OPEN ACCESS

Short report

Clinical biomarker-based biological ageing and future risk of neurological disorders in the UK Biobank

Jonathan K L Mak ,[1] Christopher E McMurran,[1,2] Sara Hägg[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2023-331917).

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[2]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Correspondence to
Jonathan K L Mak, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 171 77, Sweden; jonathan.mak@ki.se

JKLM and CEM are joint first authors.

Received 25 May 2023
Accepted 9 October 2023
Published Online First 5 November 2023

ABSTRACT

Background Many common neurological disorders are associated with advancing chronological age, but their association with biological age (BA) remains poorly understood.

Methods We studied 325 870 participants in the UK Biobank without a diagnosed neurological condition at baseline and generated three previously-described measures of BA based on 18 routinely measured clinical biomarkers (PhenoAge, Klemera-Doubal method age (KDMAge), homeostatic dysregulation age). Using survival models, we assessed the effect of advanced BA on incident neurological diagnoses, including all-cause and cause-specific dementia, ischaemic stroke, Parkinson's disease and motor neuron disease.

Results During a mean follow-up of 9.0 years, there were 1397 incident cases of dementia and 2515 of ischaemic stroke, with smaller case numbers of other diagnoses. The strongest associations with a 1 SD in BA residual were seen for all-cause dementia (KDMAge HR=1.19, 95% CI=1.11 to 1.26), vascular dementia (1.41, 1.25 to 1.60) and ischaemic stroke (1.39, 1.34 to 1.46). Weaker associations were seen for Alzheimer's disease and motor neuron disease, while, in contrast, HRs for Parkinson's disease tended to be <1. Results were largely consistent after adjustment for disease-specific covariates including common cardiometabolic risk factors.

Conclusions Advanced BA calculated from routine clinical biomarker results increases the risk of subsequent neurological diagnoses including all-cause dementia and ischaemic stroke.

INTRODUCTION

Advancing age is a principal risk factor for many of the most common neurological disorders. Measures of biological age (BA), such as telomere length, epigenetic clocks and composite biomarker predictors, have been developed to represent the heterogeneity in how people age and explain age-associated outcomes in a more nuanced way than chronological age (CA; time since birth).[1] Some of the most clinically relevant approaches to measuring BA harness variation in routinely measured clinical biomarkers, with previous work demonstrating that when such BA measures are higher than would be expected for one's CA, this increases the risk of mortality,[2] several cancers[3] and depression/anxiety.[4] However, few studies have assessed the associations between these BA measures and the risk of neurological disorders, and they often have limited power to examine the less common diagnoses.[5 6]

Building on these findings, the current study examines the association between three previously described clinical biomarker-based measures of BA and the subsequent risk of age-related neurological diagnoses among over 300 000 participants in the UK Biobank. We report and compare the effect of advanced BA on time-to-event models for all-cause and cause-specific dementia, ischaemic stroke, Parkinson's disease (PD) and motor neuron disease (MND).

METHODS

Participants

We carried out a prospective cohort analysis in the population-based UK Biobank, which recruited >500 000 volunteers aged 37–73 years between 2006 and 2010.[7] During baseline assessment, participants completed a questionnaire, had physical and functional measurements taken and provided biological samples. After excluding those who had missing data on the BA measures and the common covariates, or had a pre-existing dementia, ischaemic stroke, PD or MND, we included 325 870 participants in the analyses (online supplemental figure 1).

Biological age

Three clinical biomarker-based BA measures were previously derived in the UK Biobank, with the full methods described elsewhere.[3] Briefly, we selected 18 age-related clinical biomarkers that correlate with CA for construction of the BA algorithms (online supplemental figure 2). Using data from the US National Health and Nutrition Examination Surveys, we combined information from the biomarkers and trained and validated three composite measures of BA, namely Klemera-Doubal method age (KDMAge),[8] PhenoAge[9] and homeostatic dysregulation age (HDAge).[10] KDMAge is computed based on regression models of biomarkers on age and represents the predicted physiological age of an individual. PhenoAge is trained based on a mortality prediction score of biomarkers which captures information not only on CA, but also mortality risk. We regressed KDMAge and PhenoAge on CA (as a 3 df natural spline), such that the resulting residual values can be interpreted as the deviation between BA and CA. By contrast, HDAge is not an age measure by definition, but it is calculated as the deviation of an individual's physiology from a healthy reference sample. HDAge was log-transformed before analysis due to its skewed distribution.

Check for updates

To cite: Mak JKL, McMurran CE, Hägg S. *J Neurol Neurosurg Psychiatry* 2024;**95**:481–484.

Outcomes

Incident cases of neurological disorders were ascertained based on the International Classification of Diseases, 10th revision codes obtained from hospital inpatient and death register records, including all-cause dementia (A81.0, F00–F03, F05.1, F10.6, G30, G31.0, G31.1, G31.8), Alzheimer's disease (F00, G30), vascular dementia (F01, I67.3), ischaemic stroke (I63), PD (G20) and MND (G12.2). Participants with a diagnosis or a self-reported history of neurological disorders before baseline were excluded from the analysis.

Statistical analysis

We used Cox proportional-hazards models, where the follow-up time was calculated from date of baseline assessment to date of disease diagnosis, death or end of follow-up (1 April 2018), whichever came first. Attained age was used as the underlying timescale. Models were first adjusted for birth year and sex, and were further adjusted for baseline assessment centre, ethnicity, body mass index, smoking, alcohol and deprivation as the common covariates for all outcomes (multivariable model). We also included models with disease-specific covariates, which were selected based on the literature and the data availability (online supplemental table 1).[11–14] We tested the proportional hazard assumption of the models using Schoenfeld residuals and found no violations. The false discovery rate method was used to correct for multiple testing (corrected significance level at 0.034). All analyses were conducted using R V.4.2.3.

RESULTS

The study sample included 325 870 participants (mean age 56.4; 54.2% women). During a mean follow-up of 9.0 years, 1397 (0.4%), 2515 (0.8%), 679 (0.2%) and 203 (0.1%) participants were diagnosed with dementia, ischaemic stroke, PD and MND, respectively (table 1).

