

Antiseizure Medication Use and Multidimensional Biological Aging: A UK Biobank Study

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Abstract

Background

Antiseizure medications (ASMs) are commonly prescribed for prolonged treatment of epilepsy and other neurological or psychiatric conditions, but their association with biological aging is uncertain. We examined ASM use in relation to multiple biological aging indicators in the UK Biobank.

Methods

This cross-sectional analysis included 322,065 participants, of whom 4,940 were classified as continuous ASM users for at least 1 year before baseline. Outcomes were Klemm-Doubal method (KDM) age residual, Phenotypic Age (PhenoAge) residual, log-transformed homeostatic dysregulation (HD-log), and Z-standardized leukocyte telomere length (Z-LTL). Associations were estimated using multivariable linear regression and 1:3 propensity score matching. Drug-specific analyses compared individual monotherapies with non-use and, separately, with other ASM monotherapies.

Results

After matching, ASM use was associated with higher HD-log ($\beta = 0.184$, 95% confidence interval [CI] 0.152 to 0.216), KDM residual ($\beta = 0.818$ years, 95% CI 0.646 to 0.990), and PhenoAge residual ($\beta = 0.654$ years, 95% CI 0.482 to 0.826), and with lower Z-LTL ($\beta = -0.057$, 95% CI -0.090 to -0.024). Drug-specific estimates were heterogeneous. In one-versus-rest analyses, lamotrigine and topiramate were associated with lower values for selected indicators, whereas gabapentin, pregabalin, and phenytoin were associated with higher values for selected indicators.

Conclusions

ASM use was associated with less favorable profiles across several physiological and molecular aging indicators. The cross-sectional design and potential residual confounding, particularly by treatment indication, preclude causal interpretation.

Background

Antiseizure medications (ASMs) are central to the management of epilepsy and are also prescribed for neuropathic pain, migraine, bipolar disorder, and other neurological or psychiatric conditions [1, 2, 3]. Because treatment is often prolonged, assessment of long-term safety should consider cumulative effects across physiological systems in addition to established organ-specific adverse effects.

Biological aging reflects interindividual differences in physiological integrity that are not captured by chronological age alone [4, 5, 6]. Clinical biomarker-based measures such as the Klemm-Doual method (KDM), Phenotypic Age (PhenoAge), and homeostatic dysregulation (HD), together with leukocyte telomere length (LTL), provide complementary information on multisystem function and cellular aging [7, 8, 9, 10]. These indicators have been associated with morbidity and mortality in population studies [11, 12, 13].

Previous safety research has examined weight changes during prolonged gabapentin treatment [14] and cardiovascular outcomes associated with gabapentin and pregabalin [15]. Evaluating multiple biological aging indicators may complement these outcome-specific assessments by characterizing broader physiological and molecular profiles.

We therefore examined the association between ASM use and four biological aging indicators in the UK Biobank. We assessed overall ASM use, individual monotherapies compared with non-use, and one-versus-rest comparisons within the monotherapy cohort. We also conducted subgroup and sensitivity analyses and explored whether selected clinical biomarkers statistically accounted for part of the observed associations.

Methods

This cross-sectional analysis within the UK Biobank was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cross-sectional studies.

Study population

The UK Biobank is a population-based prospective cohort that enrolled approximately 500,000 participants aged 40–69 years at 22 assessment centres in the United Kingdom between 2006 and 2010 [16]. At baseline, participants completed questionnaires and nurse-led interviews, underwent standardized physical measurements, and provided biological samples. The UK Biobank received generic ethical approval from the North West Haydock Research Ethics Committee (REC 11/NW/0382), and all participants provided written informed consent.

This analysis was conducted under UK Biobank application 217802. We excluded 178,352 participants with missing data for biomarkers required by the biological aging algorithms, leaving 323,812 participants. We then excluded 1,653 participants with missing core covariates and 94 participants with biological aging estimates beyond ± 5 standard deviations. The final analytic sample comprised 322,065 participants (Fig. 1). Biomarkers included in the aging algorithms are listed in Supplementary Table S2 [see Additional file 1].

Covariates

Covariates were selected a priori and included baseline age, sex, race/ethnicity, Townsend Deprivation Index, smoking status, alcohol intake, and epilepsy status. Complete-case analysis was used for these

variables.

Assessment of biological aging

We assessed four complementary indicators: KDM age residual, PhenoAge residual, log-transformed homeostatic dysregulation (HD-log), and Z-standardized leukocyte telomere length (Z-LTL). KDM age, PhenoAge, and HD are composite measures based on clinical biomarkers, whereas LTL represents a molecular marker related to cellular replication and biological stress.

KDM age was calculated from 18 age-related biomarkers using the BioAge framework [17]. To obtain KDM age residuals, KDM age was regressed on chronological age modeled with a natural spline with 3 degrees of freedom. Positive residuals indicate an older biological profile than expected for chronological age.

PhenoAge was calculated using a mortality-predictive combination of clinical and hematological markers. PhenoAge was regressed on chronological age using the same spline specification; positive PhenoAge residuals indicate an older biological profile relative to participants of similar chronological age.

HD quantifies the multivariate Mahalanobis distance between an individual biomarker profile and the centroid of a reference population. Because HD was right-skewed, values were natural-log transformed. Higher HD-log values indicate greater multisystem physiological dysregulation.

LTL was measured in the UK Biobank using a validated multiplex quantitative polymerase chain reaction method. Z-LTL was used in the primary analyses; lower values indicate shorter telomeres. Unstandardized LTL was used in the exploratory mediation analyses to retain the original measurement scale.

All composite biological aging metrics were calculated using the R package BioAge [17]. The biomarkers and algorithm specifications are provided in Supplementary Table S2.

