

The exposome of brain aging across 34 countries

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The physical and social exposome affects human aging, and brain clocks may track its effects. However, most studies neglect multidomain exposures (physical, social and political) across diverse settings globally and their associations with brain aging. In this study, we characterized the associations between 73 country-level physical and social exposomal factors and multimodal brain age in 18,701 participants from 34 countries (healthy individuals and those with Alzheimer's disease, frontotemporal lobar degeneration or mild cognitive impairment). Exposome effects were assessed using generalized additive models and meta-analytic frameworks. Aggregated exposome models explained up to 15.5-fold more variance than individual exposures (delta Akaike information criterion (Δ AIC): 2,034–3,127). Physical exposome was primarily associated with accelerated structural brain aging (limbic, subcortical and cerebellar regions), whereas social exposome was more strongly associated with functional brain aging (frontotemporal and limbic networks). Exposome burden accounted for 3.3–9.1-fold higher risk of accelerated aging, exceeding effects of clinical diagnoses. Findings were out-of-sample validated in cross-sectional and longitudinal designs, remained consistent across clinical subgroups and persisted after adjustment for demographics, age correction bias, cognition, scanner type and data quality. The exposome accelerates brain aging in health and disease, underscoring the need to address physical, social and political inequities.

Understanding how physical and social environmental factors (for example, pollution, climate change, poverty and political instability) interact to shape health is one of the most pressing and unanswered questions in biomedicine^{1,2}. The exposome encapsulates the cumulative, synergistic effects of diverse environmental exposures that influence the healthspan^{2–4}. A central tenet of exposomics is the nonlinear, system-wide effects on biological functions^{1,2}. These emergent external effects may vary across different geographical contexts, regions and countries. Understanding this framework is particularly salient given that genetic factors in global settings explain only a fraction of variance in healthy aging and neurocognitive disorders^{5,6}. Thus, delayed or accelerated aging patterns may reflect the cumulative biological effects of the exposome.

Physical and social exposures have been linked to accelerated aging across biological and behavioral domains^{4,7}. Omics research has linked exposomal factors to accelerated aging via methylation, organ-based and brain-specific clocks^{2,5}. Brain clocks estimate an

individual's brain age from neuroimaging data and compare it to their chronological age, providing a framework to assess individual trajectories⁸. The brain age gap (BAG) represents the difference between predicted and chronological brain age, with positive values indicating accelerated aging and negative values indicating delayed aging⁹. The BAG is a sensitive indicator of brain aging and dementia, shaped by disease mechanisms and environmental exposures^{5,9–12}. Some environmental risk factors have been independently associated with greater BAG values in healthy individuals and those with neurocognitive disorders⁸, including Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) and mild cognitive impairment (MCI).

Despite these advances, the combined effects of the exposome on brain aging remain largely unexplored^{1,2,5,6,12,13}. Most studies isolate a few exposomal factors or assume additive effects^{5,9,14} and linear models¹², ignoring the complexity of aggregate-level interactions^{2,15}. The synergistic interplay among diverse physical and social exposomes,

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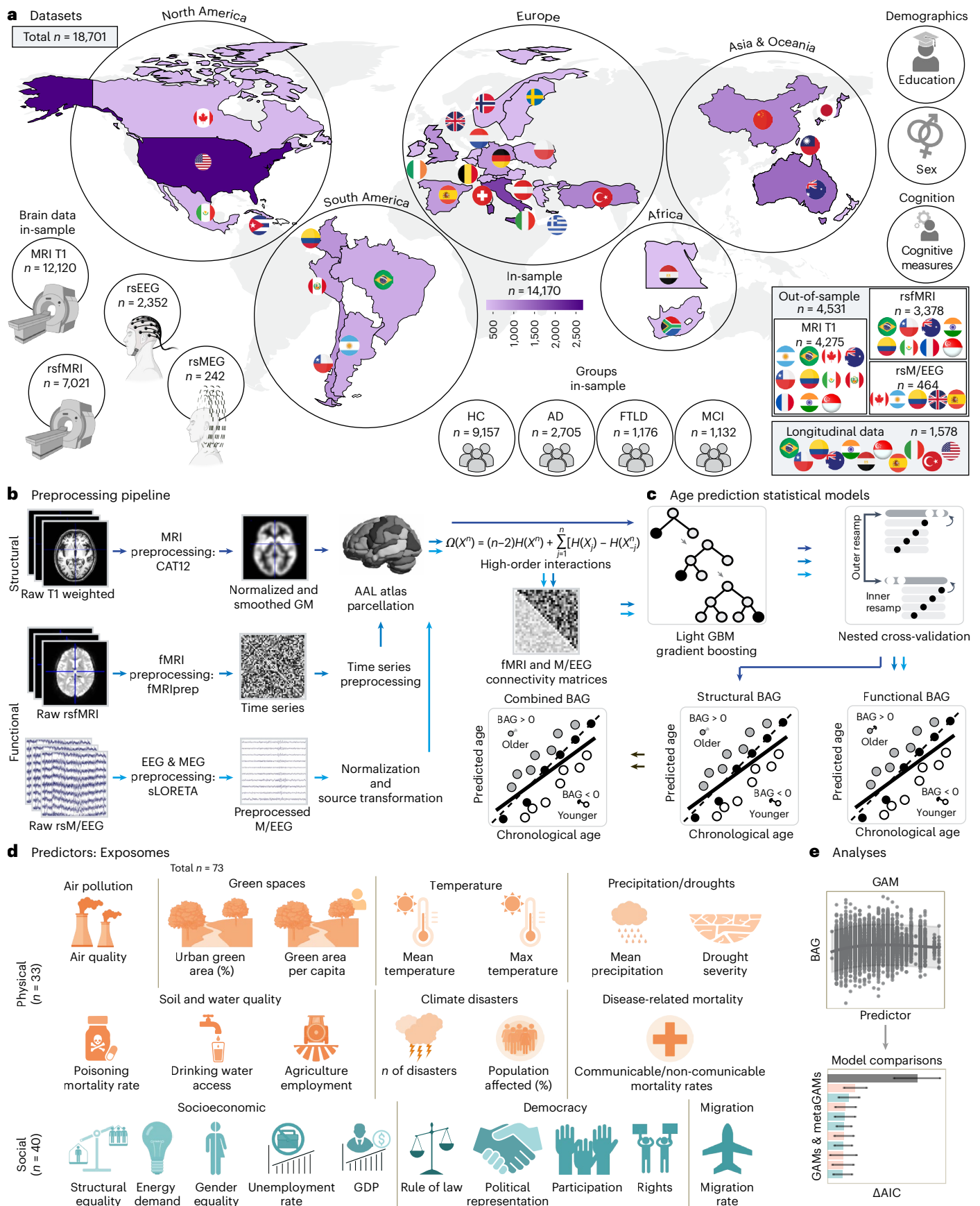


Fig. 1 | Analytical framework. **a**, Datasets. **b**, Preprocessing pipeline. **c**, BAG estimation. **d**, Exposomes. **e**, Statistics. Illustrations in **a** and **d** created in BioRender; Migeot, J. <https://biorender.com/b92f8ma> (2026). Maps in **a** were

generated in GeoPandas using a shapefile from Natural Earth (https://www.naturalearthdata.com/ne_110m_admin_0_countries). Brain scans in **b** of a random participant were generated using MRIcron. HC, healthy controls.

such as air pollution^{12,16}, precipitation¹⁰, temperature¹⁷, soil and water quality¹⁸, green spaces^{12,19}, socioeconomic inequality^{4,20,21}, gender disparities²² and sociopolitical context^{5,7}, has rarely been combined in brain aging models²³. Given that exposomal factors vary across geographical contexts, understanding these effects would require research across different populations to capture environmental interactions across countries and health-to-disease trajectories⁴. However, most studies have focused on single-country cohorts^{6,12}, with the Global South starkly underrepresented^{11,24}, thus limiting generalizability. Furthermore, the effects of the exposome across neurocognitive disorders remain poorly characterized¹⁴, and it is unknown whether exposome-related aging in healthy individuals mirrors, amplifies or diverges from patterns in disease. This is in addition to most brain age models relying on a single imaging modality and overlooking how exposures may differentially affect structural versus functional aging metrics^{1,11}. Collectively, these gaps hinder efforts to identify the cumulative environmental hallmarks of brain health, aging and dementia.

We address these gaps by applying a geospatial exposome framework, leveraging 73 aggregated physical and social factors. We examined their individual and combined associations with multimodal (functional and structural magnetic resonance imaging (fMRI) and magnetoencephalography and electroencephalography (M/EEG)) brain aging clocks in 18,701 participants across 34 countries spanning healthy aging and neurocognitive disorders (MCI, AD and FTLD). Generalized additive models (GAMs) and meta-machine learning captured nonlinear associations and cumulative effects on BAG estimates derived from structural, functional (high-order functional interactions^{1,8,15}) and combined modalities. We further quantified the relative contributions of exposome burden and health conditions (healthy aging and neurocognitive disorders) on accelerated brain aging. We hypothesized that (1) higher exposome burden would predict accelerated brain aging with distinct effects across imaging modalities and health conditions; (2) combined physical and social exposome would exert a greater impact than single exposomal factors alone; and (3) individuals with the highest exposome burden would show accelerated aging independent from neurocognitive disorders.

Results

Populations studied and analysis approach

The sample comprised participants from Africa, Europe, Latin America, North America, Asia and Oceania (Fig. 1a and Table 1). Brain gray matter volume and high-order functional interactions^{8,15,25,26} (Fig. 1b) were used as input for a LightGBM machine learning algorithm²⁷ to predict chronological age^{8,26}. To avoid overadjustment²⁸ and preserve exposure variance²⁹, no age bias adjustment was applied (Fig. 2a, but we also compared the results with age bias correction). Exposomal factors ($n = 73$) were assessed at the country level (Supplementary Tables 1 and 2) and matched to the participant's country and year of brain data acquisition^{7,8,21} (range: 2000–2025). Physical exposome ($n = 33$; measures of air pollution, green spaces, temperature, precipitation/droughts, soil and water quality, climate disasters and disease-related mortality) and social exposome ($n = 40$; measures of structural socioeconomic equality (Gini, human capital, human development (Human Development Index (HDI)), inequality-adjusted HDI and multidimensional poverty), gross domestic product (GDP), energy demand, gender equality, unemployment, democracy (political representation, rule of law, participation and rights)) and inbound migration rate) measures were included. GAMs tested nonlinear individual exposomal–BAG associations (Fig. 1d), and joint effects were assessed using meta-analytic GAMs (metaGAMs)²⁷. Model performance was compared using Δ AIC values (values >10 were considered meaningful³⁰) (Fig. 1e). Analyses were rerun within social and physical exposomes and across neurocognitive disorders. Multivariable logistic regression estimated odds ratios for accelerated aging across exposome and clinical predictors; robustness was evaluated through multiple sensitivity analyses.

BAG across imaging modalities

Brain age models for the full in-sample dataset ($n = 14,170$) built with structural (T1 MRI gray matter volume) and functional (rsfMRI and rsM/EEG connectivity) data accurately predicted chronological age (structural: $R^2 = 0.77$, $F^2 = 3.49$, mean deviation error (MDE) = 0.011; functional: $R^2 = 0.50$, $F^2 = 1.03$, MDE = -0.02 ; all $P < 0.001$; Fig. 2a). Age bias correction inflated BAG model fit (structural: $R^2 = 0.85$, $F^2 = 5.91$; functional: $R^2 = 0.83$, $F^2 = 4.97$; all $P < 0.001$; Fig. 2a), which may artificially boost associations due to collinearity²⁹. We used the models without age bias correction but compared their effects and associations with the exposome to those obtained from the age-bias-corrected models.