Estimates of the association between a 1 SD increase in BA and neurological disorders are shown in figure 1 and online supplemental table 2. After adjusting for the common covariates, KDMAge residual (HR=1.28, 95% CI=1.21 to 1.35), PhenoAge residual (1.28, 1.22 to 1.35) and HDAge (1.20, 1.13 to 1.27) were all statistically significantly associated with an increased future risk of all-cause dementia. The estimates remained significant when further adjusting for dementia-specific covariates. When stratified by dementia subtypes, all BA measures were strongly associated with vascular dementia, while weaker associations were seen for Alzheimer's disease. Similarly, there was a statistically significantly increased risk of BA measures on ischaemic stroke: KDMAge residual (HR=1.39, 95% CI=1.34 to 1.46), PhenoAge residual (1.38, 1.32 to 1.43) and HDAge (1.28, 1.22 to 1.34). There were weak positive associations between advanced BA and subsequent risk of MND, but only HDAge was statistically significantly associated with MND (HR 1.22, 95% CI 1.06 to 1.42). There were similarly no significant associations between BA residuals and PD risk, however, unlike all other outcomes studied, the HRs for PD tended to be below 1.0: KDMAge residual (HR=0.96, 95% CI=0.88 to 1.04), PhenoAge residual (0.95, 0.88 to 1.03) and HDAge (0.88, 0.80 to 0.93).

Results were largely similar when stratified by age and sex, although the association between BA and dementia appeared to be stronger in younger participants aged <60 years and in women (online supplemental table 3). Several of the individual biomarkers included in the BA measures were predictive for specific neurological outcomes. For example, a higher forced expiratory volume was associated with lower risks of dementia and ischaemic stroke, whereas a higher red blood cell count was associated with increased risks of dementia and PD (online supplemental figure 2). Meanwhile, BA measures appeared to have a more global predictive effect across different neurological outcomes.

Finally, to mitigate against BA assessments taking place after disease onset but prior to formal diagnosis, we repeated the analysis excluding individuals that were diagnosed within 5 years following their BA assessment (online supplemental table 4). Effect sizes were generally smaller but remained in the same direction, with significant associations remaining for all-cause and vascular dementia, ischaemic stroke and for PhenoAge in Alzheimer's disease.

Table 1 Baseline characteristics of participants (n=325 870)

Characteristic	N (%) or mean±SD
Age (years)	56.4±8.1
Sex	
Women	176 631 (54.2)
Men	149 239 (45.8)
Baseline assessment centre	
England	299 083 (91.8)
Wales	14 337 (4.4)
Scotland	12 450 (3.8)
Ethnicity	
White	309 556 (95.0)
Asian	7218 (2.2)
Black	4384 (1.3)
Others	4712 (1.4)
Body mass index	
<18.5	1619 (0.5)
18.5 to <25	107 682 (33.0)
25 to <30	139 343 (42.8)
≥30	77 226 (23.7)
Smoking status	
Never	179 962 (55.2)
Previous	112 699 (34.6)
Current	33 209 (10.2)
Biological age measures	
KDMAge (years)	54.12±9.42
KDMAge residual	-0.03±5.01
PhenoAge (years)	47.63±10.02
PhenoAge residual	-0.03±5.37
HDAge (log units)	6.70±1.00
Died during follow-up	12 144 (3.7)
Incident all-cause dementia during follow-up	1397 (0.4)
Incident Alzheimer's disease during follow-up	557 (0.2)
Incident vascular dementia during follow-up	297 (0.1)
Incident ischaemic stroke during follow-up	2515 (0.8)
Incident Parkinson's disease during follow-up	679 (0.2)
Incident motor neuron disease during follow-up	203 (0.1)

HDAge, homeostatic dysregulation age; *KDMAge*, Klemera-Doubal method age.

DISCUSSION

In this population-based study, we found that advanced biological ageing is associated with increased risk for several age-associated neurological diagnoses, with the largest effect sizes seen for all-cause dementia, vascular dementia and ischaemic stroke. Some of this increased risk will be a consequence of the selection of