Assessment of antiseizure medication use

Baseline ASM exposure was ascertained by integrating primary care prescription records with self-reported medication data from the initial UK Biobank assessment. Drug names were standardized to generic names using British National Formulary terminology, and medications were identified from BNF codes, drug names, and descriptive entries (Supplementary Table S10).

ASM users were participants with documented continuous prescriptions spanning at least 1 year before baseline. For monotherapy analyses, we excluded participants with less than 1 year of monotherapy, those receiving more than one ASM, and agents used by fewer than 50 participants.

Statistical analysis

Continuous variables are summarized as medians and interquartile ranges, and categorical variables as counts and percentages. Between-group comparisons used the Mann-Whitney U test for continuous variables and appropriate tests for categorical variables. Propensity scores for ASM use were estimated by logistic regression using age, sex, race/ethnicity, current smoking, and current alcohol consumption. ASM users were matched without replacement to non-users in a 1:3 ratio. Covariate balance was assessed using standardized mean differences, with an absolute value below 0.10 considered acceptable.

Multivariable linear regression was used to estimate associations of overall ASM use and individual monotherapies with each biological aging indicator. Analyses of individual drugs used two comparison frameworks: each monotherapy versus matched non-users and each monotherapy versus all other monotherapies (one-versus-rest). Models were adjusted for age, sex, race/ethnicity, Townsend Deprivation Index, epilepsy status, smoking status, and alcohol intake. Estimates are reported as unstandardized β coefficients with 95% CIs. Drug-specific, subgroup, and mediation analyses were considered exploratory, and no adjustment for multiple comparisons was applied. Analyses were conducted in R version 4.2.0 using two-sided P values.

Subgroup analyses

Associations were estimated within prespecified strata of age (≤ 60 or > 60 years), sex, race/ethnicity (White or non-White), smoking, alcohol intake, and epilepsy status. Models included the same covariates as the primary analysis except for the stratifying variable. Subgroup estimates were interpreted descriptively because formal interaction tests were not performed.

Sensitivity analyses

First, we repeated the analyses using the original HD, KDM, and PhenoAge algorithms (Supplementary Table S11; Additional file 2, Fig. S3). Second, we repeated the primary analysis after excluding participants with epilepsy to reduce confounding by indication (Supplementary Table S12; Additional file 2, Fig. S3).

Exploratory mediation analysis

Partial Spearman rank correlations, adjusted for age, sex, smoking, and alcohol intake, were used to identify clinical biomarkers associated with ASM use and the biological aging indicators. Biomarkers selected from these analyses were evaluated using the mediation package (version 4.5.0) in R [18].

Two linear regression models were used to estimate the indirect and direct components of each association, with nonparametric bootstrap resampling for uncertainty estimation. Models were adjusted for age, sex, race/ethnicity, Townsend Deprivation Index, epilepsy status, smoking status, and alcohol intake.

Because ASM exposure, biomarkers, and biological aging indicators were assessed around baseline, these analyses were interpreted as exploratory statistical decompositions rather than evidence of causal mediation.

Results

Participant characteristics

After exclusions for missing biomarker data, missing covariates, and outlying biological aging estimates, 322,065 participants were included (Fig. 1).

Of these, 4,940 participants were classified as ASM users and 317,125 as non-users. Before matching, several baseline characteristics differed between groups (Table 1; Supplementary Table S1). Propensity score matching yielded 4,940 ASM users and 14,820 non-users; standardized mean differences for the matching variables were below 0.10 (Table 1).

Table 1
Baseline characteristics before and after propensity score matching

Characteristics	Before PSM			After PSM	
	ASM	Non-ASM	SMD	Non-ASM	SMD
	(N = 4940)	(N = 317125)		(N = 14820)	
Demographics					
Age (years), median [IQR]	59 [52, 64]	58 [50, 63]	0.158	59 [52, 64]	0.000
Sex (Male), n (%)	1,944 (39.4%)	147,962 (46.7%)	0.136	5,834 (39.4%)	0.000
Race (White), n (%)	4,690 (94.9%)	299,781 (94.5%)	0.018	14,072 (94.9%)	0.000
Lifestyle					
Current smoking, n (%)	662 (13.4%)	32,115 (10.1%)	0.102	1,986 (13.4%)	0.000
Current drinking, n (%)	4,145 (83.9%)	292,892 (92.4%)	0.264	12,435 (83.9%)	0.000
Aging Biomarkers					
KDM residual	0.61 [-2.69, 4.17]	-0.30 [-3.37, 3.01]	-	-0.27 [-3.38, 3.13]	-
PhenoAge residual	-0.01 [-3.15, 3.77]	-0.36 [-3.39, 2.95]	-	-0.54 [-3.60, 2.88]	-
HD (log units)	6.69 [6.02, 7.37]	6.40 [5.73, 7.08]	-	6.53 [5.86, 7.18]	-
LTL (T/S ratio)	0.817 [0.74, 0.90]	0.822 [0.74, 0.91]	-	0.820 [0.74, 0.91]	-

Abbreviations: ASM, antiseizure medication; BA, biological age; HD-log, log-transformed homeostatic dysregulation; IQR, interquartile range; KDM, Klemere-Doubal method; LTL, leukocyte telomere length; PhenoAge, Phenotypic Age; SMD, standardized mean difference; Z-LTL, Z-standardized leukocyte telomere length. KDM and PhenoAge residuals were derived by regressing each aging estimate on chronological age modeled with a natural spline with 3 degrees of freedom.

Overall ASM use and biological aging

Characteristics after propensity score matching

After matching, age, sex, race/ethnicity, smoking, and alcohol intake were balanced between ASM users and non-users (Table 2).

