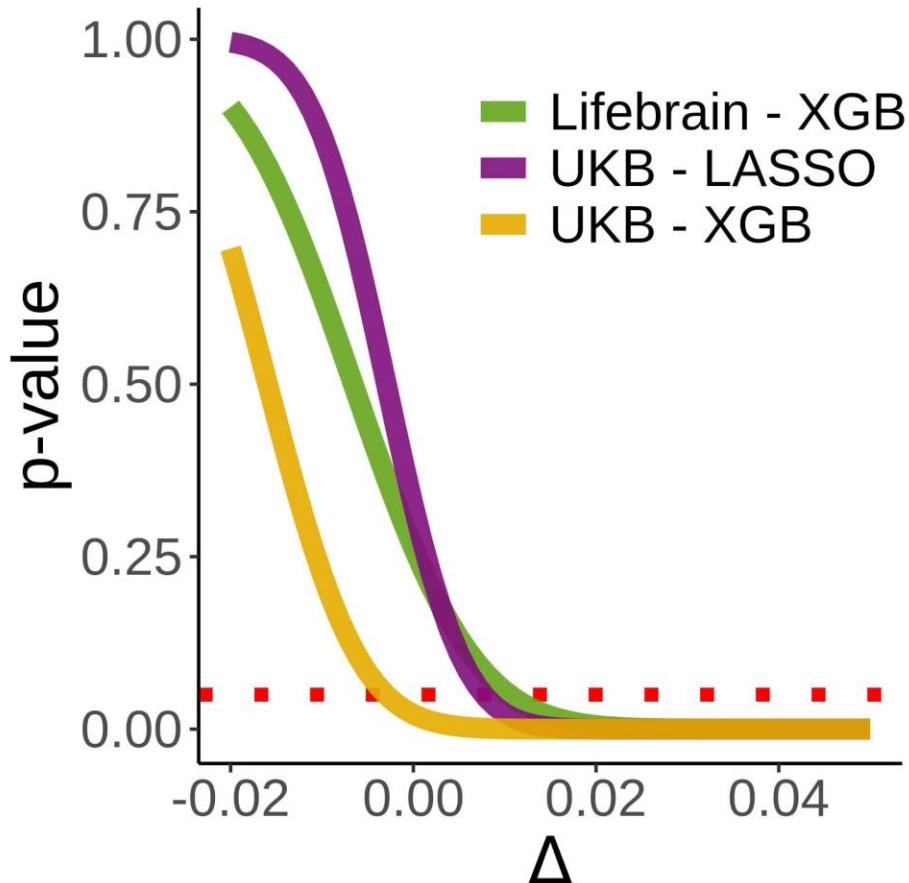
**Supplementary Fig.3** (Predictions from replication models)

**Supplementary Fig.4** (Predictions with variable cut-offs of birth weight)

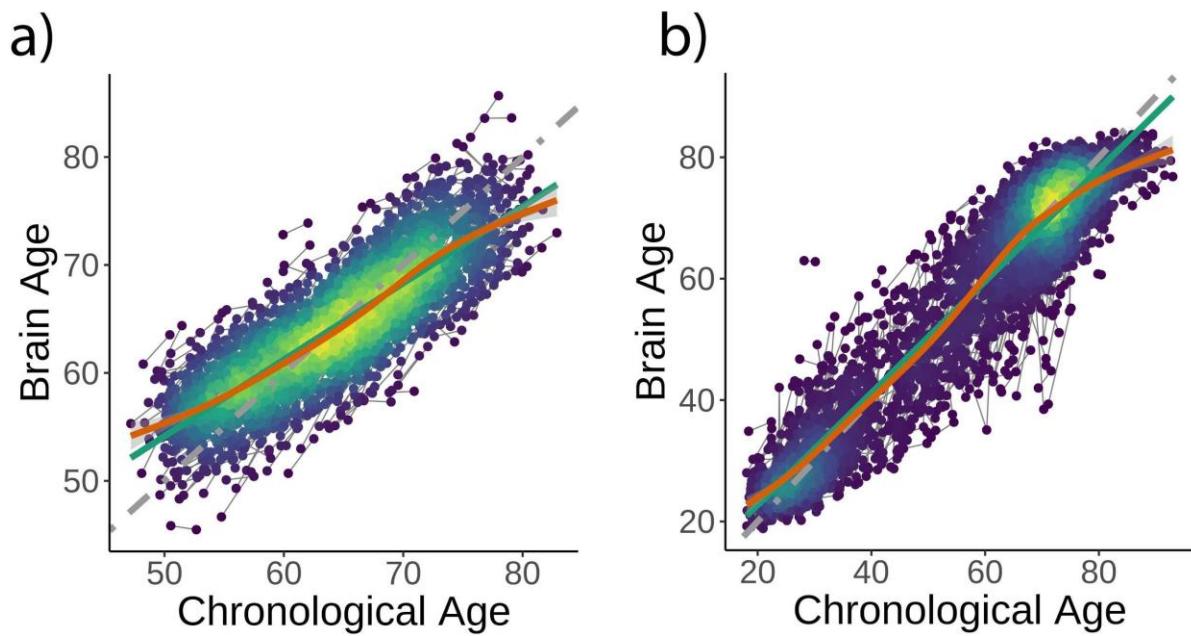
**Supplementary Fig.5** (GWAS Manhattan and QQ plots)