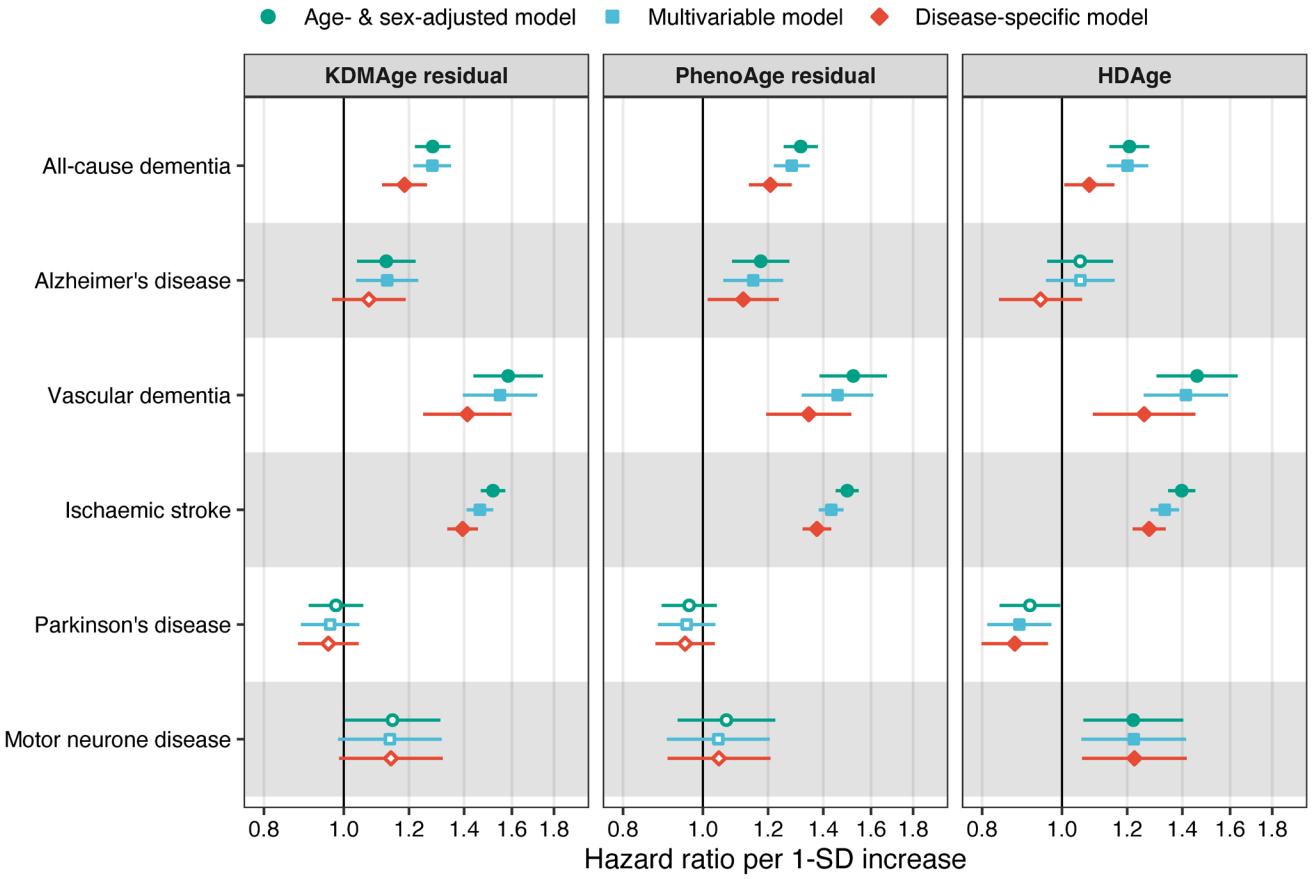


Figure 1 HRs and 95% CIs for neurological disorders in relation to 1 SD increase in biological age measures. Filled symbols represent statistically significant associations at a false discovery rate corrected significance level of 0.034. Age-adjusted and sex-adjusted models were adjusted for age (timescale), birth year and sex, and multivariable models were additionally adjusted for baseline assessment centre, ethnicity, body mass index, smoking, alcohol consumption and deprivation (n=325 870). Disease-specific models further included covariates that are relevant for each outcome based on the literature. The models for all-cause dementia, Alzheimer's disease and vascular dementia included education, physical activity, social isolation, air pollution, diabetes, hypertension, depressive symptoms, hearing impairment, traumatic brain injury, *APOE* e4 allele and family history of dementia (n=269 290). The models for ischaemic stroke included physical activity, air pollution, fresh vegetable and fruit intake, red meat intake, processed meat intake, diabetes, hypertension, depressive symptoms, dyslipidaemia, atrial fibrillation and family history of stroke (n=280 433). The models for Parkinson's disease included hypertension, depressive symptoms, traumatic brain injury and family history of Parkinson's disease (n=310 866). The models for motor neuron disease included family history of dementia (n=325 870). Details of the covariate definitions are shown in online supplemental table 1. APOE, apolipoprotein E; HDAge, homeostatic dysregulation age; KDMAge, Klemera-Doubal method age.

biomarkers used in the BA measures, many of which reflect cardiometabolic health and are independently associated with stroke and all-cause dementia (online supplemental figure 2). That said, strong associations remained after adjusting for relevant confounders in the disease-specific models (including the presence of hypertension, diabetes, dyslipidaemia and smoking history), suggesting that these BA measures have utility beyond simply cardiovascular risk prediction. Our findings are largely consistent with a previous analysis of the Rotterdam Study (n=1930, mean age 72), which used variations of phenotypic age built on a different but overlapping panel of BA biomarkers.[5] The Rotterdam Study reported a similar effect size of BA residual on ischaemic stroke risk, although effect on all-cause dementia risk was only seen with the addition of a central nervous system-specific biomarker (neurofilament light chain), highlighting the importance of comparing BA measures across different cohorts.[6]

The unparalleled scale of the UK Biobank cohort also allows for interrogation of less common age-associated neurological outcomes. Advanced BA measures have a small positive effect size on MND risk, although with wide CIs. These estimates are of a similar size to those seen for Alzheimer's disease, another age-associated neurodegenerative disease characterised by protein aggregation. Interestingly, similar to the results found in a previous study,[6] the effect sizes in PD were in the opposite direction to our other outcomes: advanced BA does not appear to increase PD risk and if anything may be protective. Estimates were similar despite adjustment for smoking history, which might drive higher BA while simultaneously reducing PD risk.[13] Alternatively, the apparent protective effect could be driven by the individual biomarkers included in the BA measures, such as systolic blood pressure and uric acid that were negatively associated with PD risk but positively associated other neurological outcomes online supplemental figure 2. While blood pressure and serum uric acid levels usually increased with advancing age,[15 16] orthostatic hypotension and reduced serum uric acid levels have been associated with a higher risk of PD diagnosis.[17 18]

Comparison between the different BA measures is informative, given there is currently no gold standard approach to

calculating BA from clinical biomarkers. For example, Alzheimer's disease—a common cause of death at the population level—had a relatively strong association with PhenoAge, a BA measure based on mortality risk. In contrast, PD and MND were more associated with HDAge, which is based on biomarker deviation from a young reference population. HDAge is naïve to the direction of biomarker deviation,[10] some of which would be expected to move in the opposite direction to 'normal' ageing in specific pathologies, for example, people with MND tend to have low serum creatinine related to muscle atrophy.[19] Some of these associations might therefore have contributions from more disease-specific biomarker signatures during a prodromal period prior to diagnosis.

Strengths of this study include the large sample size, which provides statistical power to examine some less common neurological disorders while adjusting for multiple confounding factors. Nevertheless, it should be acknowledged that UK Biobank is a relatively healthy cohort in comparison to the general UK population due to a 'healthy volunteer' selection bias.[20] While we know something about the temporal relationship between BA advancement and diagnosis (participants did not have a neurological diagnosis when their BA was assessed, and diagnoses were collected over a mean follow-up of 9.0 years), as an observational study we cannot establish causal relationships. As alluded to, the insidious onset of neurodegenerative disorders is a particular consideration, with some of the BA assessments likely occurring during a prodromal period and our ascertainment of neurological conditions relied solely on medical records. We have mitigated against this with sensitivity analysis in which participants were excluded if their diagnosis was made within 5 years following their BA assessment. Further follow-up of the UK Biobank cohort in the coming years will further help to clarify some of these points.

In summary, in a large population study, we find that higher measures of BA derived from routine clinical biomarkers increase one's risk for dementia or stroke, despite adjustment for disease-specific risk factors.

X Jonathan K L Mak @JonathanKLMak

Acknowledgements This research was conducted using the UK Biobank resource under the Application Number 22224.

Contributors CEM, JKLM and SH contributed to the conception and design of the study. JKLM contributed to data acquisition and statistical analyses. JKLM and CEM drafted the manuscript. All authors critically revised the manuscript for intellectual content.