Structural BAGs were primarily associated with limbic, subcortical, temporoparietal and cerebellar brain volume. Functional BAGs were linked to frontotemporal and limbic networks, with key nodes in the insula, hippocampus, superior frontal gyrus, cingulum, Rolandic operculum, postcentral cortex and temporoparietal hubs. A third, combined BAG (averaging functional and structural data, $n = 7,198$) also yielded robust performance ($R^2 = 0.77$, $F^2 = 3.44$, MDE = 0.124, $P < 0.001$). These three BAGs were used in subsequent regression analyses with exposome variables.

Total exposome and accelerated aging

Models aggregating all 73 exposomal factors substantially outperformed individual models in predicting brain aging (Fig. 2b, left panel, and Supplementary Table 3). Structural (Δ AIC = 2,034.1), functional (Δ AIC = 2,241.9) and combined (Δ AIC = 3,127.4) BAGs showed 8.9-fold, 9.8-fold and 13.7-fold Δ AIC increases, respectively, compared to the best individual exposomal factor (Δ AIC = 228.91).

Although smaller than those of the combined exposomal factors, individual exposomal factors showed consistent associations with brain aging across modalities (top 10 factors, false discovery rate (FDR) $P < 0.001$ and Δ AIC > 10 ; Supplementary Table 3). Common top 10 predictors across modalities included both physical and social exposomes, such as extreme mean precipitation (precipitation/droughts), lower basic welfare (democracy: rights) and lower human capital index (socioeconomic). Each individual exposomal factor showed modality-specific associations. Adverse physical exposome was primarily associated with accelerated brain structural aging, with reduced access to green spaces and higher PM_{2.5} (air pollution, measured as particulate matter with a diameter of $\leq$ or $> 2.5 \mu\text{m}$) among the strongest predictors (Extended Data Fig. 1). Adverse social exposome was mainly associated with accelerated brain functional aging, particularly lower participation, rule of law, representation, rights (democracy) and socioeconomic indicators (Extended Data Fig. 2). Both physical and social exposomes were associated with accelerated brain aging when modalities were combined, with increased non-methane volatile organic air pollutants, decreased economic equality and civil society (participation) emerging as specific predictors (Extended Data Fig. 3).

Physical exposome

A combination of 33 physical exposomal factors outperformed individual models (Fig. 2b, center panel, and Supplementary Table 4). Structural (Δ AIC = 2,091.4), functional (Δ AIC = 2,408.8) and combined (Δ AIC = 2,951.8) BAGs showed 11.0-fold, 12.7-fold and 15.5-fold Δ AIC increases, respectively, relative to the best individual factor model (Δ AIC = 190.1). Physical exposomal factors exhibited consistent associations with all BAG modalities (top 10 exposomal factors, FDR $P < 0.001$ and Δ AIC > 10 ; Supplementary Table 4). Shared top predictors across modalities were limited green space access, extreme mean precipitation, elevated non-methane volatile organic compounds and PM_{2.5} emissions (air pollution). Elevated maximum temperature also correlated with accelerated structural aging. Increased poisoning national-level mortality rates and access to drinking water (soil and water quality) and ammonia exposure (air pollution) emerged as specific predictors of accelerated functional and combined modalities aging.

Table 1 | Demographic and cognitive information for full datasets

	Healthy controls	AD	FTLD	MCI	Statistics	Post hoc comparison
Full dataset						
All participants (<i>n</i> =18,701)	<i>n</i> =12,850	<i>n</i> =3,073	<i>n</i> =1,246	<i>n</i> =1,530	-	-
MRI T1 dataset						
All participants (<i>n</i> =16,395)	<i>n</i> =11,128	<i>n</i> =2,804	<i>n</i> =1,210	<i>n</i> =1,253	-	-
Sex (female:male)	6,617:4,509	1,745:1,058	556:652	626:627	$\chi^2=134.94$; $P<2\times 10^{-16*}$	Controls-AD $P=0.007*$; Controls-FTLD $P<2\times 10^{-16*}$; Controls-MCI $P<1.1\times 10^{-10*}$
Age (years) (range: 18–100)	47.06 (21.52)	72.94 (9.05)	65.41 (8.26)	72.14 (8.1)	$F=2,069$; $P<2\times 10^{-16*}$; $\eta p^2=0.27$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P<2\times 10^{-16*}$; Controls-MCI $P<2\times 10^{-16*}$
Years of education (range: 0–32)	13.94 (4.01)	11.25 (4.98)	13.42 (4.4)	11.54 (5.33)	$F=324.3$; $P<2\times 10^{-16*}$; $\eta p^2=0.06$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P=6\times 10^{-03*}$; Controls-MCI $P<2\times 10^{-16*}$
General cognitive function (0–100)	93.7 (7.65)	72.53 (19.82)	70.14 (19.99)	82.58 (11.07)	$F=1,470$; $P<2\times 10^{-16*}$; $\eta p^2=0.33$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P<2\times 10^{-16*}$; Controls-MCI $P<2\times 10^{-16*}$
rsfMRI dataset						
All participants (<i>n</i> =10,399)	<i>n</i> =7,931	<i>n</i> =994	<i>n</i> =780	<i>n</i> =694	-	-
Sex (female:male)	4,720:3,211	673:321	371:409	349:345	$\chi^2=95.61$; $P<2\times 10^{-16*}$	Controls-AD $P=7.6\times 10^{-07*}$; Controls-FTLD $P=1.3\times 10^{-10*}$; Controls-MCI $P=2.6\times 10^{-05*}$
Age (years) (range: 18–100)	43.37 (21.6)	73.57 (10.71)	65.1 (8.27)	71.81 (8.18)	$F=1,247$; $P<2\times 10^{-16*}$; $\eta p^2=0.26$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P<2\times 10^{-16*}$; Controls-MCI $P<2\times 10^{-16*}$
Years of education (range: 0–28)	14.85 (3.27)	11.91 (5.5)	14.05 (4.19)	12.6 (5.62)	$F=204.9$; $P<2\times 10^{-16*}$; $\eta p^2=0.07$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P<1\times 10^{-07*}$; Controls-MCI $P<2\times 10^{-16*}$
General cognitive function (0–100)	94.59 (6.1)	67.24 (18.23)	71.47 (19.57)	78.93 (11.32)	$F=1381$; $P<2\times 10^{-16*}$; $\eta p^2=0.47$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P<2\times 10^{-16*}$; Controls-MCI $P<2\times 10^{-16*}$
rsM/EEG dataset						
All participants (<i>n</i> =3,058)	<i>n</i> =2,287	<i>n</i> =408	<i>n</i> =84	<i>n</i> =279	-	-
Sex (female:male)	1,222:1,025	245:148	38:45	165:100	$\chi^2=16.50$; $P=0.0008*$	Controls-AD $P=0.004*$; Controls-FTLD $P=0.15$; Controls-MCI $P=0.01*$
Age (years) (range: 17–94)	47.55 (20.98)	73.73 (8.46)	67.61 (8.64)	71.43 (8.16)	$F=338.9$; $P<2\times 10^{-16*}$; $\eta p^2=0.25$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P<2\times 10^{-16*}$; Controls-MCI $P<2\times 10^{-16*}$
Years of education (range: 0–28)	14.03 (3.96)	10.20 (5.13)	13.52 (4.98)	10.37 (5.67)	$F=124.3$; $P<2\times 10^{-16*}$; $\eta p^2=0.12$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P=0.80$; Controls-MCI $P<2\times 10^{-16*}$
General cognitive function (0–100)	96.05 (4.60)	67.63 (15.20)	72.87 (17.2)	86.46 (8.81)	$F=926$; $P<2\times 10^{-16*}$; $\eta p^2=0.61$	Controls-AD $P<2\times 10^{-16*}$; Controls-FTLD $P<2\times 10^{-16*}$; Controls-MCI $P<2\times 10^{-16*}$

Results are presented as mean (s.d.), except for country of origin and sex. The asterisk (*) indicates significant differences with an α level of $P<0.05$. Continuous variables were assessed through ANOVAs and two-sided Tukey post hoc pairwise comparisons. Sex was analyzed via Pearson's χ^2 test. Effects sizes were calculated using ηp^2 . Our age range (17–100 years) is similar to or larger than other brain age studies. Years of education reflect total formal schooling across all levels (from primary to university); lower values may partly reflect younger participants who had not yet completed their education as well as cross-country disparities in educational attainment. Although mean cognitive scores differ significantly between healthy controls and MCI groups, overlap in cognitive scores reflects global variability in data acquisition and the influence of educational differences⁶⁰. Differences increased with education-adjusted scores (Study design and participants section).

Social exposome

A combination of 40 social exposomal factors outperformed the individual factor models (Fig. 2b, right panel, and Supplementary Table 5), with Δ AIC increases of 2.0-fold, 9.7-fold and 13.7-fold for structural (Δ AIC = 455.2), functional (Δ AIC = 2,220.7) and combined (Δ AIC = 3,129.9) BAGs, respectively, compared to the best individual model (Δ AIC = 228.99). Individual social exposomal factors still predicted brain aging across modalities (top 10 factors, FDR $P<0.001$ and Δ AIC > 10; Supplementary Table 5). Lower basic welfare (democracy: rights), civil society (democracy: participation), lower human capital index and energy demand (socioeconomic) were consistently among the top 10 predictors across modalities. Increased inbound migration,

decreased GDP and lower gender equality (socioeconomic) specifically predicted accelerated structural aging. Reduced predictability enforcement, lower local representation and access to justice (democracy) specifically predicted accelerated functional aging. Lower basic welfare, social group equality (democracy: rights) and reduced economic equality (socioeconomic) were linked to accelerated aging for combined modalities.

Exposome and accelerated aging across neurocognitive conditions

Across all BAG modalities, models replicated the expected gradient of accelerated brain aging⁸ (healthy controls < MCI < AD < FTLD;