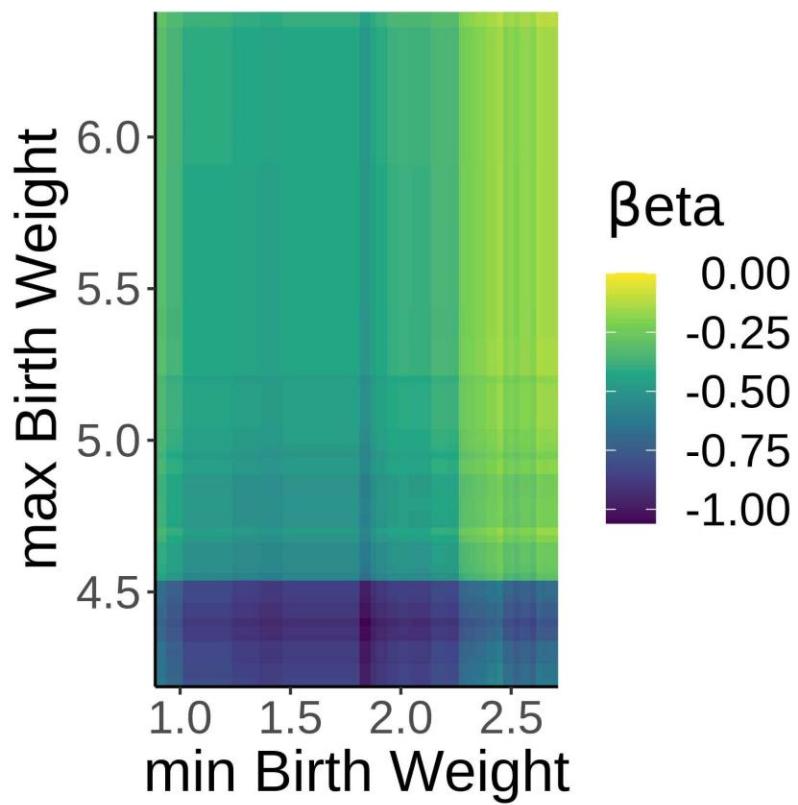
**Supplementary Fig. 1. Age distribution for the Lifebrain replication dataset. a)** Relative age distribution for the Lifebrain training and test datasets. Relative age distribution for the different cohorts of the Lifebrain **b)** training and **c)** test datasets.