Funding This study was supported by the Swedish Research Council (2022-01608) and by Karolinska Institutet Foundation and Strategic Research Program in Epidemiology. CEM was supported by a NIHR Academic Clinical Fellowship.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was obtained from the North West Multi-Centre Research Ethics Committee (11/NW/0382) and the Swedish Ethical Review Authority in Stockholm. Informed consent was obtained from all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

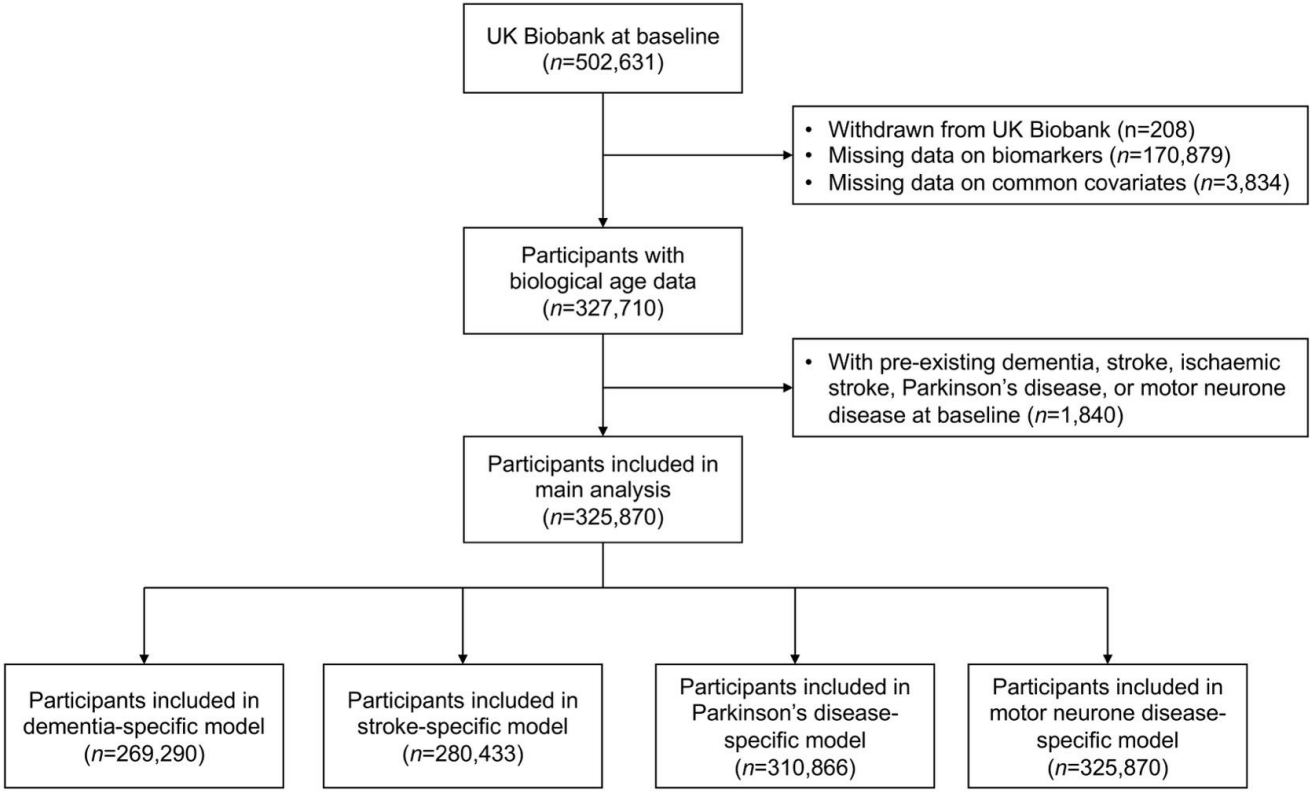
ORCID iD

Jonathan K L Mak http://orcid.org/0000-0003-4454-8580

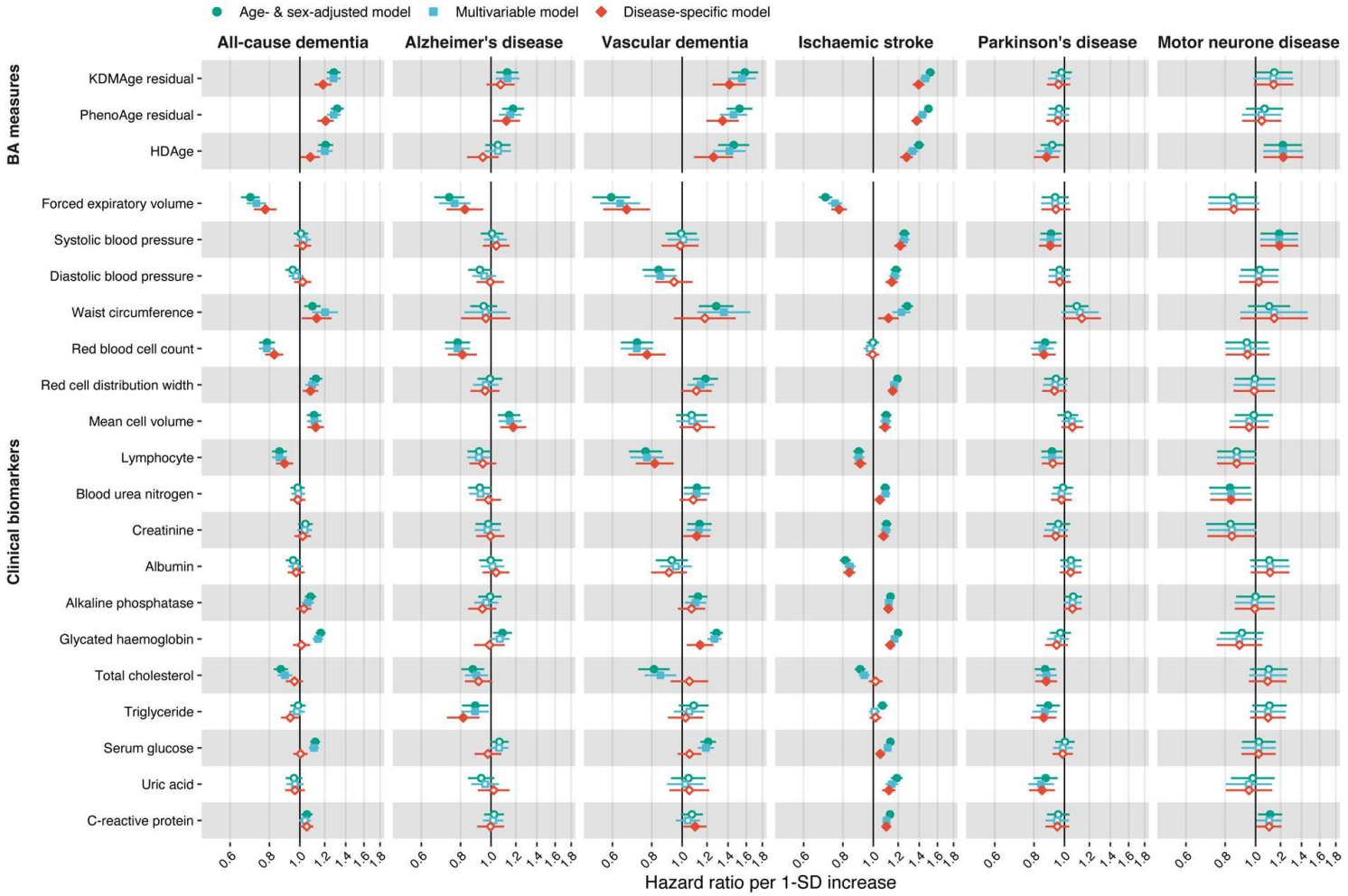
REFERENCES

1 Jylhävä J, Pedersen NL, Hägg S. Biological age predictors. *EBioMedicine* 2017;21:29–36.
2 Chan MS, Arnold M, Offer A, *et al*. A biomarker-based biological age in UK Biobank: composition and prediction of mortality and hospital admissions. *J Gerontol A Biol Sci Med Sci* 2021;76:1295–302.
3 Mak JKL, McMurran CE, Kuja-Halkola R, *et al*. Clinical biomarker-based biological aging and risk of cancer in the UK Biobank. *Br J Cancer* 2023;129:94–103.
4 Gao X, Geng T, Jiang M, *et al*. Accelerated biological aging and risk of depression and anxiety: evidence from 424,299 UK Biobank participants. *Nat Commun* 2023;14.
5 Wu JW, Yaqub A, Ma Y, *et al*. Biological age in healthy elderly predicts aging-related diseases including dementia. *Sci Rep* 2021;11:15929.
6 McMurran CE, Wang Y, Mak JKL, *et al*. Advanced biological ageing predicts future risk for neurological diagnoses and clinical examination findings. *Brain* 2023:awad252.
7 Sudlow C, Gallacher J, Allen N, *et al*. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLOS Med* 2015;12:e1001779.
8 Klemera P, Doubal S. A new approach to the concept and computation of biological age. *Mech Ageing Dev* 2006;127:240–8.
9 Levine ME, Lu AT, Quach A, *et al*. An epigenetic biomarker of aging for LifeSpan and Healthspan. *Aging (Albany NY)* 2018;10:573–91.
10 Cohen AA, Milot E, Yong J, *et al*. A novel statistical approach shows evidence for multi-system physiological dysregulation during aging. *Mech Ageing Dev* 2013;134:110–7.