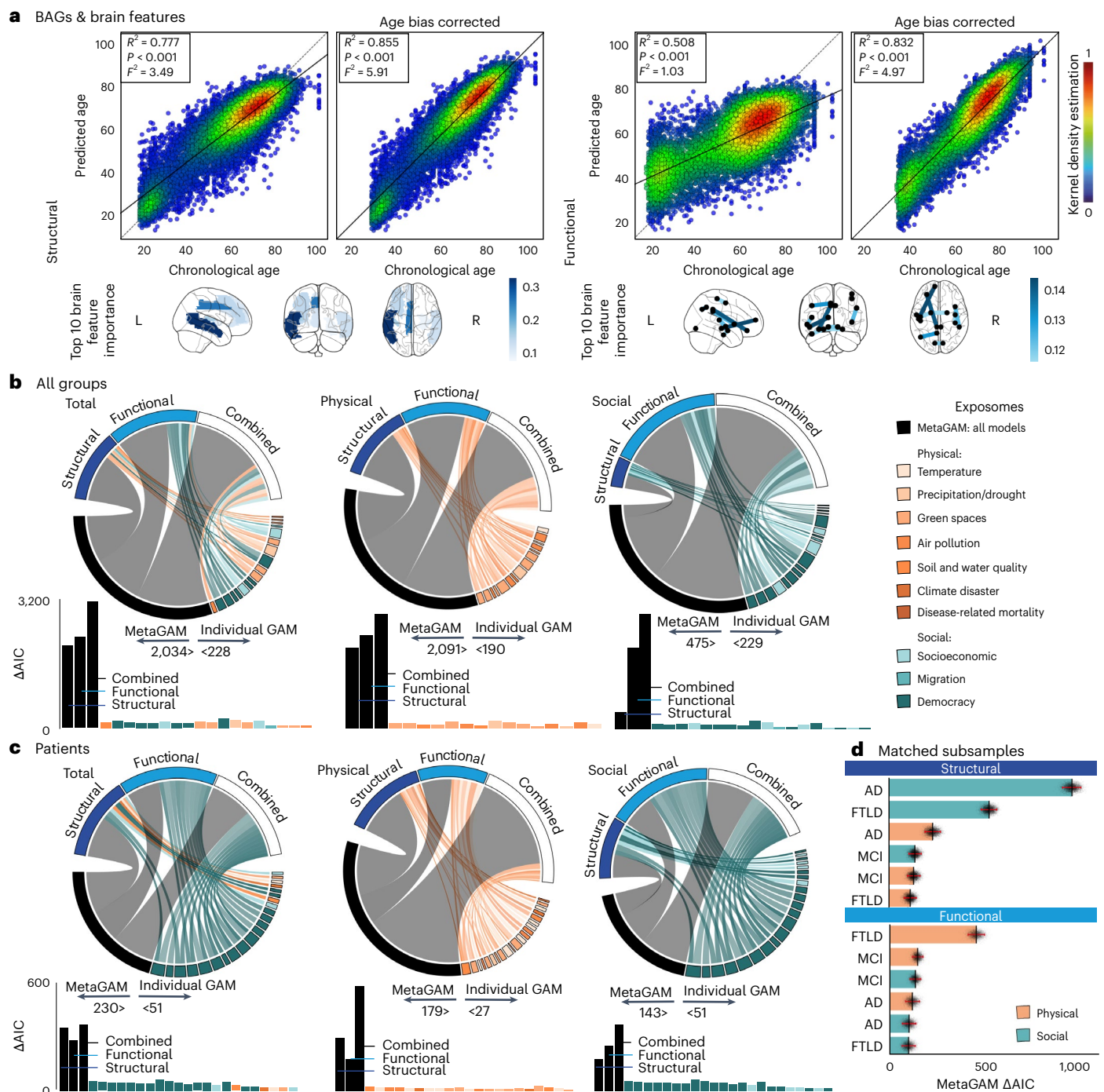


Fig. 2 | Accelerated brain aging associated with exposome. a, Main brain features predicting BAGs. Scatter plots show model accuracy for predicted brain age versus chronological age (uncorrected on the left and age bias corrected on the right) using structural (gray matter volume, left panel) and functional (rsfMRI and rsEEG/MEG, right panel) connectivity data. *P* values are derived from a two-sided *t*-test on the regression slope coefficient; no adjustments for multiple comparisons were applied. Plots use kernel density estimation to represent the distribution of data points. Because age bias correction artificially inflates the model fit, we did not use age-bias-corrected models in subsequent analyses. Brain plots indicate the top 10 most important brain features ranked by SHAP values for each model (Supplementary Tables 3–8). **b**, Full sample: BAGs and exposome associations. Individual GAMs and metaGAMs were calculated to assess the association between exposome and BAGs. Model performance was

compared using Δ AIC. Radial connection thickness and underlying bars encode Δ AIC values for physical (orange), social (green) and combined (black) metaGAM exposomal models. BAGs were modeled separately as structural (blue), functional (light blue) and combined (white). **c**, Patients only. The same analysis was repeated in patients only (AD, FTLD and MCI). Circle plots were generated using the *circize*, *readxl* and *dplyr* packages, and bar plots using *ggplot2*, in R. **d**, metaGAMs in matched subsamples. Mean Δ AIC values (bar length) were compared across matched tandems using permutation tests. 95% confidence intervals (error red lines) were derived from bootstrap resampling (dots, $n = 5,000$) (Supplementary Tables 18–20). The meta-models tested associations between physical (orange bars) and social (green bars) exposomes and structural and functional BAGs. L, left; R, right.

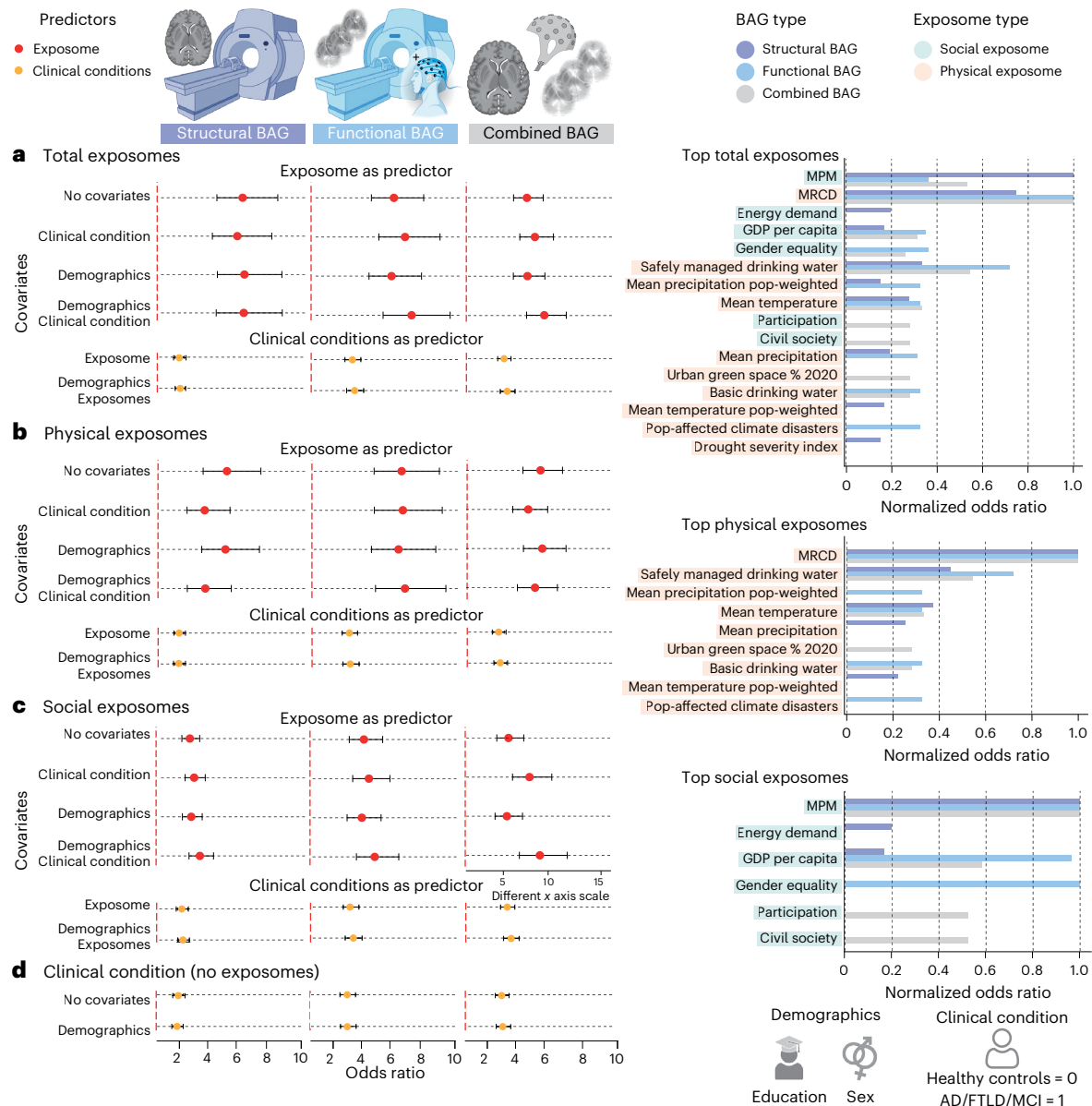


Fig. 3 | Independent contributions of exposome and clinical diagnosis. Odds ratios of accelerated brain aging for exposome burden (top row, red dots) and clinical conditions (patients: AD, FTLD and MCI), $n = 2,108$ versus healthy controls ($n = 6,241$; bottom row, yellow dots) across the total (a), physical (b) and social (c) exposome domains. d, Odds ratios of accelerated brain aging were associated with clinical conditions, independent of exposome burden. Associations are presented separately for structural, functional and combined BAGs. Higher odds ratios indicate increased odds of accelerated brain aging. Dots represent mean odds ratios, and error bars indicate 95% confidence intervals. Estimates are derived from logistic regression models, including unadjusted models (no covariates) and models adjusted for demographics, clinical condition, exposome burden, demographics + clinical condition and

demographics + exposome burden. The x axis range differs for the combined BAG in the social exposome panel (c). Each bar represents a specific exposome factor, with separate bars for structural (dark blue), functional (light blue) and combined (gray) BAGs. Odds ratios were min–max normalized within each exposome domain to highlight relative contributions across modalities. Higher normalized odds ratios indicate stronger associations with accelerated brain aging relative to other variables within the same domain. Bars are ordered according to their ranking in model relevance (ΔAIC). Figure created in BioRender; Migeot, J. <https://biorender.com/zz7oy89> (2026) (MRI and EEG device, brain scan and education, sex, and clinical condition icons). MPM, multidimensional poverty measures; MRCD, mortality rate from communicable diseases; pop, population.

Extended Data Fig. 4), supporting the validity of brain age estimates in clinical populations.

Aggregated exposomal factors outperformed the best individual models across exposomes and BAG modalities. Compared to the total sample, increased black carbon emissions, mean temperature and corruption (democracy) appeared as specific predictors of neurocognitive disorders across models. Combining the total 73 exposomal factors showed the strongest prediction for combined BAGs (approximately 5.8-fold, $\Delta AIC = 300.2$), followed by structural (approximately 5.5-fold, $\Delta AIC = 285.87$) and then functional (approximately 4.5-fold,

$\Delta AIC = 230.8$) BAGs (Fig. 2c, left panel), relative to the best individual model ($\Delta AIC = 51.14$). Across modalities, lower representation and rights (democracy) consistently predicted accelerated brain aging (top 10 factors, $FDR P < 0.001$ and overall $\Delta AIC > 10$; Supplementary Table 6).

Aggregated physical exposome (33 factors) outperformed the best individual model ($\Delta AIC = 27.39$), with the largest ΔAIC increases observed for combined BAGs (approximately 21.5-fold, $\Delta AIC = 588.4$), followed by structural (approximately 10.9-fold, $\Delta AIC = 297.41$) and then functional (approximately 6.5-fold, $\Delta AIC = 179.1$) BAGs (Fig. 2c, center panel). Elevated mean temperatures and reduced green space

access significantly predicted accelerated aging across modalities (FDR $P < 0.001$; $\Delta\text{AIC} > 10$). Increased $\text{PM}_{2.5}$ and black carbon exposure (air pollution) predicted accelerated functional aging. By contrast, the best-performing individual structural and combined models showed poorer model fit ($\Delta\text{AIC} < 10$) (Supplementary Table 7).

Aggregated social exposome (40 factors) also surpassed the best individual model ($\Delta\text{AIC} = 51.48$) with the largest effects in combined BAGs (approximately 5.7-fold, $\Delta\text{AIC} = 297.5$), followed by functional (approximately 3.9-fold, $\Delta\text{AIC} = 203.4$) and then structural (approximately 2.7-fold, $\Delta\text{AIC} = 143.23$) BAGs (Fig. 2c, right panel). Across modalities, lower rule of law, representation and rights (democracy) were the exposomal factors that appeared as consistent predictors of accelerated brain aging (FDR $P < 0.001$ and $\Delta\text{AIC} > 10$; Supplementary Table 8).