Table 2
Baseline characteristics and biological aging measures after propensity score matching

Variables	Non-ASM user (n = 14820)	ASM users (n = 4940)	P-value
Demographic variables			
Chronological age at baseline (years), median, [IQR]	59 [52,64]	59 [52,64]	1.00
Gender Male, n (%)	5834 (39.4%)	1944 (39.4%)	1.00
Race White, n (%)	14072 (95.0%)	4690 (94.9%)	0.97
Current drinking	12435 (83.9%)	4145 (83.9%)	1.00
Current smoking	1986 (13.4%)	662 (13.4%)	1.00
BA measures ^b, median, [IQR]			
KDM residual	-0.27 [-3.38, 3.13]	0.61 [-2.69, 4.17]	< 0.001
PhenoAge residual	-0.54 [-3.60, 2.88]	-0.01 [-3.15, 3.77]	< 0.001
HD (log units)	6.53 [5.86, 7.18]	6.69 [6.02,7.37]	< 0.001
Z-LTL	-0.016 [-0.660,0.635]	-0.041 [-0.701,0.594]	0.017
Biomarkers included in BA, algorithms, median, [IQR]			
FEV1 (L)	2.58 [2.16,3.11]	2.54 [2.11,3.08]	< 0.001
SBP (mmHg)	139 [126,153]	137 [125,151]	< 0.001
Waist circumference (cm)	89 [70,98]	91 [82,101]	< 0.001
Red cell distribution width (%)	13.4 [12.9,13.9]	13.4 [12.9,14.0]	0.001
Albumin (g/dL)	4.51[4.34,4.68]	4.50 [4.32,4.68]	0.040
Alkaline phosphatase (U/L)	81.2 [67.5,97.6]	84 [69.8,101.0]	< 0.001
Triglyceride (mg/dL)	131.0 [93.1,189.0]	144.0 [101.0,209.0]	< 0.001
Mean cell volume (fL)	91.2 [88.6,93.8]	91.3 [88.6,94.1]	0.043
Uric acid (mg/dL)	4.94 [4.12,5.93]	4.91 [4.03,5.93]	0.051
Abbreviations: ALP, alkaline phosphatase; ASM, antiseizure medication; BA, biological age; BUN, blood urea nitrogen; CRP, C-reactive protein; DBP, diastolic blood pressure; FEV1, forced expiratory volume in 1 second; HbA1c, glycated hemoglobin; HD-log, log-transformed homeostatic dysregulation; IQR, interquartile range; KDM, Klemmera-Doubal method; LTL, leukocyte telomere length; RBC, red blood cell count; RDW, red cell distribution width; SBP, systolic blood pressure; Z-LTL, Z-standardized leukocyte telomere length. P values are from Mann-Whitney U tests for continuous variables and appropriate tests for categorical variables.			

Variables	Non-ASM user (n = 14820)	ASM users (n = 4940)	P-value
Demographic variables			
Lymphocyte (%)	28.9 [24.2,33.8]	28.8 [23.8,33.7]	0.106
RBC (million cells/ μ L)	4.47 [4.21,4.74]	4.44 [4.17,4.72]	< 0.001
C-reactive protein (mg/dL)	0.14 [0.07,0.28]	0.18 [0.09,0.37]	< 0.001
DBP (mmHg)	81 [75.0,89]	82 [74.8,89]	0.306
HbA1c (%)	5.39 [5.18,5.64]	5.41 [5.17,5.66]	0.025
Total cholesterol (mg/dL)	220 [191,250]	219 [187,251]	0.043
Creatinine (μ mol/L)	68.9 [60.11,78.68]	68.1 [60.11,79.56]	0.645
Serum glucose (mmol/L)	4.95 [4.62,5.32]	4.96 [4.62,5.38]	0.050
Blood urea nitrogen (mg/dL)	14.8 [12.7,17.3]	14.7 [12.4,17.4]	0.023
Abbreviations: ALP, alkaline phosphatase; ASM, antiseizure medication; BA, biological age; BUN, blood urea nitrogen; CRP, C-reactive protein; DBP, diastolic blood pressure; FEV1, forced expiratory volume in 1 second; HbA1c, glycated hemoglobin; HD-log, log-transformed homeostatic dysregulation; IQR, interquartile range; KDM, Klemmera-Doubal method; LTL, leukocyte telomere length; RBC, red blood cell count; RDW, red cell distribution width; SBP, systolic blood pressure; Z-LTL, Z-standardized leukocyte telomere length. P values are from Mann-Whitney U tests for continuous variables and appropriate tests for categorical variables.			

ASM users had higher median KDM residual, PhenoAge residual, and HD-log values and lower median Z-LTL than matched non-users. They also had lower forced expiratory volume in 1 second (FEV1) and higher waist circumference and triglyceride concentrations. Differences were also observed for mean cell volume, albumin, and red cell distribution width (Table 2).

Corresponding characteristics before matching are shown in Supplementary Table S1.

Association between overall ASM use and biological aging indicators

In adjusted analyses after matching, ASM use was associated with higher HD-log ($\beta = 0.184$, 95% CI 0.152 to 0.216), KDM residual ($\beta = 0.818$ years, 95% CI 0.646 to 0.990), and PhenoAge residual ($\beta = 0.654$ years, 95% CI 0.482 to 0.826), and with lower Z-LTL ($\beta = -0.057$, 95% CI -0.090 to -0.024) (Supplementary Table S3). Estimates before matching were directionally similar (Additional file 2, Fig. S1).

Individual monotherapies compared with non-use

Compared with non-users, carbamazepine, gabapentin, pregabalin, and valproic acid were associated with higher HD-log values, whereas topiramate was associated with a lower value (Fig. 2; Table 3).