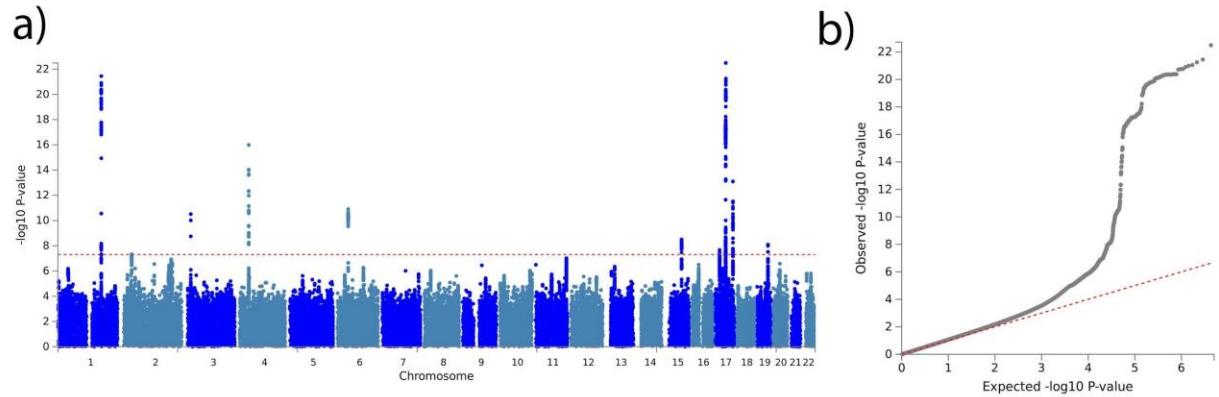
**Supplementary Fig. 2. Equivalence tests.** Inferiority tests for the three main models used to assess the relationship between cross-sectional and *brain age delta<sub>long</sub>*. Inferiority tests test whether a null hypothesis of an effect as large as  $\Delta$  can be rejected. In the x-axis,  $\Delta$  reflects the null hypothesis as  $\beta$ etas (years/ $\delta$ ta). A null hypothesis of an effect at least as large as 0.11 years/ $\delta$ ta can be rejected ( $p < 0.05$ ) in all three tests.  $\Delta$  has been evaluated at [-0.02, 0.05, 0.001]. The dashed red line indicates a  $p = 0.05$  criterion for the null hypothesis rejection.



**Supplementary Fig. 3. Brain age model predictions.** Brain age model prediction (i.e. on test data) as estimated **a)** using LASSO in the UK Biobank dataset and **b)** extreme boosting gradient in the Lifebrain sample. Grey, green, and orange lines represent the identity, the linear, and the GAM functions fitting brain on chronological age.



**Supplementary Fig. 4. Robust effects of birth weight on *brain age delta*.** Beta-estimates showing the relationship between *brain age delta* and birth weight with variable minimum and maximum birth weight exclusion thresholds. Note negative  $\beta$ s irrespective of the minimum and maximum self-reported birth-weight thresholds.



**Supplementary Fig. 5. Brain age delta GWAS.** a) Manhattan plot of the GWAS results for the test set on *brain age delta* (38163 individuals). The horizontal line represents the threshold for genome-wide significance. b) Quantile-quantile (QQ) plot illustrating the deviation of the observed p-values from the null hypothesis.

	GWC	Vol	Area	Cth	GWC	Vol	Area	Cth	GWC	Vol	Area	Cth	GWC	Vol	Area	Cth
	UB Biobank								Lifebrain							
	Left hemisphere				Right hemisphere				Left hemisphere				Right hemisphere			
<b>Total surface</b>	--	--	.00	.10	--	..	.00	.10			.17	.60			.16	.58
<b>Cingulate, caudal ant</b>	.06	.01	.00	.01	.07	.01	.00	.00	.38	.09	.02	.09	.40	.13	.05	.11
<b>Cingulate, rostral ant</b>	.20	.01	.00	.02	.15	.01	.00	.00	.52	.16	.03	.26	.44	.14	.06	.12
<b>Cingulate, posterior</b>	.13	.01	.00	.02	.16	.02	.01	.03	.48	.23	.09	.30	.52	.22	.10	.27
<b>Cingulate, isthmus</b>	.06	.00	.00	.03	.04	.00	.00	.02	.50	.14	.01	.29	.48	.14	.02	.25
<b>Insula</b>	.09	.00	.00	.02	.10	.00	.00	.02	.39	.17	.00	.42	.40	.15	.00	.44
<b>Frontal, superior</b>	.26	.05	.00	.14	.27	.04	.00	.13	.65	.40	.11	.53	.66	.37	.12	.45
<b>Frontal, caudal middle</b>	.18	.03	.00	.08	.20	.02	.00	.07	.60	.23	.06	.42	.61	.20	.06	.39
<b>Frontal, rostral middle</b>	.22	.04	.01	.11	.23	.04	.01	.08	.61	.45	.16	.43	.60	.35	.14	.34
<b>Frontal, pars opercularis</b>	.20	.03	.01	.07	.22	.03	.00	.06	.61	.30	.10	.51	.63	.30	.09	.48
<b>Frontal, pars triangularis</b>	.18	.04	.01	.07	.21	.04	.01	.08	.62	.34	.12	.47	.63	.31	.10	.46
<b>Frontal, pars orbitalis</b>	.16	.04	.01	.04	.19	.05	.01	.04	.56	.37	.16	.26	.58	.38	.16	.26
<b>Frontal, lateral orbital</b>	.18	.03	.02	.02	.16	.03	.01	.01	.54	.39	.18	.32	.49	.31	.11	.19