Epidemiological analysis of exposomes and accelerated aging

Across all samples, odds ratios (binarized values) for the top exposomal predictors indicated increased risk of accelerated brain aging (Fig. 3, left panels) and remained consistent after controlling for clinical conditions (AD, FTLN and MCI), demographics (education and sex), cognition and all of these combined (Supplementary Table 9). The top total exposome predictors (Fig. 3, right panels) increased the likelihood of accelerated aging between 4.6 and 6.9 times (95% confidence interval: 3.8–9.4) across modalities. The top physical exposome predictors increased the likelihood of accelerated aging between 3.7 and 6.6 times (95% confidence interval: 2.6–9.2). The top social exposome predictors showed the most pronounced effect, increasing the likelihood of accelerated aging between 3.3 and 9.1 times across models (95% confidence interval: 2.7–12.2). The presence of neurocognitive conditions (as a predictor) also significantly increased the odds of accelerated aging across modalities (odds ratio range: 2.2–3.0) although to a lesser extent than exposome predictors. These effects remained after adjusting for exposome burden, demographics and their combined effect (Supplementary Table 10), with non-imputed missing values in education and cognition (Supplementary Tables 11 and 12) and after excluding individuals with MCI and considering only individuals with dementia who showed the highest levels of accelerated aging (Supplementary Table 13). Exposome-based predictors amplified the likelihood of accelerated aging, with larger differences relative to clinical-condition-based models (Bonferroni $P < 0.001$, Cohen's $d = 3.7$ –17.6; Extended Data Fig. 5). Odds ratios for exposome burden–clinical condition associations remained consistent after adjusting for demographics (education, gender, age and individual socioeconomic status (SES)) and cognition, indicating minimal multicollinearity and independence of effects (Supplementary Table 14 and Extended Data Fig. 6).

Sensitivity analyses

We performed multiple tests to assess the validity of the results and explore additional effects.

Participant demographics and income. Shapley additive explanations (SHAP)-based XGBoost models assessed the effects of participants' demographics (education and sex), cognition and country-level GDP. Lower cognitive scores and female sex mainly influenced structural BAGs, whereas functional BAGs were linked to lower GDP (Fig. 4a). Results remained consistent with imputed missing values (Extended Data Fig. 7a). We tested exposome associations after adjusting for the same individual demographics and regional income. These variables were included as covariates in the metaGAM model. To control for acquisition variability, overall data quality (ODQ) metrics and scanner type were regressed out from BAG values before model training. ΔAIC values were similar or slightly higher after covariate adjustment (Fig. 4b). We ran additional models adjusting for individual SES in a subsample. Although structural and functional ΔAIC values changed after covariate adjustment, exposome effects remained strong,

with high ΔAIC values and consistent ranking of exposomal factors (Extended Data Fig. 7b,c).

Exposome comparisons between uncorrected and age-bias-corrected BAGs. Exposome associations remained similar between uncorrected and age-bias-corrected BAGs when evaluating metaGAMs across all exposome domains (total, physical and social) and brain modalities (all FDR $P < 0.001$) (Extended Data Fig. 7d).

Healthy aging subsample. BAG models restricted to control participants were consistent with all-sample BAGs (structural: $R^2 = 0.75$, $F^2 = 2.94$, MDE = 0.02; functional: $R^2 = 0.41$, $F^2 = 0.69$, MDE = −0.04; all FDR $P < 0.001$; Extended Data Fig. 8a). The total exposome metaGAMs were similar to those of the full sample for functional ($\Delta\text{AIC} = 2,013.34$) and combined ($\Delta\text{AIC} = 2,567.90$) BAGs and to a lesser extent for structural ($\Delta\text{AIC} = 490.67$) BAGs, with the top 10 exposomal factors remaining consistent (Supplementary Table 15). Physical exposome metaGAM ΔAIC values remained similar to the full sample except for structural BAGs ($\Delta\text{AIC} = 482.94$), with a consistent set of top 10 exposomal factors identified (Supplementary Table 16). Social exposome metaGAM ΔAIC values and the top 10 exposomal factors closely matched those of the full sample (Supplementary Table 17).

Exposome comparisons between healthy aging and patient groups. Exposome effects explained brain aging significantly better in healthy individuals than in patients when comparing the aggregate exposome across all exposome domains and brain modalities (all FDR $P < 0.001$) (Extended Data Fig. 8b).

Matched samples. Main analyses for exposome effects were rerun for tandems (Controls-AD, Controls-FTLD and Controls-MCI) with age-matched, sex-matched and education-matched subsamples (Supplementary Tables 18 and 19). The main effects were replicated. Aggregate exposome significantly outperformed individual exposomal factors; physical exposome was associated with functional BAGs, particularly for Controls-FTLD and Controls-MCI pairs; and social exposome primarily influenced structural BAGs, with the strongest effects for Controls-AD (Fig. 2d and Supplementary Table 20).

Control for scanner effects. Multi-scanner influence was assessed with scanner identity and BAG estimates, with no significant effects observed in either modality (Supplementary Table 21).

Control for imaging data quality. Data quality was assessed with composite structural and functional ODQ metrics. No significant associations were found between ODQ and BAGs in either modality in the full sample (Fig. 4c) or in the subsample including patients (Extended Data Fig. 8c).

BAGs and disease severity. Higher Clinical Dementia Rating (CDR) scores were significantly associated with greater BAGs across structural and functional models, indicating a gradient of accelerated brain aging with increasing severity (Extended Data Fig. 8d).

BAG replication by modality (fMRI and M/EEG). Separate BAG models were calculated for resting-state fMRI (rsfMRI) and resting-state M/EEG (rsM/EEG). Similar model performance was observed for rsfMRI ($R^2 = 0.51$, $F^2 = 1.06$, $P < 0.001$) and rsM/EEG ($R^2 = 0.52$, $F^2 = 1.09$, $P < 0.001$) (Extended Data Fig. 9).

Sex-stratified analyses. Female and male subsamples were matched for age (Supplementary Table 22). Aggregate exposome effects in both sexes mirrored full-sample results, with socioeconomic equality, democracy and extreme precipitation/droughts as top predictors. However, ΔAIC values were consistently higher

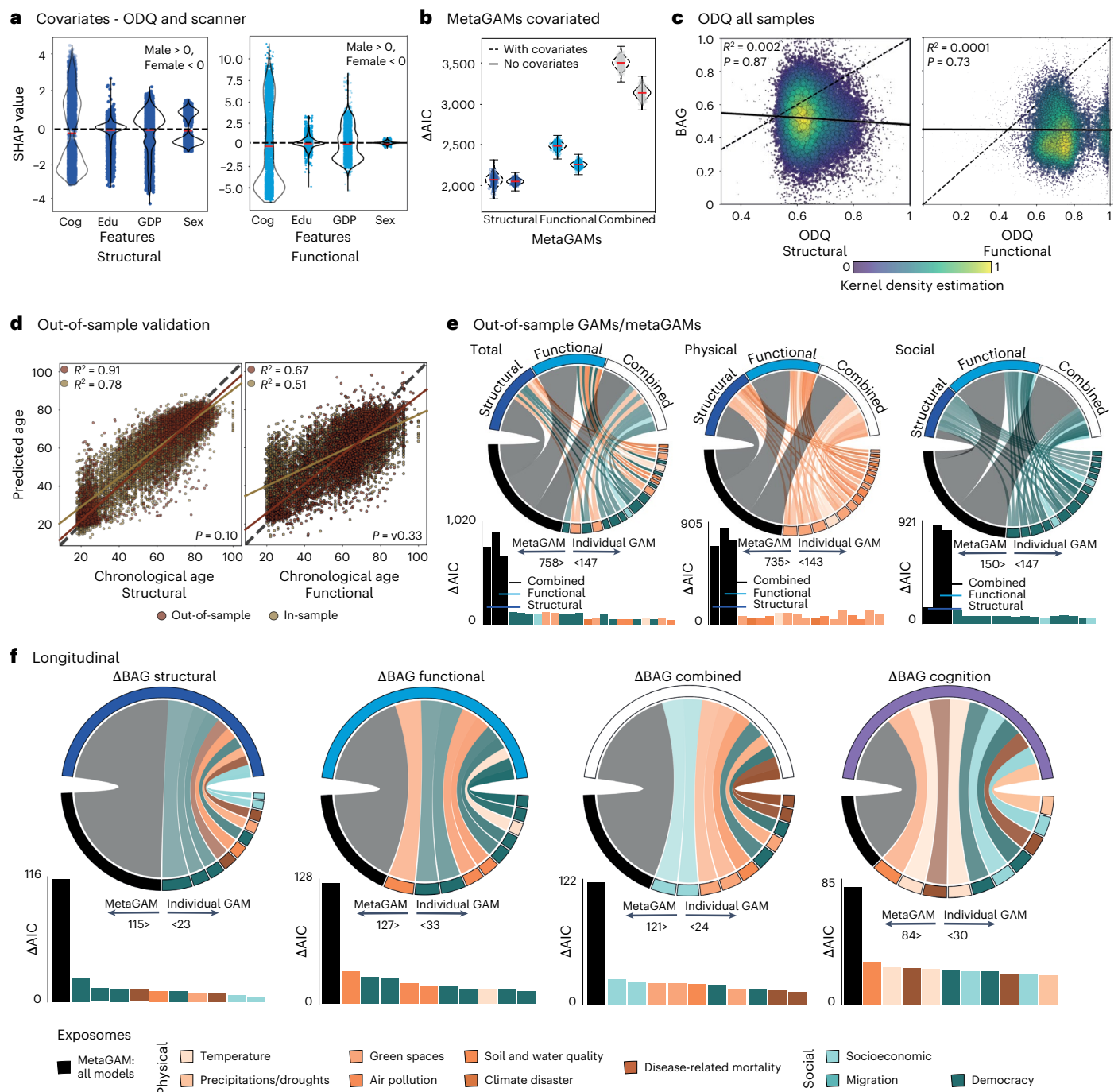


Fig. 4 | Sensitivity analyses. **a**, Participant demographics, cognition and country-level GDP effects. Individual (demographics and cognition) and aggregate (country-level GDP) effects on brain clocks were tested with XGBoost models. Before, ODQ metrics and scanner type were regressed out from BAGs. Lower cognitive scores and females (T1 model) and lower GDP (functional model) were associated with worse outcomes. SHAP values indicate the direction and magnitude of each feature's contribution. Violin plots show SHAP distributions; dots represent participants. **b**, metaGAM covariation. The effects of total aggregate exposome in accelerated brain aging remained after controlling for (a) covariates. Violin plots show bootstrapped effect sizes; dots are samples ($n = 5,000$); red lines are the mean ΔAIC ; black lines indicate 95% confidence intervals. **c**, ODQ across samples. Associations between ODQ and BAGs in structural and functional models. ODQ was a composite score (0–1) derived from image quality metrics. Significance was assessed using permutation-based linear regression (10,000 iterations). No significant associations were

observed. **d**, Out-of-sample external validation. Statistical similarity was evaluated using randomization-based overlap of normalized two-dimensional histograms between in-sample and out-of-sample datasets, indicating good generalization (non-significant differences) of structural and functional models. P values (unadjusted) are derived from a two-sided t -test on the regression slope coefficient. **e**, Out-of-sample GAMs/metaGAMs. Individual (GAMs) and aggregate (metaGAMs) models were calculated to assess the association between exposome and BAGs. Model performance was compared using ΔAIC . BAGs were modeled separately as structural (blue), functional (light blue) and combined (white). **f**, Longitudinal: rate of change and exposome associations. Individual GAMs and metaGAMs were calculated to assess the associations of exposome with ΔBAG s and Δ Cognition. Radial connection thickness and underlying bars encode ΔAIC values for physical (orange), social (green) and aggregated (black) models. Cog, cognition; Edu, education.

in females. Lower soil and water quality, increased air pollution and reduced rights-related factors specifically predicted accelerated aging in females (Supplementary Table 23). In males, top predictors included elevated temperatures and higher disease-related mortality (Supplementary Table 24). Additionally, females exhibited significantly stronger positive correlations between macro-level gender inequality measures and BAGs, with accelerated aging strongly associated with gender disparities (Extended Data Fig. 10).