Table 3
Associations of individual ASM monotherapies with biological aging indicators compared with matched non-users

Drug Name	N	BA indicators	Estimate (95% CI)	P-value
Control	14820	HD-log	Reference	NA
		KDM residual	Reference	NA
		PhenoAge residual	Reference	NA
		Z-LTL	Reference	NA
Carbamazepine	1079	HD-log	0.161 (0.101, 0.221)	< 0.001
		KDM residual	0.642 (0.322, 0.963)	< 0.001
		PhenoAge residual	0.057 (-0.263, 0.377)	0.727
		Z-LTL	-0.020 (-0.082, 0.041)	0.517
Clonazepam	149	HD-log	0.140 (-0.013, 0.292)	0.073
		KDM residual	0.406 (-0.409, 1.222)	0.329
		PhenoAge residual	0.159 (-0.656, 0.973)	0.703
		Z-LTL	0.084 (-0.072, 0.240)	0.293
Gabapentin	1363	HD-log	0.211 (0.158, 0.263)	< 0.001
		KDM residual	1.134 (0.853, 1.415)	< 0.001
		PhenoAge residual	0.972 (0.692, 1.252)	< 0.001
		Z-LTL	-0.094 (-0.147, -0.040)	< 0.001
Lamotrigine	86	HD-log	-0.147 (-0.350, 0.056)	0.157
		KDM residual	-0.844 (-1.931, 0.242)	0.128
		PhenoAge residual	0.286 (-0.798, 1.371)	0.605
		Z-LTL	-0.121 (-0.329, 0.086)	0.253
Phenytoin	118	HD-log	0.177 (-0.002, 0.356)	0.052
		KDM residual	1.798 (0.843, 2.752)	< 0.001
Abbreviations: ASM, antiseizure medication; CI, confidence interval; HD-log, log-transformed homeostatic dysregulation; KDM, Klemera-Doubal method; PhenoAge, Phenotypic Age; Z-LTL, Z-standardized leukocyte telomere length. Estimates are unstandardized β coefficients from multivariable linear regression adjusted for age, sex, race/ethnicity, Townsend Deprivation Index, epilepsy status, smoking status, and alcohol intake. Drug-specific analyses were exploratory and were not adjusted for multiple comparisons.				

Drug Name	N	BA indicators	Estimate (95% CI)	P-value
Pregabalin	450	PhenoAge residual	1.872 (0.919, 2.825)	< 0.001
		Z-LTL	-0.049 (-0.232, 0.134)	0.599
		HD-log	0.334 (0.245, 0.423)	< 0.001
		KDM residual	1.391 (0.916, 1.865)	< 0.001
		PhenoAge residual	0.873 (0.399, 1.346)	< 0.001
		Z-LTL	-0.128 (-0.219, -0.037)	0.006
Topiramate	76	HD-log	-0.276 (-0.489, -0.062)	0.011
		KDM residual	-0.927 (-2.068, 0.214)	0.111
		PhenoAge residual	0.312 (-0.827, 1.451)	0.592
		Z-LTL	-0.214 (-0.432, 0.004)	0.054
Valproic Acid	348	HD-log	0.213 (0.107, 0.318)	< 0.001
		KDM residual	0.713 (0.149, 1.277)	0.013
		PhenoAge residual	0.812 (0.249, 1.374)	0.005
		Z-LTL	0.008 (-0.100, 0.116)	0.886
Abbreviations: ASM, antiseizure medication; CI, confidence interval; HD-log, log-transformed homeostatic dysregulation; KDM, Klemere-Doubal method; PhenoAge, Phenotypic Age; Z-LTL, Z-standardized leukocyte telomere length. Estimates are unstandardized β coefficients from multivariable linear regression adjusted for age, sex, race/ethnicity, Townsend Deprivation Index, epilepsy status, smoking status, and alcohol intake. Drug-specific analyses were exploratory and were not adjusted for multiple comparisons.				

Carbamazepine, gabapentin, phenytoin, pregabalin, and valproic acid were associated with higher KDM residuals. Lamotrigine and topiramate were not significantly associated with KDM residual in this comparison (Fig. 2; Table 3).

Gabapentin, phenytoin, pregabalin, and valproic acid were associated with higher PhenoAge residuals; the other agents were not significantly associated with this indicator (Fig. 2; Table 3).

Most associations with Z-LTL were not statistically significant; gabapentin and pregabalin were associated with lower Z-LTL (Fig. 2; Table 3).

Drug-specific estimates before propensity score matching were directionally similar (Additional file 2, Fig. S2).

One-versus-rest comparisons among monotherapy users

Within the ASM monotherapy cohort, lamotrigine and topiramate were associated with lower HD-log values, whereas pregabalin was associated with a higher value. Lamotrigine and topiramate were associated with lower KDM residuals, while phenytoin and pregabalin were associated with higher residuals. Carbamazepine was associated with a lower PhenoAge residual, whereas gabapentin and phenytoin were associated with higher residuals. No individual ASM was significantly associated with Z-LTL in the one-versus-rest analyses (Fig. 3; Supplementary Table S4). Descriptive mean values are provided in Supplementary Table S5.

Subgroup analyses

Adjusted associations with HD-log, KDM residual, and PhenoAge residual were positive in most prespecified subgroups (Fig. 4; Supplementary Tables S6-S9). Point estimates varied across strata, but these differences should be interpreted cautiously because no formal interaction tests were performed and several subgroups were small. Associations with Z-LTL were less consistent, particularly among non-White participants, smokers, non-drinkers, and participants with epilepsy.