<b>Frontal, medial orbital</b>	.20	.02	.00	.02	.22	.03	.00	.01	.53	.19	.03	.27	.53	.24	.08	.16
<b>Frontal, pole</b>	.19	.02	.01	.03	.17	.01	.01	.02	.53	.27	.14	.12	.47	.21	.09	.07
<b>Frontal, precentral gyrus</b>	.13	.04	.00	.09	.15	.04	.00	.10	.61	.25	.01	.45	.63	.26	.01	.45
<b>Parietal, postcentral gyrus</b>	.09	.02	.00	.06	.09	.02	.00	.06	.53	.20	.03	.37	.52	.19	.02	.36
<b>Parietal, paracentral gyrus</b>	.12	.03	.00	.07	.13	.03	.00	.07	.54	.17	.02	.30	.57	.15	.01	.26
<b>Parietal, superior</b>	.15	.03	.00	.07	.13	.04	.00	.08	.53	.26	.10	.30	.53	.29	.11	.32
<b>Parietal, inferior</b>	.16	.03	.00	.08	.14	.04	.00	.11	.53	.29	.12	.40	.54	.32	.11	.46
<b>Parietal, supramarginal</b>	.16	.02	.00	.09	.18	.02	.00	.09	.55	.27	.08	.53	.57	.28	.05	.54
<b>Parietal, precuneus</b>	.20	.05	.00	.09	.18	.03	.00	.08	.57	.31	.11	.47	.56	.28	.10	.43
<b>Temporal, parahippocampal</b>	.06	.03	.02	.02	.06	.02	.01	.02	.24	.15	.12	.06	.32	.16	8.0	.10
<b>Temporal, entorhinal</b>	.09	.00	.00	.04	.09	.00	.00	.03	.25	.02	.01	.07	.25	.01	.00	.07
<b>Temporal, pole</b>	.10	--	--	--	.11	--	--	--	.31	.06	.05	.07	.29	.12	.03	.10
<b>Temporal, superior</b>	.15	.04	.00	.10	.19	.05	.00	.11	.53	.34	.09	.56	.57	.36	.11	.56
<b>Temporal, middle</b>	.17	.04	.01	.04	.19	.04	.01	.05	.51	.40	.19	.49	.54	.40	.19	.48
<b>Temporal, inferior</b>	.17	.02	.02	.02	.17	.02	.01	.03	.48	.28	.18	.35	.48	.27	.16	.32

<b>Temporal, transverse</b>	.02	.00	.01	.00	.03	.00	.01	.00	.47	.17	.06	.27	.47	.20	.17	.29
<b>Temporal, bank sup temp sulc</b>	.09	.02	.01	.03	.13	.02	.01	.03	.47	.19	.08	.32	.49	.28	.13	.36
<b>Temporal, fusiform</b>	.17	.03	.01	.05	.16	.03	.01	.06	.48	.27	.19	.30	.48	.23	.14	.31
<b>Occipital, lateral</b>	.03	.02	.01	.03	.02	.03	.01	.02	.36	.25	.15	.21	.35	.21	.11	.25
<b>Occipital, pericalcarine</b>	.00	.00	.00	.00	.02	.00	.00	.00	.27	.06	.03	.18	.22	.06	.04	.13
<b>Occipital, lingual</b>	.00	.01	.01	.01	.00	.01	.01	.00	.27	.18	.09	.30	.26	.19	.09	.30
<b>Occipital, cuneus</b>	.00	.01	.01	.00	.00	.00	.01	.00	.27	.12	.08	.18	.27	.12	.08	.19