Out-of-sample validation. Structural and functional BAGs were tested in an independent external dataset ($n = 4,531$; Supplementary Table 25). Model performance remained consistent between in-sample and out-of-sample datasets for both structural ($R^2 = 0.91$ versus $R^2 = 0.78$, $P = 0.10$) and functional ($R^2 = 0.67$ versus $R^2 = 0.51$, $P = 0.33$) BAGs (Fig. 4d). Exposome–BAG associations (Fig. 4e) followed the same in-sample hierarchy (individual exposomal factors < aggregate exposome), yielding ΔAIC values (structural = 861.67; functional = 1,017.24; combined = 758.59) that achieved similar, although minor, fold improvements (as expected given the smaller samples and aggregate-level variability; approximately 5.9-fold, approximately 6.9-fold and approximately 5.2-fold), relative to the best individual model ($\Delta AIC = 147.05$) and to the in-sample analyses. Consistent top 10 exposomal factors were also observed (Supplementary Table 26).

Physical aggregate exposome showed similar patterns (structural $\Delta AIC = 735.1$; functional $\Delta AIC = 904.6$; combined $\Delta AIC = 782.3$), indicating substantially better model fit relative to the best individual model ($\Delta AIC = 143.2$) (Supplementary Table 27). Top physical exposomal factors included green space access and air pollution, alongside new disease-related mortality, temperature and drinking water exposures. Social aggregate exposome closely mirrored the in-sample dataset results (Supplementary Table 28; structural $\Delta AIC = 150.98$; functional $\Delta AIC = 920.44$; combined $\Delta AIC = 897.89$): compared to the best individual exposure model ($\Delta AIC = 147.03$), aggregate models showed substantially stronger effects, and the associations with structural BAG showed the lowest ΔAIC . As in the in-sample models, democracy-related factors ranked highest, followed by socioeconomic exposures (top 10 GAMs $FDR P < 0.001$ and overall $\Delta AIC > 10$).

Longitudinal analyses. Greater exposome adversity was associated with greater accelerated brain aging observed in future assessments (reflected by increased BAG values relative to previous BAG measures as well as cognitive scores). Aggregate exposome outperformed individual exposomal models in predicting longitudinal rate of change in structural, functional and combined BAGs and cognitive scores across samples (Fig. 3f and Supplementary Table 29) and healthy controls (Supplementary Table 30).

Exposome temporal stability. Across the study period (2000–2025), exposome indicators showed high year-to-year stability, with median lag-1 correlations of approximately 0.73 across 73 variables (Supplementary Table 31).

Discussion

This study examined how the exposome (33 physical and 40 social exposomal factors) was associated with accelerated aging across diverse settings in brain health and disease. Aggregated nonlinear exposome explained up to 15.5 times more variance in brain aging than individual predictors. Adverse physical exposures (such as lack of green space access, extreme precipitation, poor water quality and $PM_{2.5}$) were primarily associated with accelerated structural aging, particularly in limbic, subcortical and cerebellar regions. Unfavorable social exposures (such as socioeconomic inequality, reduced GDP, poverty, limited rule of law, decreased participation, low representation and short welfare) were primarily associated with accelerated functional aging (fronto-temporal and limbic networks). Results were consistent after adjusting

for demographics, cognitive status, country-level income, scanner and data quality. The associations between exposome and brain clocks remained consistent when considering only healthy individuals. In models involving neurocognitive disorders, top exposomal predictors included specific physical and democracy-related indicators. Within matched samples, structural aging in AD was most associated with the social exposome, and functional aging in FTLD and MCI was most associated with the physical exposome. The top exposomal factors surpassed the role of neurocognitive disorders in increasing the risk of accelerated aging. Higher exposome burden was also associated with accelerated brain aging and cognitive decline in a longitudinal subsample. These findings support the relevance of exposome and call for neurosyndemic frameworks^{1,3,15} in brain health.

The exposome appears to influence brain aging through synergistic interactions rather than isolated effects^{1,2}. Previous models treating exposomal factors as independent and linear^{9,12,13} have overlooked this complexity. Findings underscore the importance of neurosyndemic models, describing how co-occurring physical, social and political adversities accumulate and interact with biological risk factors to heighten vulnerability³¹. For instance, socioeconomic inequality and air pollution may combine with limited healthcare access to increase dementia risk, and political instability and cardiovascular disease can interact to accelerate brain aging³. These cross-domain pathways may help to explain why environmental complexity drives divergence in brain aging trajectories beyond clinical diagnoses. Brain clocks provide a means to target the compound biological embedding of simultaneous exposures through person-specific metrics^{5,8,11}.

The exposome may operate across biological mechanisms, contributing to modality-specific patterns in the brain¹. Chronic physical exposures (for example, air pollution¹² and contaminated water¹⁸) may damage brain tissue, activating neuroimmune responses and systemic inflammation, leading to DNA damage and epigenetic alterations^{5,14,32}. Neurotoxic mechanisms for black carbon (most of $PM_{2.5}$) occur directly through the blood–brain barrier or via olfactory/optic nerves, where they trigger microglial activation, oxidative stress and proinflammatory cytokine release^{33–35}. These processes can impair synaptic integrity, reduce neurotrophic support and promote neurodegeneration^{33–35}. Molecular changes would also influence cardiometabolic efficiency, resulting in structural brain degradation, particularly in limbic regions^{13,36}. Social exposures, such as poverty or fragile sociopolitical conditions^{20,21}, may trigger allostatic responses to environmental demands, resulting in compensatory alterations in brain functional interactions. Their effects may be mediated by cumulative stress and hypothalamic–pituitary–adrenal (HPA) axis dysregulation^{1,32,37–39}, potentially inducing rapid changes in functional connectivity⁵. Beyond these differences, exposomal factors may be associated with synergistic effects. For example, chronic exposure to social stressors could lead to allostatic load, driving long-term cardiovascular and metabolic disruption with structural consequences^{1,5,32}. Similarly, physical exposures, such as extreme precipitation¹⁰ or limited green space¹⁹, may reflect acute climate change events or policy-driven design and may influence the brain indirectly by amplifying other physical burdens or mimicking psychosocial stressors^{5,40}. In real-world settings, social and physical exposures co-occur. This may account for the superior performance of combined exposome models and multimodal brain clocks over single-domain and single-modality approaches, as they better capture complex interactions. A multimodal approach may enhance sensitivity to complementary neural signals and reduce measurement error. This could improve the detection of compounding environmental embedding across levels.

Clinical status alone is insufficient to capture the full burden of brain aging. The exposome exerted a stronger association with the risk of accelerated brain aging than models driven by clinical conditions. The stronger longitudinal association between exposome burden and accelerated functional brain aging (reflecting transient changes^{5,20,37})

was more pronounced in healthy controls, in whom large structural changes are not expected over relatively short-term follow-ups. Environmental adversity may precede or exacerbate neurodegenerative processes¹¹, and disease status could also shape sensitivity to exposomal factors. Our findings align with the vulnerability to cumulative physical stressors (for example, extreme temperature, soil and water contamination and PM_{2.5} and black carbon air pollutants) in neurocognitive disorders^{16,35}, including FTLD¹⁴ and MCI⁴¹. However, stronger associations with social exposures, particularly in AD, may indicate heightened sensitivity to cumulative allostatic load, potentially induced by stressful democratic breakdowns or social exclusion^{14,36}. People may rely more on stable institutions, social protection and healthcare access to preserve functional autonomy and basic rights⁴². Although still understudied^{7,43}, the political environment may amplify neurobiological vulnerability. These findings underscore the need for neurosyndemic frameworks^{2,3} that capture the ecological and sociopolitical underpinnings of brain aging.

Present findings advocate for a transition in brain health policy from reactive, disease-focused strategies to proactive, structural interventions aimed at disease prevention. Traditional strategies targeting individual lifestyle or late-stage care miss the broader drivers of structural vulnerability^{43,44} beyond individual choice. By showing how cumulative exposures are associated with brain aging in healthy aging, exposome-based models may help identify at-risk subpopulations for early intervention, reframing responsibility as a shared endeavor between individuals and governments^{4,45}. These insights support strategies that integrate well-established individual-level risk modifiers (for example, physical activity, diet and cognitive engagement) with policies that tackle structural determinants^{44,45}. Strengthening democratic institutions (for example, by enhancing civil participation, expanding local representation and ensuring basic welfare) and improving environmental quality (for example, by increasing urban green spaces and mitigating structural inequalities) may benefit healthy aging. For example, reducing air pollution alone could prevent dementia globally by 3%⁴⁶. However, interventions should consider optimal exposure ranges and synergies between physical and social domains rather than assuming isolated linear dose–response relationships. The syndemic¹, nonlinear nature of exposomal risks³¹ calls for integrated public health approaches, linking environmental regulation, social protection and cognitive aging strategies across the healthspan. Translating this framework into action requires embedding exposome science into precision brain health¹. Artificial intelligence tools⁴⁷ could support both early detection of at-risk individuals and identification of context-specific levers for population-level prevention¹. Context-sensitive models should incorporate policy-relevant determinants of brain aging^{5,43,48}, capturing macro-to-micro dynamics to enable more equitable, globally scalable strategies.

The strengths of this study lie in its scale, diversity and analytical design. The report included 18,701 participants, spanning those who are healthy and those who have neurocognitive disorders from 34 countries as well as incorporating representation from Global South countries, which are underrepresented in exposome research^{11,24,40,49}. This improves both the generalizability and the equity of brain aging models. The geospatially derived indicators targeting physical, socioeconomic and political dynamics provided high dimensionality to capture complex aggregate-level exposome burdens. Multimodal neuroimaging enabled the triangulation of brain aging signatures across modalities. Beyond the use of independent datasets, the adoption of nested cross-validation ensured separation between model selection and evaluation. Furthermore, exposome effects were independent of demographic covariates and multiple confounding. Longitudinal results supported the exposome–accelerated brain aging associations observed in cross-sectional models.

This study has important limitations. Our cross-sectional design and small longitudinal sample preclude causal inference. Although a

comprehensive array of 73 exposomal factors was used, the reliance on country-level metrics reduced spatial resolution, potentially masking local or individual-level variation. Although sensitivity analyses in available subsamples with harmonized SES data provide convergent evidence supporting the validity of country-level proxies, the absence of fully individual-level SES measures is a limitation. Future work should incorporate fine-grained geospatial data (neighborhood or individual level)⁴⁷.

Our analyses showed temporal stability of exposome indicators, confirming that lagged indices do not substantially alter brain–environment associations⁵⁰. Linking yearly indicators to imaging time increased variability compared to long-term averages^{8,21}, enhancing validity. However, the coarse temporal resolution limits separation of early-life and later-life effects. Childhood adversity can induce lasting epigenetic changes^{51,52}, and migration modifies cumulative exposures⁵³. To clarify the direction and timing of exposome-related effects, future studies should replicate longitudinal analyses in larger samples.

Although internationally standardized diagnostic frameworks were applied across sites, local adaptations of clinical procedures reflect the diverse international context of the study. Partial cognitive overlap between healthy controls and MCI is expected in diverse global cohorts due to variability in educational systems and assessment tools. Although our sensitivity analyses showed that main findings remained unchanged after adjusting for education, this variability should be considered when interpreting associations.

As in previous studies^{8,26,54}, acquisition and protocol variability was mitigated by sensitivity analyses (comparisons, regressions and covarying for scanner and ODQ metrics). Future work should incorporate novel vascular clocks (that is, diffusion MRI-based white matter measures, fractional anisotropy and mean diffusivity), which may provide additional sensitivity to environmental influences on aging⁵⁵. Individual variability in terms of lifestyle, infections, psychosocial stress traits, multilingualism^{7,46,56,57} and genetic and epigenetic factors^{6,38,58} may interact with aggregate-level exposome in shaping vulnerability or resilience^{49,59}. Multilevel, longitudinal frameworks combining exposomic, genomic and neurobiological data will be critical to fully capture person-specific vulnerability and refine precision prevention strategies, particularly in global populations.