1. (a) Heatmap of partial Spearman rank correlations between clinical biomarkers, ASM use, and biological aging indicators, adjusted for age, sex, smoking, and alcohol intake. Asterisks indicate statistical significance (* $P < 0.05$; ** $P < 0.001$).
2. (b) Exploratory mediation models for selected biomarkers. ACME (average causal mediation effect) denotes the estimated indirect component, ADE (average direct effect) the estimated direct component, and proportion mediated the estimated percentage of the total association statistically accounted for by the biomarker. These estimates should not be interpreted causally because exposure, biomarkers, and outcomes were assessed around baseline. Abbreviations: FEV1, forced expiratory volume in 1 second; TG, triglycerides; RDW, red cell distribution width; LTL, leukocyte telomere length. Biomarkers included in the aging algorithms are listed in Supplementary Table S2.

Exploratory biomarker and mediation analyses

Several clinical biomarkers were correlated with ASM use and with one or more biological aging indicators (Fig. 5a). Exploratory mediation models suggested that metabolic, inflammatory, hematologic, and respiratory markers statistically accounted for part of the observed associations (Fig. 5b).

For HD-log, the estimated proportions accounted for by triglycerides, waist circumference, C-reactive protein, and alkaline phosphatase were 50.1%, 39.1%, 29.2%, and 19.0%, respectively (Fig. 5b).

For KDM residual, FEV1 and waist circumference accounted for estimated proportions of 52.9% and 49.5%, respectively (Fig. 5b).

For PhenoAge residual, the corresponding estimates were 59.6% for FEV1, 51.2% for C-reactive protein, 48.6% for waist circumference, and 31.6% for red cell distribution width (Fig. 5b).

For LTL, waist circumference and red cell distribution width accounted for smaller estimated proportions of 10.8% and 10.3%, respectively (Fig. 5b).

Results were directionally consistent when the original biological aging algorithms were used (Supplementary Table S11; Additional file 2, Fig. S3). After participants with epilepsy were excluded, ASM use remained associated with higher HD-log, KDM residual, and PhenoAge residual and with lower Z-LTL (Supplementary Table S12; Additional file 2, Fig. S3).

Discussion

In this large cross-sectional analysis of UK Biobank participants, ASM use was associated with less favorable values across four complementary biological aging indicators. The overall estimates were similar before and after propensity score matching and remained directionally consistent after exclusion of participants with epilepsy. Drug-specific associations were heterogeneous, and the one-versus-rest analyses did not support a uniform class effect.

The observed differences were modest at the individual level but consistent across several measures of physiological dysregulation. These measures include clinical biomarkers that can be directly influenced by medication, comorbidity, and treatment indication; they should therefore be interpreted as aging-related profiles rather than proof that ASMs accelerate the underlying biological aging process. Residual confounding remains plausible despite matching and multivariable adjustment.

Compared with non-users, gabapentin and pregabalin were associated with less favorable values for several indicators, and phenytoin and valproic acid were associated with higher values for selected composite measures. Weight gain and edema are recognized during gabapentinoid treatment [14, 15], and metabolic and inflammatory pathways are relevant to age-related physiological dysregulation [19]. Experimental studies have reported mitochondrial, autophagic, or oxidative effects of valproate and phenytoin, whereas findings for gabapentin vary by experimental model [20, 21, 22, 23, 24]. However, these mechanisms cannot be inferred from the present data, and differences in clinical indication and disease severity may explain part of the drug-specific pattern.

Topiramate and lamotrigine were associated with lower values for selected indicators in the one-versus-rest analyses, but these findings should not be interpreted as protective effects. Topiramate inhibits carbonic anhydrase and is associated with weight loss and improved metabolic measures in some populations [25, 26, 27, 28]. Lamotrigine is generally considered weight neutral and has shown neuroprotective or anti-inflammatory effects in experimental settings [29, 30, 31, 32, 33]. Nevertheless, the lamotrigine and topiramate groups were small, multiple drug-specific comparisons were performed, and confounding by prescribing preference is likely.

The exploratory mediation analyses highlighted triglycerides, waist circumference, C-reactive protein, red cell distribution width, and FEV1 as possible statistical pathways. These findings are consistent with a multisystem interpretation but do not establish temporal or causal mediation because exposure,

biomarkers, and aging indicators were measured around the same period. Longitudinal studies with repeated prescriptions, cumulative dose, and repeated biological aging assessments are needed before clinical treatment recommendations can be made.

Strengths and limitations

Strengths include the large sample, standardized UK Biobank measurements, use of four complementary aging indicators, propensity score matching, and several sensitivity analyses. The study also has important limitations. First, its cross-sectional design precludes determination of temporality and causality. Second, confounding by indication, disease severity, comorbidity, and co-medication may persist. Third, prescription and self-report data may not fully capture adherence, cumulative dose, or changes in treatment. Fourth, complete-case selection may introduce bias, and UK Biobank participants are not fully representative of the general population. Fifth, some monotherapy groups were small, and exploratory drug-specific, subgroup, and mediation analyses were not adjusted for multiple testing. Finally, composite aging measures include biomarkers that may reflect direct pharmacological effects rather than a generalized aging process.

Conclusions

ASM use was associated with less favorable profiles across multiple biological aging indicators in the UK Biobank. Associations varied among individual agents, but causal and treatment-ranking interpretations are not warranted. Studies using longitudinal exposure histories, repeated aging measurements, active comparators, and independent replication are needed to determine whether these associations reflect medication effects, treatment indications, or both.

List of abbreviations

ASM: antiseizure medication; BA: biological age; BNF: British National Formulary; CI: confidence interval; CRP: C-reactive protein; DBP: diastolic blood pressure; FEV1: forced expiratory volume in 1 second; HD: homeostatic dysregulation; IQR: interquartile range; KDM: Klemmer-Doubal method; LTL: leukocyte telomere length; PhenoAge: Phenotypic Age; PSM: propensity score matching; RBC: red blood cell count; RDW: red cell distribution width; SBP: systolic blood pressure; UKB: UK Biobank; Z-LTL: Z-standardized leukocyte telomere length.