11 Livingston G, Huntley J, Sommerlad A, *et al*. Dementia prevention, intervention, and care: 2020 report of the lancet Commission. *The Lancet* 2020;396:413–46.
12 Logroscino G, Piccininni M, Marin B, *et al*. Global, regional, and national burden of motor neuron diseases 1990–2016: a systematic analysis for the global burden of disease study 2016. *The Lancet Neurology* 2018;17:1083–97.
13 Noyce AJ, Bestwick JP, Silveira-Moriyama L, *et al*. Meta-analysis of early Nonmotor features and risk factors for Parkinson disease. *Ann Neurol* 2012;72:893–901.
14 O'Donnell MJ, Xavier D, Liu L, *et al*. Risk factors for ischaemic and intracerebral Haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112–23.
15 Buford TW. Hypertension and aging. *Ageing Res Rev* 2016;26:96–111.
16 Kuzuya M, Ando F, Iguchi A, *et al*. Effect of aging on serum uric acid levels: longitudinal changes in a large Japanese population group. *J Gerontol A Biol Sci Med Sci* 2002;57:M660–4.
17 Goldstein DS. Orthostatic hypotension as an early finding in Parkinson's disease. *Clin Auton Res* 2006;16:46–54.
18 Wen M, Zhou B, Chen Y-H, *et al*. Serum uric acid levels in patients with Parkinson's disease: A meta-analysis. *PLoS One* 2017;12:e0173731.
19 Verber NS, Shepheard SR, Sassani M, *et al*. Biomarkers in motor neuron disease: A state of the art review. *Front Neurol* 2019;10:291.
20 Fry A, Littlejohns TJ, Sudlow C, *et al*. Comparison of Sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017;186:1026–34.

Supplementary Figure 1. Flowchart for the selection of participants.



Supplementary Figure 2. Hazard ratios and 95% confidence intervals for neurological disorders in relation to 1-SD increase in biological age measures and the 18 individual clinical biomarkers.



Filled symbols represent statistically significant associations a false discovery rate corrected significance level of 0.034. *HDAge*, homeostatic dysregulation age; *KDMAge*, Klemera-Doubal method age; *SD*, standard deviation.

Supplementary Table 1. Definitions of the covariates included in the disease-specific models