In conclusion, the cumulative imprint of physical, socioeconomic and political exposomes may exert a synergetic influence on accelerated brain aging across health and disease. These findings highlight the importance of considering how multiple contextual factors jointly shape brain vulnerability and resilience, with direct implications for neuroscience research, public health initiatives and dementia prevention strategies. Aligning neuroscience with environmental justice may help improve global brain health. Where and how people live may be as important for brain aging as the specific disease they develop.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-026-04302-z>.

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Methods

Study design and participants

This study included 18,701 participants (Table 1). Main analyses were run with an in-sample dataset. An external cross-validation was run with an independent out-of-sample dataset. The in-sample dataset comprised 14,170 participants (12,120 with MRI T1, 7,021 with rsfMRI and 2,594 with rsM/EEG). Of these, 9,197 were healthy controls; 2,705 were diagnosed with probable AD; 1,176 fulfilled criteria for FTLD; and 1,132 met the Petersen criteria for MCI (Supplementary Table 32). Inclusion criteria required fulfillment of established diagnostic frameworks (probable AD: National Institute on Aging and Alzheimer's Association (NIA-AA)⁶¹; FTLD: Rascovsky, Gorno-Tempini and Cairns^{62,63}; MCI: Petersen⁶⁴). Healthy controls had no history of major neurological or psychiatric disorders and did not meet criteria for MCI or dementia. Although international standards were applied, each site incorporated additional local clinical assessments to implement these frameworks. The out-of-sample dataset comprised 4,531 individuals (4,275 with MRI T1 and 3,842 with functional data), including 3,693 healthy controls and 368 AD, 72 FTLD and 398 MCI participants (Supplementary Table 25). Out-of-sample datasets were allocated based on the availability of data. The out-of-sample validation group included participants from 12 countries, providing a basic representation across Latin America, Europe, North America, Asia and Oceania. This group also incorporated countries not present in the in-sample dataset (France, India and Singapore). Although the country overlap was approximately 26.47% (nine out of 34 countries), independence was enforced at the dataset level (with only 1.64% overlap; Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat) consortium) as exposome indicators are aggregated. Detailed information about diagnostic status, country of residence and year of brain data acquisition (range: 2000–2025) was acquired for each participant. Demographic and cognitive data (Table 1) were obtained for each participant where available, including age (mean = 54.3, s.d. = 21.68, range: 17–100, similar to or larger than other brain age studies⁶⁵); sex (57.81% female, 42.19% male); years of education (mean = 13.16, s.d. = 4.54), which included total formal schooling across all levels (primary, secondary, high school and postsecondary/tertiary education); and a general cognitive score (0–100) derived from harmonized scores among the Addenbrooke's Cognitive Examination III (ACE-III), the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA) scales. MMSE and MoCA scores were rescaled from 0–30 to 0–100, and then all three scales were averaged to create a single cognitive score per participant. Mean cognitive scores significantly differentiated healthy controls and MCI groups across modalities (Table 1 and Supplementary Table 32), even when accounting for overlap at the individual level. This is expected for cognitive measures pooled across diverse educational and global contexts. Individuals with fewer years of schooling and/or from countries with lower educational quality typically perform worse on global cognitive tests, even in the absence of clinical impairments. Educational-adjusted scores reduced the overlap between healthy controls and MCI groups (Supplementary Fig. 1 and Sensitivity analyses). Sex information was determined by self-report. No information regarding gender was collected. Individual-level socioeconomic measures were available in a subsample ($n = 2,931$; see distribution across datasets in Supplementary Fig. 2). All datasets adhered to the Declaration of Helsinki, with informed consent and institutional review board ethical approvals (Ethical approval section; Supplementary Table 33).

Brain data acquisition

Acquisition protocols for MRI, fMRI, EEG and MEG are detailed in Supplementary Tables 24–30, including scanner type, field strength, sequence parameters and preprocessing pipelines. Across sites, MRI data were acquired predominantly on 3 T scanners (82%), with additional contributions from 1.5 T scanners. Major manufacturers included Siemens

(Trio/Prisma/Skyra/Verio), Philips (Achieva/Ingenia/Intera) and GE (Signa/Discovery). fMRI protocols varied in repetition time (0.7–3 s) and voxel size (2–4 mm). EEG was recorded with Biosemi (64–264 channels), BrainAmp (32–128 channels) and Neuroscan (72 channels), with sampling rates ranging from 200 Hz to 2,048 Hz. MEG data were collected using Elekta Neuromag and CTF systems (275–306 channels). Because acquisition parameters varied across sites, scanner identity and ODQ metrics were included as covariates in all models to address this variability. Not all modalities were available for all participants; analyses were performed modality by modality, and combined models included only participants with both structural and functional modalities available.

MRI dataset

The structural MRI data involved 16,395 participants (11,128 healthy controls, 2,804 AD⁶¹, 1,210 FTLD^{62,63} and 1,253 MCI⁶⁴; Table 1; group distribution per dataset in Supplementary Table 34) from African (Egypt, South Africa), Asian (China, India, Japan, Singapore, Taiwan), European (Austria, Belgium, France, Germany, Greece, Ireland, Italy, The Netherlands, North Macedonia, Poland, Spain, Sweden, Switzerland, Türkiye, United Kingdom), Latin American (Argentina, Brazil, Chile, Colombia, Mexico, Peru), North American (Canada, United States) and Oceania (Australia, New Zealand) cohorts (Supplementary Table 35). T1-weighted structural MRI data were derived from 178 scanners (scanning protocols in Supplementary Table 36).

fMRI dataset

The rsfMRI dataset included 10,399 participants (7,931 healthy controls, 994 AD⁶¹, 780 FTLD^{62,63} and 694 MCI⁶⁴; Table 1; group distribution per dataset in Supplementary Table 37) from Asian (China, India, Japan, Singapore), European (Belgium, France, Germany, Italy, The Netherlands, Poland, Spain, United Kingdom), Latin American (Argentina, Brazil, Chile, Colombia, Mexico), North American (Canada, United States) and Oceania (Australia) cohorts (Supplementary Table 35). rsfMRI images were derived from 115 scanners (Supplementary Table 38).

M/EEG dataset

The rsM/EEG dataset comprised 3,058 participants (2,287 healthy controls, 408 AD⁶¹, 84 FTLD^{62,63} and 279 MCI⁶⁴; Table 1; group distribution per dataset in Supplementary Table 39) from European (Greece, Ireland, Italy, Norway, Poland, Spain, Türkiye, United Kingdom), Latin American (Argentina, Brazil, Chile, Colombia, Cuba) and North American (Canada, United States) cohorts (Supplementary Table 35). A total of 23 amplifiers/magnets were included (Supplementary Table 40).

Brain data preprocessing

Standardized and harmonized preprocessing pipelines were consistently applied across datasets.

MRI T1 preprocessing

Structural preprocessing followed standard voxel-based morphometry CAT12 toolbox (version 2.9, <https://neuro-jena.github.io/cat/>) pipelines in MATLAB R2022a, comprising bias field correction, noise reduction, skull stripping, segmentation and normalization to the Montreal Neurological Institute (MNI) space at a 1.5-mm isotropic resolution, with default parameters. All structural segmentations were visually inspected for quality by trained raters. Gray matter volume values were extracted based on 116 regions of interest (ROIs) from the Automated Anatomical Labeling (AAL116) atlas and normalized by total intracranial volume. All features were scaled to zero mean and unit variance before model training to ensure comparability and prevent bias in regression coefficients.

rsfMRI preprocessing

rsfMRI preprocessing was conducted using the fMRIPrep toolbox (version 22.0.2, <https://fmripred.org/>). The CONN22 toolbox was used

for additional steps: Gaussian kernel of $6 \times 6 \times 6$ mm smoothing; signal denoising through linear regression to account for confounding effects from white matter, cerebrospinal fluid, realignment and scrubbing; and a band-pass filter (0.008–0.09 Hz) application. Although fMRIPrep provides detailed motion reports, no participants were excluded based on predefined thresholds. Instead, motion confounds were modeled during denoising and further accounted for using the rsfMRI ODO score, defined from TSNR and DVARS metrics (Data quality assessment section). To reduce dimensionality, time series were extracted with Nilearn library (version 0.10.0) in Python (version 3.8, Python Software Foundation) based on the AAL116 atlas.

rsEEG and rsMEG preprocessing

We used a convergent pipeline for resting-state MEG and EEG (rsM/EEG) as done previously for brain age estimations⁸. Data were preprocessed offline using harmonized pipelines optimized for brain functional connectivity estimation in large-scale aging and dementia studies⁸. Both modalities were filtered between 0.5 Hz and 40 Hz using an eighth-order zero-phase Butterworth filter and resampled to 512 Hz. For EEG, artifacts such as ocular, cardiac and muscular noise were classified and removed using independent component analysis (ICA) in combination with ICLabel and EyeCatch. These artifact removal procedures are part of a standardized pipeline applied identically across all datasets and previously implemented in large-scale multicenter studies of aging and dementia⁸. Malfunctioning channels were replaced via weighted spherical interpolation, followed by visual inspection. EEG signals were re-referenced (average reference) and aligned to REST, whereas MEG preprocessing followed equivalent denoising steps with 2-second analysis windows.

For both modalities, source localization was performed using standardized low-resolution electromagnetic tomography (sLORETA) to estimate current densities from 5-minute preprocessed data at predefined virtual sensors located in a reference brain (MNI305, Brain Imaging Centre, MNI). sLORETA employs a standardized version of the minimum norm current density estimation to overcome challenges associated with deep source localization. Voxel-level signals were averaged to derive regional time series using 82 anatomical regions from the AAL90 atlas, selected to maximize EEG source reconstruction accuracy and ensure consistency with multimodal integration procedures. To reduce site-related variability, time series were z-scored per dataset⁶⁶.

High-order interactions in functional data

Parcellated time series were used to compute high-order functional interactions across brain regions. We applied the organizational information (Ω or O -info) metric, a multivariate extension of Shannon's mutual information that quantifies how synergistic or redundant the relationship is between two brain regions relative to the rest of the brain⁸. The O -info is computed for a triplet comprising two univariate signals (regions i and j) and a multivariate signal (the whole brain minus i and j). Positive Ω values reflect redundancy-dominant interactions, and negative values reflect synergy-dominant interactions. The O -info metric quantifies high-order interactions by comparing the entropy of a set of variables with the entropy of its subsets. For a set X^n , it is defined as:

$$\Omega(X^n) = (n-2)H(X^n) + \sum_{j=1}^n [H(X_j) - H(X^{n-j})]$$

where $H(X^n)$ denotes Shannon's entropy and X^{n-j} indicates the set excluding variable X_j . In the case of triplets (x, y, z) , Ω simplifies to:

$$\Omega(x, y, z) = H(x, y, z) - H(x, y) - H(x, z) - H(y, z) + H(x) + H(y) + H(z)$$

Entropy terms were estimated using a Gaussian copula approximation, which retains non-parametric dependence structures while assuming Gaussian marginals.

To maximize statistical power and ensure comparability with the larger structural dataset, we combined fMRI and M/EEG data into a single functional modality. From the initial 116×116 rsfMRI connectivity matrix (6,670 features), we retained the 3,321 connections corresponding to an 82×82 subset of AAL regions, matching those used in rsM/EEG⁸. This selection aimed to ensure anatomical alignment across modalities and was based on predefined EEG-compatible ROIs to enable fair feature-level comparison and multimodal fusion.