**Supplementary Table 1. List of cortical brain features.** List of cortical features included in the brain age model and age variance explained in the UK Biobank and the Lifebrain training datasets. Vol = volume. GWC = Gray-white matter contrast. Cth = Cortical Thickness.

	Vol	Int	Vol	Int	Vol	Int	Vol	Int	Vol	Int	Vol	Int
	UK Biobank						Lifebrain					
	Left hemi		Right hemi		Bilateral		Left hemi		Right hemi		Bilateral	
<b>Ventricular ROIs</b>												
<b>3rd Ventricle</b>	--	--	--	--	.19	.22	--	--	--	--	.55	.45
<b>4th Ventricle</b>	--	--	--	--	.02	.02	--	--	--	--	.02	.01
<b>5th Ventricle</b>	--	--	--	--	.00	.00	--	--	--	--	.05	.03
<b>Inf lat vent</b>	.18	.12	.15	.06	--	--	.41	.11	.39	.02	--	--
<b>Lat vent</b>	.16	.11	.16	.11	--	--	.43	.11	.45	.12	--	--
<b>CSF total</b>	--	--	--	--	.06	.12	--	--	--	--	.21	.23
<b>Volumetric ROIs</b>												
<b>Accumbens</b>	.18	.11	.12	.15	--	--	.45	.31	.41	.38	--	--
<b>Amygdala</b>	.11	.01	.06	.05	--	--	.33	.21	.25	.31	--	--
<b>Brainstem</b>	--	--	--	--	.00	.13	--	--	--	--	.07	.06
<b>Caudate</b>	.00	.01	.00	.01	--	--	.18	.22	.16	.15	--	--
<b>Cerebellum</b>	.01	.01	.01	.01	--	--	.35	.02	.32	.01	--	--

<b>Hippocampus</b>	.11	.02	.11	.02	--	--	.37	.24	.39	.25	--	--
<b>Pallidum</b>	.01	.04	.01	.03	--	--	.09	.10	.04	.12	--	--
<b>Putamen</b>	.04	.01	.04	.00	--	--	.35	.13	.37	.12	--	--
<b>Thalamus</b>	.10	.15	.07	.16	--	--	.45	.04	.43	.04	--	--
<b>White matter</b>												
<b>CC anterior</b>	--	--	--	--	.02	.06	--	--	--	--	.10	.10
<b>CC central</b>	--	--	--	--	.08	.05	--	--	--	--	.28	.04
<b>CC mid anterior</b>	--	--	--	--	.10	.04	--	--	--	--	.22	.06
<b>CC mid posterior</b>	--	--	--	--	.05	.13	--	--	--	--	.24	.12
<b>CC posterior</b>	--	--	--	--	.00	.07	--	--	--	--	.03	.08
<b>Cerebellum WM</b>	.07	.00	.06	.00	--	--	.08	.02	.10	.02	--	--
<b>Cerebral WM</b>	.03	--	.03	--	--	--	.15	--	.13	--	.14	--
<b>WM hypointensities</b>	--	--	--	--	.14	.05	--	--	--	--	.31	.15
<b>Non WM hypointensities</b>	--	--	--	--	.00	.00	--	--	--	--	.21	.00
<b>Global features</b>												
<b>Brain Seg</b>	--	--	--	--	.02	--	--	--	--	--	.23	--
<b>Brain Seg not vent</b>	--	--	--	--	.05	--	--	--	--	--	.32	--