Covariate	Description	Categorization	Field ID	Dementia-specific model	Stroke-specific model	Parkinson's disease-specific model	Motor neurone disease-specific model
Age (timescale)	Date of baseline assessment minus date of birth	Continuous	53, 34, 52	Yes	Yes	Yes	Yes
Year of birth	Year of birth	1930–1939; 1940–1949; 1950–1959; ≥1960	34	Yes	Yes	Yes	Yes
Sex	Self-reported sex or NHS-derived	Women; Men	31	Yes	Yes	Yes	Yes
Assessment centre	UK Biobank assessment centre	England; Wales; Scotland	54	Yes	Yes	Yes	Yes
Ethnicity	Self-reported ethnic background	White; Asian; Black; Others	21000	Yes	Yes	Yes	Yes
Body mass index	Body mass index calculated from measured height and weight	Underweight (<18.5); Normal weight (18.5 to <25); Overweight (25 to <30); Obese (≥30)	21001	Yes	Yes	Yes	Yes
Smoking	Self-reported smoking status	Never; Previous; Current	20116	Yes	Yes	Yes	Yes
Alcohol	Self-reported alcohol intake frequency	Less than 3 times a month; 1–4 times a week; Daily or almost daily	1558	Yes	Yes	Yes	Yes
Deprivation	Townsend deprivation index derived from national census data	Quintiles of deprivation index	22189	Yes	Yes	Yes	Yes
Education	Self-reported highest qualifications	Low (no relevant qualifications); Intermediate (A levels, O levels/GCSEs, CSEs, NVQ/HND/HNC, other professional qualifications); High (college or university degree)	6138	Yes	-	-	-
Physical activity	Physical Activity Questionnaire activity group	Low; Moderate; High	22032	Yes	Yes	-	-
Social isolation	Defined based on three questions: (1) "Including yourself, how many people are living together in your household?" (1 point if living alone); (2) "How often do you visit friends or family or have them visit you?" (1 point if less than once a month); (3) "Which of the following [leisure/social activities] do you engage in once a week or more often?" (1 point if no activity)	No (total score <2); Yes (total score ≥2)	709, 1031, 6160	Yes	-	-	-
Air pollution	Particulate matter air pollution ($PM_{2.5}$)	Continuous ($\mu g/m^3$)	24006	Yes	Yes	-	-
Fresh vegetable and fruit intake	Self-reported intake frequency of salad/raw vegetables and fresh fruits	<5 portions a day; ≥5 portions a day	1299, 1309	-	Yes	-	-
Red meat intake	Self-reported intake frequency of beef, lamb, and pork	Less than twice a week; Twice a week or more	1369, 1379, 1389	-	Yes	-	-
Processed meat intake	Self-reported intake frequency of processed meat	Less than twice a week; Twice a week or more	1349	-	Yes	-	-
Diabetes	Self-reported diabetes	No; Yes	2443, 20002	Yes	Yes		-
Hypertension	Self-reported high blood pressure	No; Yes	6150, 20002	Yes	Yes	Yes	-
Depressive symptoms	Self-reported frequency of depressed mood in last 2 weeks	Not at all; Several days; More than half the days; Nearly every day	2050	Yes	Yes	Yes	-

Supplementary Table 1. (*continued*)

Covariate	Description	Categorization	Field ID	Dementia-specific model	Stroke-specific model	Parkinson's disease-specific model	Motor neurone disease-specific model
Hearing impairment	Self-reported hearing difficulty/problems	No; Yes	2247	Yes	-		-
Traumatic brain injury	Self-reported head injury	No; Yes	20002	Yes	-	Yes	-
Dyslipidaemia	Self-reported use of cholesterol lowering medication	No; Yes	6153, 6177	-	Yes	-	-
Atrial fibrillation	Self-reported atrial fibrillation	No; Yes	20002	-	Yes	-	-
***ApoE* e4 allele**	Determined based on two single nucleotide polymorphisms: rs7412 and rs429358	None (e2e2, e2e3 or e3e3), One (e3e4 or e2e4), and Two (e4e4)	rs7412, rs429358	Yes	-	-	-
Family history of dementia	Self-reported illnesses in father, mother, or siblings	No; Yes	20107, 20110, 20111	Yes	-	-	Yes
Family history of Parkinson's disease	Self-reported illnesses in father, mother, or siblings	No; Yes	20107, 20110, 20111	-	-	Yes	-
Family history of stroke	Self-reported illnesses in father, mother, or siblings	No; Yes	20107, 20110, 20111	-	Yes	-	-

Supplementary Table 2. Association between biological age measures and neurological disorders

Model	KDMAge residual		PhenoAge residual		HDAge	
	HR per SD increase (95% CI)	*p*	HR per SD increase (95% CI)	*p*	HR per SD increase (95% CI)	*p*
All-cause dementia						
Age- & sex-adjusted model[a]	1.28 (1.22, 1.35)*	1.0×10^{-22}	1.31 (1.25, 1.38)*	4.8×10^{-29}	1.21 (1.14, 1.28)*	3.1×10^{-11}
Multivariable model[b]	1.28 (1.21, 1.35)*	4.1×10^{-20}	1.28 (1.22, 1.35)*	3.0×10^{-22}	1.20 (1.13, 1.27)*	6.0×10^{-10}
Disease-specific model[c]	1.19 (1.11, 1.26)*	1.1×10^{-7}	1.21 (1.14, 1.28)*	6.9×10^{-10}	1.08 (1.01, 1.16)*	0.033
Alzheimer's disease						
Age- & sex-adjusted model[a]	1.13 (1.04, 1.22)*	0.004	1.18 (1.08, 1.27)*	7.8×10^{-5}	1.05 (0.96, 1.15)	0.281
Multivariable model[b]	1.13 (1.04, 1.23)*	0.006	1.15 (1.06, 1.25)*	0.001	1.05 (0.96, 1.16)	0.296
Disease-specific model[c]	1.07 (0.97, 1.19)	0.181	1.12 (1.01, 1.24)*	0.026	0.94 (0.84, 1.06)	0.312
Vascular dementia						
Age- & sex-adjusted model[a]	1.58 (1.44, 1.75)*	2.0×10^{-20}	1.52 (1.39, 1.67)*	2.4×10^{-18}	1.46 (1.30, 1.63)*	7.6×10^{-11}
Multivariable model[b]	1.55 (1.39, 1.72)*	1.8×10^{-16}	1.46 (1.32, 1.61)*	1.6×10^{-13}	1.41 (1.26, 1.59)*	9.0×10^{-9}
Disease-specific model[c]	1.41 (1.25, 1.60)*	4.6×10^{-8}	1.34 (1.19, 1.51)*	1.1×10^{-6}	1.26 (1.09, 1.45)*	0.002
Ischemic stroke						
Age- & sex-adjusted model[a]	1.52 (1.47, 1.57)*	5.9×10^{-127}	1.50 (1.45, 1.55)*	1.5×10^{-133}	1.40 (1.35, 1.45)*	3.6×10^{-66}
Multivariable model[b]	1.46 (1.41, 1.52)*	1.3×10^{-89}	1.43 (1.38, 1.48)*	2.1×10^{-91}	1.33 (1.28, 1.39)*	2.8×10^{-44}
Disease-specific model[c]	1.39 (1.34, 1.46)*	3.4×10^{-52}	1.38 (1.32, 1.43)*	6.2×10^{-55}	1.28 (1.22, 1.34)*	4.4×10^{-25}
Parkinson's disease						
Age- & sex-adjusted model[a]	0.98 (0.91, 1.06)	0.575	0.96 (0.89, 1.04)	0.329	0.91 (0.84, 1.00)	0.038
Multivariable model[b]	0.96 (0.89, 1.04)	0.362	0.96 (0.88, 1.04)	0.270	0.89 (0.81, 0.97)*	0.009
Disease-specific model[c]	0.96 (0.88, 1.04)	0.318	0.95 (0.88, 1.03)	0.242	0.88 (0.80, 0.96)*	0.005
Motor neurone disease						
Age- & sex-adjusted model[a]	1.15 (1.00, 1.31)	0.046	1.07 (0.93, 1.22)	0.344	1.22 (1.06, 1.40)*	0.005
Multivariable model[b]	1.14 (0.98, 1.32)	0.081	1.04 (0.90, 1.21)	0.557	1.22 (1.06, 1.42)*	0.007
Disease-specific model[c]	1.14 (0.99, 1.32)	0.074	1.05 (0.91, 1.21)	0.541	1.22 (1.06, 1.42)*	0.007