BAG estimation

BAG was computed as the difference between predicted and chronological age, with negative values indicating delayed brain aging and positive values indicating accelerated brain aging⁸. We trained two BAG models in all samples using preprocessed, modality-specific features: structural gray matter volume from T1 MRIs and functional connectivity from rsfMRI and rsM/EEGs. This approach allowed us to capture brain aging variability across a wide exposomal range and the full continuum of aging trajectories, from healthy controls to individuals with neurocognitive disorders. We obtained a third, combined BAG from the average of the structural and functional BAGs. Brain age was predicted using light gradient boosting machines (LightGBM), a model well suited for large, high-dimensional datasets due to its scalability and computational efficiency²⁷. We implemented an intrasubject harmonization technique, aiming to minimize confounding effects arising from differences between scanner models^{8,67}. We did not apply age bias correction in the main analyses, as this post hoc adjustment can artificially inflate performance metrics (for example, correlations and R^2 values) and lead to overadjustment, masking true model variability²⁹. We, therefore, prioritized uncorrected BAG values to preserve exposome-related variance (Fig. 2a). Data were normalized to a fixed range using min–max scaler, ensuring that the minimum and maximum values were consistent across different scanners, thereby reducing variability.

Model optimization and nested cross-validation

We applied a nested 10-fold cross-validation procedure to compute BAGs and optimize model performance. In each iteration of the outer loop, one fold was reserved for testing, and the remaining nine were used in the inner loop to optimize hyperparameters via grid search. The parameters that were tuned included learning rate (range: 0.01–0.1), maximum tree depth (range: 3–7) and number of estimators (range: 100–200). Once the best hyperparameters were identified, a model was trained on the full inner nine-fold training set and tested on the outer fold. This procedure was repeated across all outer folds, ensuring that each fold was used once for testing. During the nested cross-validation, all countries were iteratively cycled across in–out folds. Compared to standard cross-validation approaches, nested cross-validation strictly separates hyperparameter tuning (inner loop, 10-fold) from unbiased performance estimation (outer loop, 10-fold). This design prevents any data leakage, ensures that no individuals from training folds are included in test folds and provides a reliable estimate of true generalization^{66,67}. Unlike single validation splits with independent datasets, which can be variance heavy and biased, nested cross-validation generates a distribution of performance metrics across folds and maximizes the use of available data. This is particularly critical in studies such as ours, which involve large feature spaces. For these reasons, nested cross-validation is widely regarded as the gold standard for model evaluation, providing more reliable estimates of performance than simple out-of-sample validation⁶⁸ (Fig. 1c).

Model evaluation

Model performance was assessed in each outer fold, and metrics were averaged across the 10 folds. Metrics included the coefficient of determination (R^2 proportion of variance in chronological age explained by the model); MDE (prediction accuracy of models by measuring the average absolute error between predicted and chronological

age⁸); Cohen's F^2 (effect size, with >0.35 indicating a large effect); and P values (obtained via 5,000-iteration non-parametric permutation tests). To interpret models, we computed SHAP values to rank ROI-level feature importance⁶⁹.

Multicenter imaging control

All analyses were adjusted for scanner effects and ODQ metrics to further control for site and quality variability.

Scanner effects

To rule out multi-scanner artifacts, we assigned each participant a numerical identifier based on their scanner identity considering the scanners' manufacturer, model and magnet strength (Supplementary Tables 36, 38 and 40), which was then used in the sensitivity analyses (see Sensitivity analyses section).

Data quality assessment

To rule out data quality artifacts, we computed composite ODQ scores for each modality. For T1 MRI, we used min–max normalized MRIQC metrics⁸: the contrast-to-noise ratio (CNR; higher values reflect better tissue contrast), signal-to-noise ratio (SNR; higher values reflect better signal clarity) and coefficient of joint variation (CJV; higher values reflect greater variability at the interface of gray and white matter, often due to head motion or scanner artifacts)⁶⁷. Weights (w) were set to 1 for all components to reflect equal contribution. The T1 MRI ODQ score was computed as follows:

$$ODQ_{T1} = w_{CNR} \times CNR_{norm} + w_{SNR} \times SNR_{norm} - w_{CJV} \times CJV_{norm}$$

For rsfMRI, we included min–max normalized MRIQC metrics: the temporal signal-to-noise ratio (TSNR; reflecting BOLD signal stability) and standard deviation of DVARS (standard deviation of voxel-wise signal changes across time, sensitive to head motion and abrupt intensity shifts)⁶⁷. Weights were set to 1. The rsfMRI ODQ score was defined as follows:

$$ODQ_{rsfMRI} = TSNR_{norm} - w_{DVARS} \times DVARS_{norm}$$

For rsM/EEG, signals were divided into 1-second segments and evaluated using four metrics: the detection of weak or constant signals based on standard deviation, identification of artifacts through signal amplitude ratios, presence of high-frequency noise and low correlation between channels. Each segment was labeled as good or poor quality. The rsM/EEG ODQ score was calculated as the percentage of good-quality segments, with 0 indicating all poor-quality and 100 all high-quality segments⁷⁰.

All ODQ values were rescaled to a 0–1 range for interpretability and comparability across modalities, where 1 indicates the best quality and 0 the worst. The resulting rsfMRI and rsM/EEG scores were used as indicators of functional ODQ, whereas T1 MRI scores represented structural ODQ.

A very small fraction of scans ($<0.36\%$) did not yield valid ODQ values due to a pipeline-level failure in MRIQC, specifically an empty-mask error after inhomogeneity correction. However, these scans were successfully processed by fMRIPrep and CAT12 and passed our visual quality control, confirming that the images were structurally valid. The missing ODQ, therefore, stems from technical extraction failure, not image corruption, and no systematic bias is expected given the proportion and nature of failure (MRI T1: 0.36%, rsfMRI: 0.06%, rsM/EEG: 0%). These cases were retained in all downstream BAG modeling but excluded from ODQ-specific analyses.

Data sources of exposome variables

We compiled yearly country-level exposome data from available sources, covering both physical and social indicator types. Exposome

factors were selected from established international databases (for example, World Bank, World Health Organization, United Nations and Organisation for Economic Co-operation and Development (OECD)) based on availability across countries and years (range: 2000–2025), relevance to physical, social or political domains and standardized metrics ensuring cross-country comparability. All variables were provided in harmonized form by the source institutions. Physical exposome included air pollution (PM_{2.5} exposure, nitrogen oxides (NOx), sulfur dioxide (SO₂), carbon monoxide, black carbon, ammonia (NH₃) and non-methane volatile organic compound (NMVOC)) emissions; access to green spaces (mean share of urban green areas and green urban areas per capita); temperature (mean, anomalies and maximum rates), precipitation and droughts (mean and maximum rates and self-calibrated Palmer drought severity index); soil and water quality (poisoning mortality, basic and safely managed drinking water access and agriculture employment—an indirect measure of agrotoxics exposure); climate disasters (number of climate disaster events and proportion of affected population); and disease-related mortality (mortality rate for communicable and non-communicable diseases) indicators (Supplementary Table 1). Social exposome encompassed socioeconomic measures (Gini index, human capital index, HDI and inequality-adjusted HDI, gender inequality index, multidimensional poverty, GDP per capita, unemployment rate and electricity consumption per capita); democracy across multiple dimensions (representation (credible elections, inclusive suffrage, free political parties, elected government, effective parliament, local democracy); rights (access to justice, civil liberties including freedom of expression, freedom of the press, freedom of association and assembly, freedom of religion and freedom of movement, basic welfare and political equality including social group equality, economic equality and gender equality); rule of law (judicial independence, absence of corruption, predictability enforcement, personal integrity and security); and participation (civil society, civic engagement, electoral participation and direct democracy)); and inbound migration rate (Supplementary Table 2).

Exposome and covariate data processing

Each participant was assigned specific exposome values based on their country of residence and year of imaging acquisition. Missing yearly values (6.24%) were imputed through temporal interpolation by averaging adjacent years; 2023–2025 values were extrapolated from the most recent data. When no country-level data were available for a specific exposome, those values remained missing (NaN). Accordingly, participants were included in all analyses for other exposomes (GAMs and metaGAMs) but were not considered for the specific missing exposome variable. This strategy ensured maximum sample retention while maintaining data integrity (see Supplementary Table 41, which reports mean exposome values per country and indicates NaN where data were unavailable). Variables with inverse interpretations were direction corrected.

We also examined missingness across covariates. Education was missing in 16.4% of cases; cognitive scores were missing in 36.7% of cases; and GDP data were complete (except for Cuba; see missingness details per modality in Supplementary Table 42). To handle missing data, we applied a groupwise mean imputation strategy stratified by subregion within each continent, ensuring that missing values were replaced with the mean of the corresponding subregional stratum (imputation procedure and summary in Supplementary Table 43).

Statistical analysis

We applied a two-level modeling framework to examine the exposome influence on BAGs. First, individual GAMs were used to estimate the nonlinear association between each exposomal factor and BAGs. This approach uses smooth functions to flexibly capture complex associations. Nonlinearity was quantified through the effective degrees of freedom (EDF; 1: linear associations; 2: highly nonlinear associations),

and model fit was assessed using AIC. GAMs were applied to each exposome factor individually. To compare model performance between predictors, we used Δ AIC values as effect sizes. Δ AIC values represent the relative fit of each model against a null model: an intercept-only regression that predicts all observations using the sample mean, serving as a baseline for model comparison with a single parameter ($k = 1$). A Δ AIC > 10 is considered strong evidence of significance for the proposed model and no support for the null model, analogous to rejecting a null hypothesis at a $P < 0.05$ threshold in classical inference. A Δ AIC < 2 suggests that the proposed and null models are indistinguishable, whereas 4–7 indicates considerably less support for the null model³⁰. This approach is consistent with established standards in model selection⁷¹. Higher Δ AIC values indicate better performance.

To capture the joint effects of multiple predictors, we combined the GAM-derived outputs into second-level meta-models (metaGAMs) using LightGBM, a gradient-boosted algorithm suitable for handling complex nonlinear interactions²⁷. metaGAM models incorporated combined exposomal factors simultaneously. LightGBM effectively handles multicollinearity through its tree-based architecture and built-in regularization mechanisms, allowing redundant predictors to compete while automatically selecting the most informative features³¹. The model performance of GAMs and metaGAMs was compared using Δ AIC values.

Physical and social exposome variables were modeled jointly (total exposome) and separately to compare the combined and differential contributions to BAGs. All analyses were replicated in patients (AD, FTLN and MCI) to evaluate exposome effects in clinical conditions.

To confirm that BAGs increase with clinical severity, we compared group distributions across structural, functional and combined modalities using two-sided permutation tests (with 5,000 iterations). This non-parametric approach avoids distributional assumptions and controls for multiple comparisons by relying on empirical null distributions. Additionally, in a dementia subsample with available CDR scores (n total = 1,356; AD = 981; FTLN = 375), the association between disease severity and BAGs was implemented with linear regressions using permutation testing (100,000 iterations). At each iteration, CDR values were randomly permuted to generate a null distribution of regression slopes under the assumption of no association. Empirical slopes were then compared against this null distribution, and FDR-corrected P values were derived accordingly (Extended Data Fig. 8d).

To evaluate potential collinearity between exposome and demographic or cognitive variables, we grouped each exposome score (top exposome predictors identified by the GAM models) together with age, sex, education, cognition and individual SES, and we computed the variance inflation factor (VIF) for each combination. All VIF values were lower than 1.82 (Supplementary Table 14 and Extended Data Fig. 6), indicating minimal collinearity.

Epidemiological analyses

To assess how exposome and clinical conditions increase the likelihood of accelerated brain aging, we used odds ratios by calculating the exponent of the logistic model coefficients (B):

$$\text{Odds ratio}_n = e^{B_n}$$

We calculated the odds ratios individually for each exposomal predictor and ranked them from highest to lowest. We then selected only those predictors with odds ratio values greater than 2.5 to define the top exposomes within each domain. This cutoff balanced sensitivity and interpretability, given our sample's power to detect small-to-moderate associations. Exposome scores (total, physical and social) were computed as the mean of the top odds ratio predictors identified from the total exposomal factors (Extended Data Fig. 3, right panel). Outliers were limited to 10%.