Declarations

Ethics approval and consent to participate

The UK Biobank was conducted in accordance with the UK Biobank Ethics and Governance Framework and received generic ethical approval from the North West Haydock Research Ethics Committee (REC reference 11/NW/0382). All participants provided written informed consent. The present analysis was conducted under UK Biobank application 217802.

Consent for publication

Not applicable. The manuscript contains no identifiable individual participant data.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

JX, SD, and XW conceived and designed the study. JX and SD performed data curation, data preprocessing, and statistical analyses; developed and validated the analytical pipeline; and prepared the main results and figures. ZZ contributed to data verification, documentation, and manuscript preparation. YiL, YuL, YX, JL, YZ, YC, ML, AG, LP, and YLuo assisted with data management, quality control, literature review, and figure and table preparation. JX drafted the manuscript. XW supervised the study. All authors critically reviewed and revised the manuscript, approved the final version, and agreed to be accountable for the work.

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Availability of data and materials

The data that support the findings of this study are available from the UK Biobank. Restrictions apply to the availability of these data, which were used under approved access for the current study and are therefore not publicly available. Data are available to eligible researchers through the UK Biobank data access and application process. This study was conducted under UK Biobank application 217802. Analytic code is available from the corresponding author on reasonable request, subject to UK Biobank data-use requirements.

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Figures

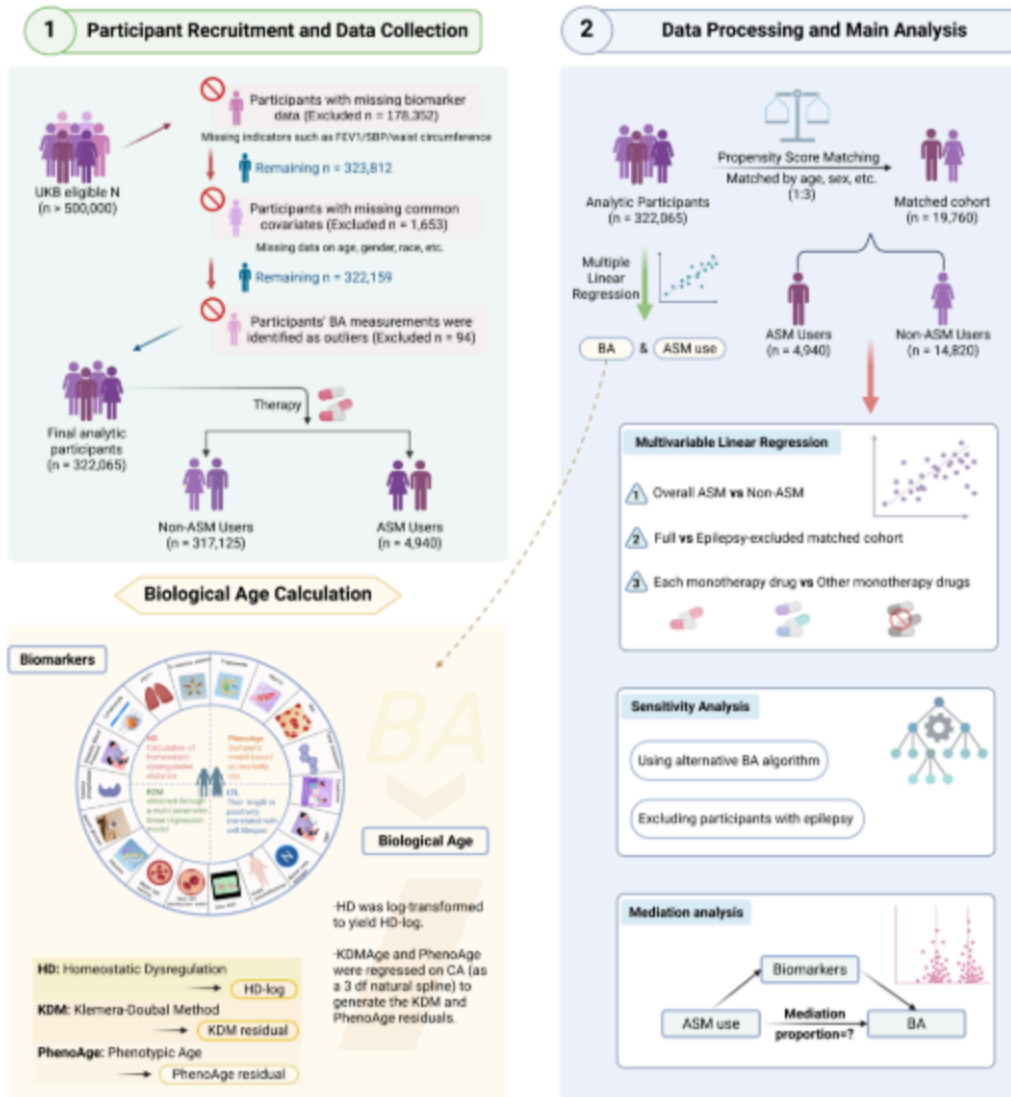


Figure 1

Study design and analytical workflow.