<b>Brain Seg not vent surf</b>	--	--	--	--	.05	--	--	--	--	--	.32	--
<b>Cortex</b>	.05	--	.05	--	--	--	.45	--	.44	--	.45	--
<b>eICV</b>	--	--	--	--	.00	--	--	--	--	--	.00	--
<b>Subcort gray</b>	--	--	--	--	.06	--	--	--	--	--	.44	--
<b>Supratentorial</b>	--	--	--	--	.02	--	--	--	--	--	.21	--
<b>Supratentorial not vent</b>	--	--	--	--	.05	--	--	--	--	--	.30	--
<b>Total gray</b>	--	--	--	--	.05	--	--	--	--	--	.47	--
<b>Other</b>												
<b>Choroid plexus</b>	.18	.17	.18	.18	--	--	.35	.33	.34	.32	--	--
<b>Optic chiasm</b>	--	--	--	--	.05	.00	--	--	--	--	.09	.01
<b>Ventral DC</b>	.05	.06	.06	.05	--	--	.19	.11	.25	.09	--	--
<b>Ventricle choroid</b>	--	--	--	--	.18	--	--	--	--	--	--	--
<b>Vessel</b>	.00	.00	.01	.00	--	--	.02	.02	.03	.01	--	--

**Supplementary Table 2. List of subcortical brain features.** List of subcortical features included in the brain age model and age variance explained in the UK Biobank and the Lifebrain training datasets. Vol = volume; Int = Intensity; hemi = hemisphere.

	Training dataset				Test dataset				
Cohort	N	Age	Age Range	Sex (f:m)	N (Obs)	Age	Age Range	Sex (f:m)	Follow-up
UK Biobank	38682	64.4 (7.6)	44.8 - 82.6	20470:18212	1372 (2)	63.4 (7.2)	47.2 - 80.6	685:687	2.3 (.1)
Lifebrain Total	1792	50.3 (21.8)	18.0 - 94.4	1075:717	1500 (2.8 [1.2])	56.9 (18.9)	18.1 - 89.0	769:731	3.4 (2.2)
LCBC	838	35.5 (16.5)	18.0 - 93.4	563:275	556 (3.7 [1.5])	48.9 (20.7)	18.1 - 85.4	1229:848	4.8 (2.7)
Cam-CAN	386	54.7 (18.7)	18.6 - 87.4	196:190	255 (2)	55.0 (18.1)	19.3 - 89.0	262:248	1.4 (0.7)
Base-II	126	59.8 (18.1)	25.0 - 82.0	58:68	319 (2)	62.0 (16.6)	24.1 - 81.3	224:414	1.9 (0.7)
Betula	139	64.8 (13.0)	25.9 - 84.6	75:64	170 (2)	59.8 (13.8)	25.5 - 80.8	166:174	4.0 (0.2)
UB	6	64.3 (11.8)	43.5 - 77.7	2:4	80 (2.7 [.4])	67.3 (6.9)	36.8 - 78.1	135:84	3.7 (0.9)
AIBL*	297	75.1 (5.7)	61.8 - 94.4	181:116	120 (3.4 [.8])	73.0 (7.0)	62.6 - 88.4	214:195	4.0 (1.4)

**Supplementary Table 3. Sociodemographics.** Main sample descriptives for the training and test datasets. Obs = Mean number of observations per participant [SD]. Follow-up = Mean time (years) between the first and the last MRI observation (SD). For the test datasets, Age and Age Range refers to Age at baseline. \*AIBL does not belong to the Lifebrain consortium but was included to enrich the replication sample.