CI, confidence interval; *HDAge*, homeostatic dysregulation age; *HR*, hazard ratio; *KDMAge*, Klemera-Doubal method age; *SD*, standard deviation.

[a] Age- & sex-adjusted models: adjusted for age (timescale), birthyear, and sex (n=325,870).

[b] Multivariable models: additionally adjusted for baseline assessment centre, ethnicity, body mass index, smoking, alcohol consumption, and deprivation (n=325,870).

[c] Disease-specific models further included covariates that are relevant for each outcome based on the literature (**Supplementary Table 1**). The models for all-cause dementia, Alzheimer's disease, and vascular dementia included education, physical activity, social isolation, air pollution, diabetes, hypertension, depressive symptoms, hearing impairment, traumatic brain injury, *ApoE* e4 allele, and family history of dementia (n=269,290). The models for ischaemic stroke included physical activity, air pollution, fresh vegetable and fruit intake, red meat intake, processed meat intake, diabetes, hypertension, depressive symptoms, dyslipidaemia, atrial fibrillation, and family history of stroke (n=280,433). The models for Parkinson's disease included hypertension, depressive symptoms, traumatic brain injury, and family history of Parkinson's disease (n=310,866). The models for motor neurone disease included family history of dementia (n=325,870).

* Significant at a false discovery rate corrected significance level of 0.034

Supplementary Table 3. Subgroup analysis of the association between biological age measures and neurological disorders

Subgroup	KDMAge residual		PhenoAge residual		HDAge	
	HR per SD increase (95% CI)	$P_{interaction}$	HR per SD increase (95% CI)	$P_{interaction}$	HR per SD increase (95% CI)	$P_{interaction}$
All-cause dementia						
Age <60 (n=154,828)	1.32 (1.14, 1.54)	0.062	1.41 (1.23, 1.62)	0.005	1.13 (0.96, 1.32)	0.389
Age ≥60 (n=114,462)	1.16 (1.08, 1.24)		1.17 (1.09, 1.25)		1.07 (0.99, 1.16)	
Women (n=143,956)	1.17 (1.07, 1.29)	0.771	1.32 (1.21, 1.45)	0.029	1.21 (1.08, 1.35)	0.037
Men (n=125,334)	1.19 (1.10, 1.30)		1.13 (1.05, 1.22)		1.00 (0.91, 1.10)	
Alzheimer's disease						
Age <60 (n=154,828)	1.21 (0.92, 1.60)	0.489	1.42 (1.12, 1.80)	0.059	0.87 (0.64, 1.18)	0.443
Age ≥60 (n=114,462)	1.05 (0.94, 1.18)		1.08 (0.97, 1.20)		0.95 (0.84, 1.08)	
Women (n=143,956)	1.12 (0.96, 1.30)	0.442	1.30 (1.13, 1.50)	0.009	1.03 (0.86, 1.22)	0.128
Men (n=125,334)	1.03 (0.89, 1.19)		0.98 (0.85, 1.12)		0.87 (0.74, 1.02)	
Vascular dementia						
Age <60 (n=154,828)	1.96 (1.39, 2.76)	0.010	2.03 (1.47, 2.80)	0.002	1.50 (0.98, 2.31)	0.232
Age ≥60 (n=114,462)	1.35 (1.18, 1.54)		1.28 (1.13, 1.46)		1.22 (1.05, 1.42)	
Women (n=143,956)	1.28 (1.02, 1.61)	0.666	1.33 (1.08, 1.65)	0.611	1.29 (0.99, 1.67)	0.414
Men (n=125,334)	1.50 (1.30, 1.74)		1.35 (1.17, 1.56)		1.22 (1.03, 1.45)	
Ischemic stroke						
Age <60 (n=160,957)	1.37 (1.27, 1.49)	0.511	1.39 (1.29, 1.50)	0.125	1.28 (1.18, 1.39)	0.493
Age ≥60 (n=119,476)	1.40 (1.33, 1.47)		1.37 (1.31, 1.44)		1.26 (1.19, 1.34)	
Women (n=151,275)	1.30 (1.21, 1.40)	0.127	1.35 (1.26, 1.45)	0.911	1.35 (1.25, 1.47)	0.012
Men (n=129,158)	1.46 (1.38, 1.54)		1.40 (1.33, 1.47)		1.23 (1.16, 1.30)	
Parkinson's disease						
Age <60 (n=178,385)	0.87 (0.71, 1.07)	0.368	0.86 (0.70, 1.05)	0.343	0.78 (0.63, 0.97)	0.241
Age ≥60 (n=132,481)	0.97 (0.89, 1.07)		0.97 (0.89, 1.07)		0.90 (0.81, 1.00)	
Women (n=167,679)	0.99 (0.87, 1.13)	0.288	1.02 (0.90, 1.17)	0.090	0.99 (0.85, 1.15)	0.025
Men (n=143,187)	0.94 (0.84, 1.04)		0.91 (0.82, 1.01)		0.81 (0.72, 0.92)	
Motor neurone disease						
Age <60 (n=187,275)	1.26 (1.00, 1.59)	0.133	1.18 (0.94, 1.48)	0.048	1.26 (1.00, 1.57)	0.577
Age ≥60 (n=138,595)	1.06 (0.88, 1.28)		0.96 (0.80, 1.16)		1.19 (0.98, 1.44)	
Women (n=176,631)	1.12 (0.89, 1.40)	0.801	1.03 (0.82, 1.30)	0.847	1.21 (0.96, 1.54)	0.969
Men (n=149,239)	1.15 (0.95, 1.39)		1.05 (0.87, 1.26)		1.23 (1.02, 1.48)	