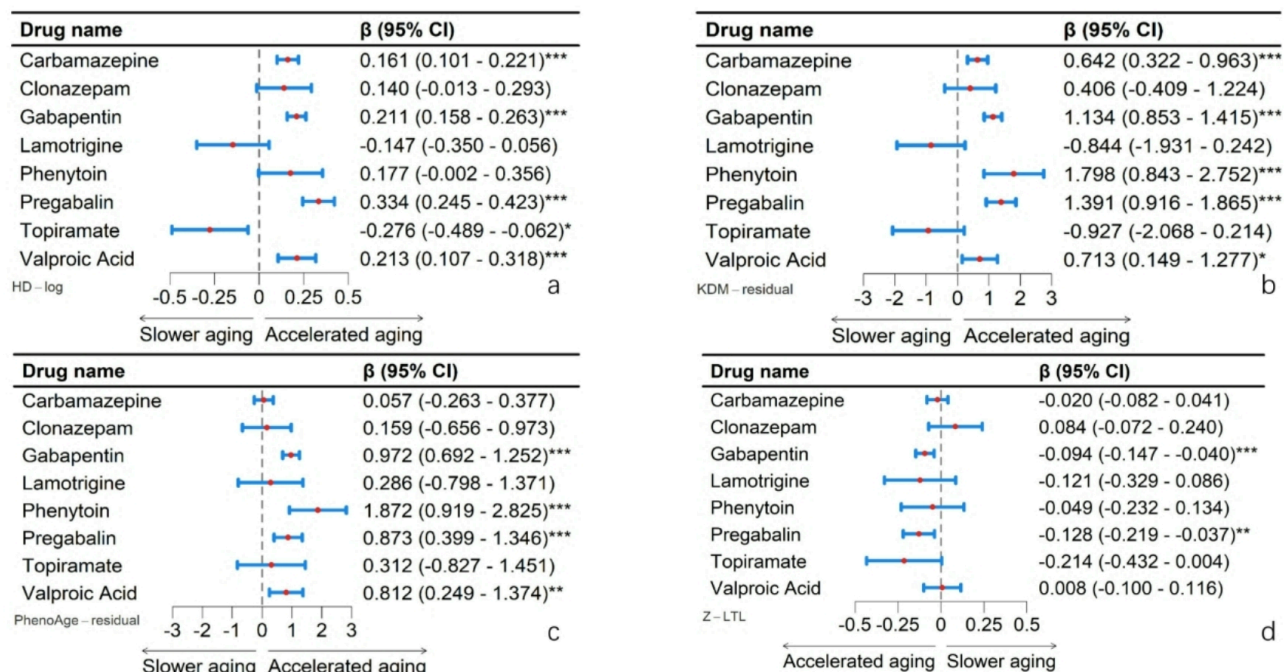


Figure 2

Associations of individual ASM monotherapies with biological aging indicators compared with non-users. The reference group comprised matched participants not using an ASM. Effect sizes are unstandardized regression coefficients (β) with 95% CIs. Positive coefficients indicate higher HD-log, KDM residual, or PhenoAge residual; negative coefficients for Z-LTL indicate shorter telomeres. Models were adjusted for age, sex, race/ethnicity, Townsend Deprivation Index, epilepsy status, smoking status, and alcohol intake.

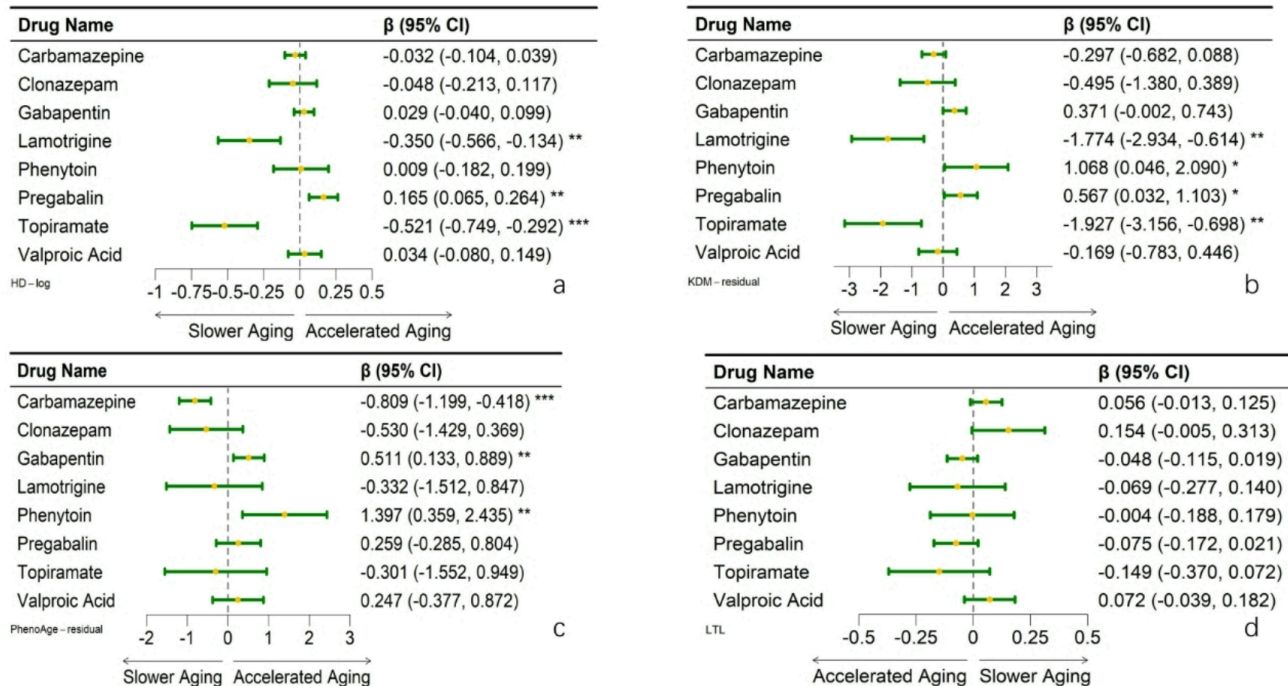


Figure 3

Associations of individual ASM monotherapies with biological aging indicators compared with other monotherapy users. Each estimate compares one agent with all other ASM monotherapies. Effect sizes are unstandardized regression coefficients (β) with 95% CIs. Models were adjusted for age, sex, race/ethnicity, Townsend Deprivation Index, epilepsy status, smoking status, and alcohol intake.