<b>Lifebrain Consortium (<a href="http://www.lifebrain.uio.no/about/">http://www.lifebrain.uio.no/about/</a>)</b>				
<b>LCBC</b>	<a href="http://www.oslobrain.no">http://www.oslobrain.no</a>	Kristine B. Walhovd	<a href="mailto:k.b.walhovd@psykologi.uio.no">k.b.walhovd@psykologi.uio.no</a>	Norwegian Regional Committee for Medical and Health Research Ethic; Regional Ethical Committee of South Norway
<b>BETULA</b>	<a href="http://www.ufbi.umu.se/english">http://www.ufbi.umu.se/english</a>	Lars Nyberg	<a href="mailto:lars.nyberg@umu.se">lars.nyberg@umu.se</a>	Regional Ethical Vetting Board at Umeå University
<b>BASE-II</b>	<a href="https://www.mpib-berlin.mpg.de/en/research/lifespan-psychology">https://www.mpib-berlin.mpg.de/en/research/lifespan-psychology</a>	Ulman Lindenberger	<a href="mailto:lindenberger@mpib-berlin.mpg.de">lindenberger@mpib-berlin.mpg.de</a>	Ethics committee of the Charité-Universitätsmedizin Berlin
<b>Cam-CAN</b>	<a href="https://www.cam-can.org/">https://www.cam-can.org/</a>	Lorraine K. Tyler & Richard Henson	<a href="mailto:lktyler@csl.psychol.cam.ac.uk">lktyler@csl.psychol.cam.ac.uk</a> & <a href="mailto:rik.henson@mrc-cbu.cam.ac.uk">rik.henson@mrc-cbu.cam.ac.uk</a>	Cambridgeshire 2 Research Ethics Committee
<b>UB</b>	<a href="http://www.ub.edu/bbslab/bbslab/">http://www.ub.edu/bbslab/bbslab/</a>	David Bartrés-Faz	<a href="mailto:dbartres@ub.edu">dbartres@ub.edu</a>	Comisión de Bioética de la Universidad de Barcelona and Hospital Clinic
<b>AIBL*</b>	<a href="https://aibl.csiro.au/research/">https://aibl.csiro.au/research/</a>	Christopher Rowe	<a href="mailto:christopher.rowe@austin.org.au">christopher.rowe@austin.org.au</a>	Institutional ethics committees of Austin Health, StVincent's Health, Hollywood Private Hospital and Edith Cowan University

**Supplementary Table 4. Contact information.** Contact information and ethical committees for the different cohorts of the Lifebrain consortium.

\*AIBL does not belong to the Lifebrain consortium.

Sample	Scanner	Sequence	Tesla	Slices	Voxel size (mm)	Time parameters (TR / TE / TI [ms])	Other parameters (FA / FOV [°/mm])
<b>UK Biobank (main sample)</b>							
UK Biobank*	Skyra Siemens	3D MP-RAGE	3.0	256	1 x 1 x 1	2000/-/880	
<b>Lifebrain (replication sample)</b>							
LCBC	Avanto Siemens	3D MP-RAGE	1.5	160	1.25 x 1.25 x 1.25	2400/3.61/1000	8/240x240
	Skyra Siemens	3D MP-RAGE	3.0	176	1 x 1 x 1	2300/2.98/850	8/256 x 256
	Prisma Siemens	3D MP-RAGE	3.0	208	1 x 1 x 1	2400/2.22/1000	8/240 x 256
Cam-CAN	Tim Trio Siemens	3D MP-RAGE	3.0	192	1 x 1 x 1	2250/2.98/900	9/256 x 240
Base-II	Tim Trio Siemens	3D MP-RAGE	3.0	176	1 x 1 x 1	2500/4.77/1100	7/256 x 256
Betula	Discovery GE	3D FSPGR	3.0	176	1 x 1 x 1	8.19/3.2/450	12/250 x 250
UB	Tim Trio Siemens	3D MP-RAGE	3.0	240	1 x 1 x 1	2300/2.98/900	9/256 x 256
AIBL**	Avanto Siemens	3D MP-RAGE	1.5	160	1 x 1 x 1.2	2300/2.98/900	9/240 x 256
	Verio Siemens	3D MP-RAGE	3.0	160	1 x 1 x 1.2	2300/2.98/900	9/240 x 256
	Tim Trio Siemens	3D MP-RAGE	3.0	160	1 x 1 x 1.2	2300/2.98/900	9/240 x 256

**Supplementary Table 5. Data acquisition parameters.** Data acquisition parameters for the T1w sequences. \*UK Biobank employed three scanners of the same model and with equivalent parameters (Cheadle, Reading, and Newcastle centers). \*\*AIBL does not belong to the Lifebrain consortium but was included in the Lifebrain replication dataset.