CI, confidence interval; *HDAge*, homeostatic dysregulation age; *HR*, hazard ratio; *KDMAge*, Klemera-Doubal method age; *SD*, standard deviation. All models were disease-specific models adjusted for the covariates listed in **Supplementary Table 1**. $P_{interaction}$ represent p-values of the multiplicative interaction terms between the continuous biological age measures and the subgroup indicator.

Supplementary Table 4. Association between biological age measures and neurological disorders after excluding diagnoses within 5 years from baseline

Model	KDMAge residual		PhenoAge residual		HDAge	
	HR per SD increase (95% CI)	*p*	HR per SD increase (95% CI)	*p*	HR per SD increase (95% CI)	*p*
All-cause dementia						
Age- & sex-adjusted model[a]	1.25 (1.18, 1.33)*	1.5×10^{-13}	1.26 (1.19, 1.33)*	1.6×10^{-14}	1.17 (1.10, 1.26)*	2.8×10^{-6}
Multivariable model[b]	1.25 (1.17, 1.33)*	6.2×10^{-12}	1.22 (1.15, 1.30)*	1.8×10^{-10}	1.17 (1.09, 1.25)*	1.4×10^{-5}
Disease-specific model[c]	1.17 (1.09, 1.26)*	2.9×10^{-5}	1.17 (1.09, 1.26)*	1.9×10^{-5}	1.05 (0.97, 1.14)	0.26
Alzheimer's disease						
Age- & sex-adjusted model[a]	1.11 (1.01, 1.23)	0.033	1.17 (1.06, 1.29)*	0.001	1.06 (0.95, 1.18)	0.326
Multivariable model[b]	1.12 (1.01, 1.24)	0.034	1.15 (1.04, 1.27)*	0.008	1.06 (0.95, 1.19)	0.292
Disease-specific model[c]	1.08 (0.96, 1.22)	0.209	1.13 (1.00, 1.27)	0.042	0.96 (0.84, 1.10)	0.591
Vascular dementia						
Age- & sex-adjusted model[a]	1.66 (1.48, 1.86)*	1.5×10^{-17}	1.54 (1.38, 1.73)*	1.5×10^{-13}	1.46 (1.27, 1.68)*	1.3×10^{-7}
Multivariable model[b]	1.61 (1.42, 1.82)*	6.1×10^{-14}	1.46 (1.29, 1.65)*	1.2×10^{-9}	1.40 (1.21, 1.62)*	6.0×10^{-6}
Disease-specific model[c]	1.42 (1.22, 1.64)*	3.8×10^{-6}	1.29 (1.12, 1.50)*	5.5×10^{-4}	1.20 (1.00, 1.43)	0.044
Ischemic stroke						
Age- & sex-adjusted model[a]	1.49 (1.42, 1.56)*	1.8×10^{-56}	1.46 (1.40, 1.54)*	3.6×10^{-57}	1.31 (1.24, 1.38)*	9.5×10^{-21}
Multivariable model[b]	1.44 (1.37, 1.52)*	4.6×10^{-41}	1.41 (1.34, 1.48)*	5.0×10^{-40}	1.25 (1.17, 1.32)*	3.0×10^{-13}
Disease-specific model[c]	1.37 (1.28, 1.45)*	1.2×10^{-22}	1.35 (1.28, 1.43)*	5.5×10^{-24}	1.19 (1.11, 1.27)*	1.2×10^{-6}
Parkinson's disease						
Age- & sex-adjusted model[a]	1.01 (0.92, 1.11)	0.842	0.98 (0.89, 1.07)	0.643	0.92 (0.83, 1.02)	0.133
Multivariable model[b]	1.01 (0.92, 1.12)	0.819	0.99 (0.90, 1.09)	0.800	0.91 (0.81, 1.01)	0.075
Disease-specific model[c]	1.01 (0.91, 1.11)	0.920	0.98 (0.89, 1.09)	0.738	0.89 (0.79, 1.00)	0.047
Motor neurone disease						
Age- & sex-adjusted model[a]	1.12 (0.93, 1.35)	0.223	1.10 (0.92, 1.32)	0.301	1.11 (0.92, 1.36)	0.281
Multivariable model[b]	1.11 (0.91, 1.35)	0.306	1.07 (0.88, 1.30)	0.477	1.11 (0.90, 1.36)	0.341
Disease-specific model[c]	1.11 (0.91, 1.35)	0.304	1.07 (0.88, 1.30)	0.475	1.11 (0.90, 1.36)	0.339

CI, confidence interval; *HDAge*, homeostatic dysregulation age; *HR*, hazard ratio; *KDMAge*, Klemera-Doubal method age; *SD*, standard deviation.

[d] Age- & sex-adjusted models: adjusted for age (timescale), birthyear, and sex (n=325,459).

[e] Multivariable models: additionally adjusted for baseline assessment centre, ethnicity, body mass index, smoking, alcohol consumption, and deprivation (n=325,459).

[f] Disease-specific models further included covariates that are relevant for each outcome based on the literature (**Supplementary Table 1**). The models for all-cause dementia, Alzheimer's disease, and vascular dementia included education, physical activity, social isolation, air pollution, diabetes, hypertension, depressive symptoms, hearing impairment, traumatic brain injury, *ApoE* e4 allele, and family history of dementia (n=269,000). The models for ischaemic stroke included physical activity, air pollution, fresh vegetable and fruit intake, red meat intake, processed meat intake, diabetes, hypertension, depressive symptoms, dyslipidaemia, atrial fibrillation, and family history of stroke (n=279,344). The models for Parkinson's disease included hypertension, depressive symptoms, traumatic brain injury, and family history of Parkinson's disease (n=325,644). The models for motor neurone disease included family history of dementia (n=325,777).

* Significant at a false discovery rate corrected significance level of 0.025