Figure 4

Subgroup associations between ASM use and biological aging indicators. Forest plots show adjusted β coefficients and 95% CIs within strata of age, sex, race/ethnicity, smoking, alcohol intake, and epilepsy status. Models included the primary covariates except for the stratifying variable. Subgroup comparisons are descriptive; formal interaction tests were not performed.

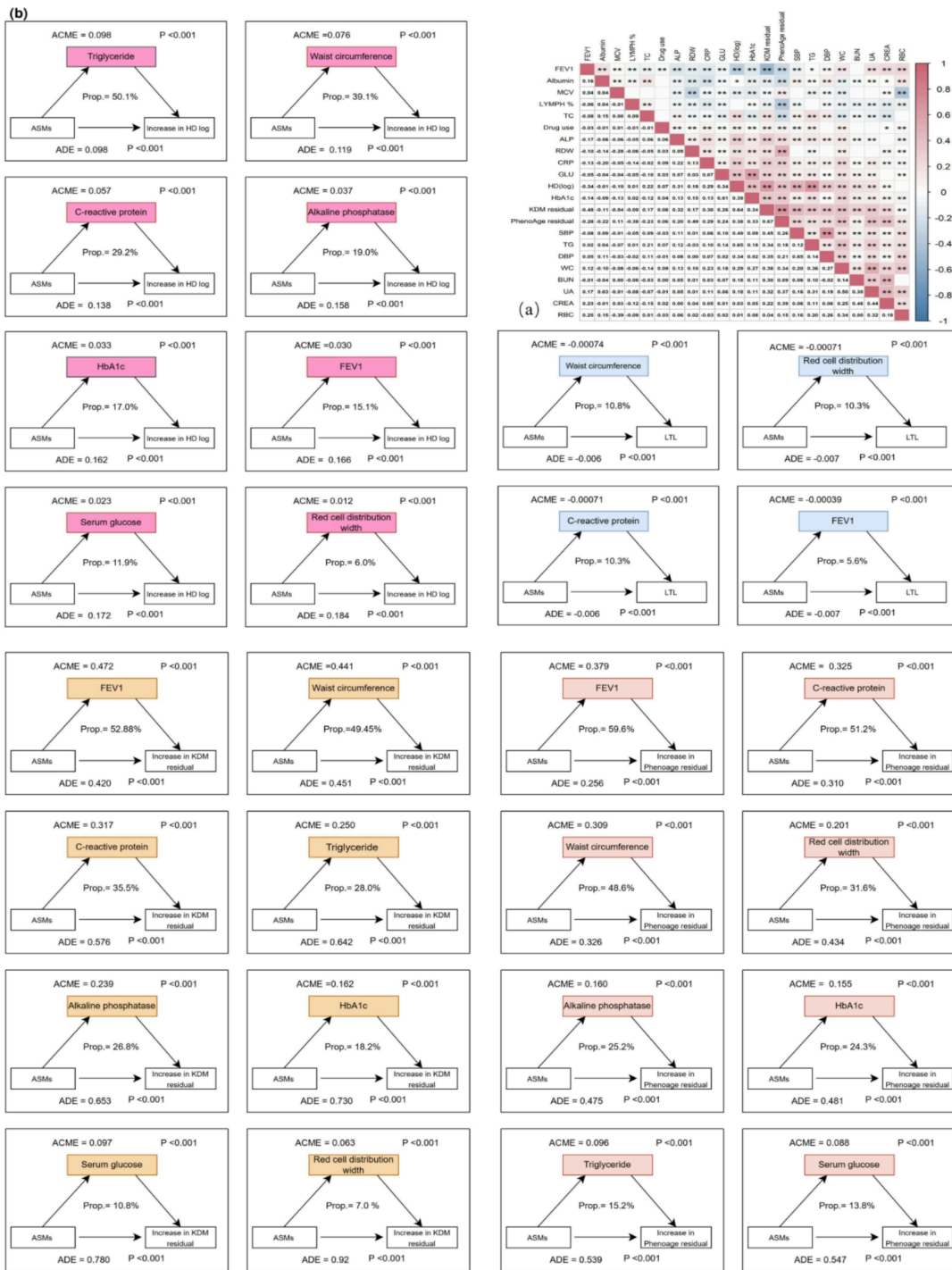


Figure 5

Correlations and exploratory mediation analyses of clinical biomarkers, ASM use, and biological aging indicators.

(a) Heatmap of partial Spearman rank correlations between clinical biomarkers, ASM use, and biological aging indicators, adjusted for age, sex, smoking, and alcohol intake. Asterisks indicate statistical

significance (*P < 0.05; **P < 0.001).

(b) Exploratory mediation models for selected biomarkers. ACME (average causal mediation effect) denotes the estimated indirect component, ADE (average direct effect) the estimated direct component, and proportion mediated the estimated percentage of the total association statistically accounted for by the biomarker. These estimates should not be interpreted causally because exposure, biomarkers, and outcomes were assessed around baseline. Abbreviations: FEV1, forced expiratory volume in 1 second; TG, triglycerides; RDW, red cell distribution width; LTL, leukocyte telomere length. Biomarkers included in the aging algorithms are listed in Supplementary Table S2.

Supplementary Files

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