Structural, functional and combined BAGs were binarized, with values higher than zero indicating accelerated brain aging and lower

than zero indicating delayed aging. Models were run unadjusted and adjusted for clinical conditions (binary variable: healthy controls = 0; AD, FTLN or MCI = 1), demographics (sex and education), both combined and combining demographics and cognition. Analyses were run with both imputed and non-imputed education and cognitive data.

We also tested whether clinical conditions were independently associated with BAGs. These models were run unadjusted and adjusted for exposome burden, demographics or both combined.

Finally, to evaluate the relative explanatory strength of exposome versus clinical conditions, we compared the distributions of odds ratios derived from models using exposome factors as predictors against those using clinical condition as predictors. Independent two-sample t -tests were used to assess whether odds ratio values differed significantly between these model types, with Bonferroni-corrected P values and Cohen's d reported as indices of statistical significance and effect magnitude (Extended Data Fig. 5).

Sensitivity analyses

Sensitivity analyses assessed the robustness of the BAG–exposome associations.

To study the direction and contribution magnitude of key covariates (years of education, sex, cognitive score and country-level GDP) on structural and functional BAGs, we applied XGBoost models with SHAP values⁶⁹. Analyses were rerun after imputation of education and cognitive missing values, yielding consistent results (Extended Data Fig. 7a). These covariates were then incorporated into the LightGBM metaGAM models, alongside the predictions from the exposome-specific GAMs. Before model training, ODQ and scanner identity were regressed out from BAG values using linear regression to control for potential acquisition-related confounds. This procedure allows the model to partition variance among exposomal factors and covariates, akin to traditional covariate adjustment in linear models. Model performance was evaluated using Δ AIC, and confidence intervals were computed via bootstrapping.

Exploratory models were run using harmonized SES data in a subsample with available data. Raw SES indicators (for example, education, income and assets) were transformed into standardized within-dataset z -scores, which were then merged into a single harmonized SES variable (Supplementary Table 44). In all cases, the final SES measure was expressed as a z -score (mean = 0, s.d. = 1) within each dataset, reflecting participants' relative socioeconomic position in their national sample. Participants with available BAGs were retained to include in SHAP-based models (see SES distribution in Supplementary Fig. 2).

To evaluate model sensitivity to age bias correction, we compared Δ AIC distributions between metaGAMs built on age-bias-corrected versus uncorrected BAGs (main results) via two-sided 5,000-iteration permutation testing. The same approach was applied to assess diagnostic specificity by metaGAMs between healthy controls and patients (AD, FTLN and MCI) across exposome (total, physical and social) and BAG modalities (structural, functional and combined).

To confirm that results were not driven by diagnostic composition—and considering the greater availability of healthy participants across datasets—we also retrained and tested the BAG models exclusively in healthy controls. We applied the same statistical pipeline as in the Statistical analysis section.

To enable a clearer assessment of exposome effects within each diagnostic group while controlling for potential demographic confounding, we replicated GAM and metaGAM analyses in matched tandems (Controls-AD, Controls-FTLN and Controls-MCI). Matching was applied separately for structural and functional subsamples using nearest neighbor (1:1) matching based on age, education and sex. Calipers were optimized per diagnostic contrast (Controls-MCI: 0.01 structural / 2.51×10^{-5} functional; Controls-AD: 1×10^{-4} structural / 8×10^{-4} functional; Controls-FTLN: 2.5×10^{-6} structural / 1 functional).

Balanced diagnostic groups were evaluated using standardized mean differences (all <0.15, confirming adequate matching). Pre-matching and post-matching covariate balance was assessed using standardized mean differences⁷² and confirmed via ANOVAs and two-sided Tukey post hoc pairwise comparisons for education and age and Pearson's χ^2 test for sex. Effects sizes were calculated as η^2 .

To evaluate the potential influence of scanner-related bias, we applied multinomial logistic regression models using scanner identity as the dependent variable and BAG scores as predictors. Prior to modeling, BAG scores were z-scored to facilitate coefficient interpretation. L2-regularized ridge models ($\alpha = 1.0$) were used to prevent overfitting due to the large number of scanners. The overall significance of each model was evaluated using likelihood ratio tests. Separate models were run for structural and functional BAGs. We also tested linear regressions between ODQ and BAG scores, with statistical significance estimated through 10,000-iteration permutation testing. BAG values were randomly permuted to generate a null distribution of regression slopes for FDR P value calculation.

BAG models were rerun separately for functional rsfMRI and rsM/EEG datasets and stratified by sex. For both analyses, the same statistical pipeline was applied as in the Statistical analysis section. Sex-stratified models were run on matched subsamples to test whether top 10 exposome effects differed by sex. Matching was conducted using 1:1 nearest neighbor propensity score matching including age as covariate (caliper = 0.0205 for structural data and caliper = 0.055 for functional data). Balance was assessed using standardized mean differences, all <0.04, confirming adequate matching. We also examined whether gender-related exposome effects differed between matched males and females by performing separate iterative correlations between BAGs and gender inequality indicators (gender inequality index and gender inequality (the inverse of gender equality, rights and democracy)). Between-group differences were tested using non-parametric comparisons of r value distributions across sexes.

To test BAG generalizability, we ran an external cross-validation with out-of-sample structural and functional datasets not used during training or main testing analyses (Study design and participants section, Fig. 1a and Supplementary Table 25). Predicted age values were compared against chronological age. Distributional similarity between in-sample and out-of-sample BAG predictions was assessed by comparing the normalized two-dimensional histogram overlap for structural and functional models. Empirical P values were generated using randomization testing. In functional models, Gaussian mixture models⁷³ were used for data augmentation, followed by standardization to improve distributional alignment with the training sample.

To provide an independent validation of our in-sample results, we replicated GAMs and metaGAMs in out-of-sample datasets, applying the same statistical pipeline as in the Statistical analysis section.

To assess cognitive overlap between healthy controls and MCI groups, we ran an ANCOVA on the in-sample dataset including diagnosis, education (mean-centered) and their interaction. Type III sums of squares and η^2 quantified effects and estimated marginal means (emmeans in R) were compared at the 25th, 50th and 75th education percentiles to visualize education-adjusted Controls-MCI differences (Supplementary Fig. 1).

For longitudinal analyses, we leveraged a subsample of participants ($n = 1,578$) with repeated assessments (t_0 and t_1) in structural (MRI T1; $n = 1,078$), functional (rsfMRI, rsEEG, rsMEG; $n = 974$) and combined ($n = 638$) modalities and cognitive assessments ($n = 1,192$) (Supplementary Tables 45 and 46). The longitudinal subsample included 11 countries (Australia, Brazil, Chile, Colombia, Egypt, India, Italy, Singapore, Spain, Türkiye and the United States). For brain structural and functional data, we computed BAGs at t_1 following the same pipeline as in main analyses and derived a longitudinal rate of change (Δ BAG)⁷⁴ using a standardized slope formulation:

$$\Delta\text{BAG} = 12 \times \frac{\text{BAG}_{t_1} - \text{BAG}_{t_0}}{T}$$

where T denotes the interval between acquisitions (in months).

We then applied the same formulation for cognition (Δ Cognition) using the composite cognitive scores:

$$\Delta\text{Cognition} = 12 \times \frac{\text{Cognitive score}_{t_1} - \text{Cognitive score}_{t_0}}{T}$$

Following the same pipeline as the main analyses (Statistical analysis section), nonlinear associations between 73 exposomal factors (t_0) and Δ BAG structural, Δ BAG functional, Δ BAG combined and Δ Cognition were assessed using GAMs. We then aggregated the 73 GAM-derived outputs into a second-level ensemble model (metaGAM). Analyses were stratified into (1) all samples and (2) healthy controls.

We assessed the temporal stability of exposome indicators over the study period (2000–2025) using country-level year-to-year (lag-1) correlations. For each variable, we computed Pearson's correlation coefficients between values at year t and year $t + 1$ within each country, restricting analyses to series with at least two consecutive data points. Correlation coefficients were then summarized across countries to obtain the median, interquartile range and the proportion of countries showing $r \geq 0.8$ for each indicator. This approach allowed us to quantify short-term temporal consistency and identify potential sources of interannual variability (Supplementary Table 31).

To address the multiple comparisons problem, we employed permutation tests with 5,000 iterations and applied Benjamini–Hochberg FDR correction to P values within models. The permutation procedure randomly reassigned group labels while preserving the original sample sizes, generating an empirical null distribution against which our observed test statistics were compared. This method effectively controlled the familywise error rate across all comparisons.

Software and tools

Analyses were conducted in MATLAB (version R2022a), Python (version 3.8) and R (version 4.4.2). Specific packages included the following: for imaging preprocessing: CAT12 (version 2.9), CONN toolbox (version 22), fMRIprep toolbox (version 22.0.2), MRIQC software (version 24.1.0) and Nilearn library (version 0.10.0); for machine learning: scikit-learn (version 1.5.1) and XGBoost (version 2.1.3); for statistical analysis: numpy (version 1.26.4), pandas (version 2.2.2), scipy (version 1.11.4), readxl (version 1.4.3), dplyr (version 1.1.4) and MatchIt (version 4.6.0); and for visualization: circlize (version 0.4.16), geopandas (version 1.0.1), matplotlib (versions 3.7.5 and 3.10.0), MRICron (version 1.0.20201102) and seaborn (version 0.13.2).

Ethical approval

The local institutions that contributed MRI T1, rsfMRI and/or rsM/EEG data to this study approved the acquisitions and protocols with informed consent from participants in accordance with the Declaration of Helsinki (Supplementary Table 33). The overall study was approved by the ReDLat consortium under multiple institutional review boards (FWA00028264, FWA00001035, FWA00028864, FWA00001113, FWA00010121, FWA000014416, FWA00008475, FWA00029236, FWA00029089 and FWA00000068). Data collection and analysis posed no risks concerning stigmatization, incrimination, discrimination, animal welfare, environmental, health, safety, security or personal concerns. No transfer of biological materials, cultural artifacts or traditional knowledge occurred.

Ethics and inclusion statement

Researchers from multiple countries and sites collaborated on this study and are listed as co-authors based on their specific contributions. Researchers from low/middle-income countries (LMICs) actively

participated in study design, implementation, methodological procedures and reviewing processes. The research holds substantial local relevance, particularly given the pronounced disparities observed in Africa, Latin America and other regions. Roles and responsibilities were predefined and agreed upon by all collaborators. Ethical approval was obtained for all datasets involving brain data (details in Supplementary Table 33). To safeguard privacy and prevent any potential stigmatization, all identifying information has been removed. We fully support Nature Portfolio journal guidelines on LMIC authorship and inclusion. Authorship was determined based on intellectual contributions, commitment and active involvement in the study, ensuring the inclusion of researchers born in LMICs and other underrepresented regions.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Preprocessed BAGs and exposome values are provided online (<https://osf.io/yagdh>). The brain datasets used in this study are available from different sources (Supplementary Table 35). The MRI T1, rsfMRI and rsM/EEG datasets comprise sources: (1) currently publicly available for direct download after registration, (2) available after contacting the researcher or (3) accessible after institutional review board approval of formal data-sharing agreement in a process that can last up to 12 weeks, depending on the nature of the request and compliance with institutional guidelines. The exposome datasets come from sources that are either publicly available for direct download or accessible upon reasonable request (Supplementary Tables 1 and 2). Individual-level neuroimaging and clinical data are not publicly shared due to ethical and institutional restrictions imposed by the original data providers. External requests for individual-level data must be directed to the corresponding data-owning institutions listed in Supplementary Table 35 and will be evaluated according to their local governance, institutional review board requirements and data-sharing policies; response times typically range from 4 weeks to 12 weeks.

Code availability

Preprocessing and analysis codes are freely available on the Open Science Foundation repository: <https://osf.io/yagdh>. A README file has been added to the repository, which includes (1) a project overview, (2) data description and input/output formats, (3) setup and dependencies, (4) step-by-step instructions for running preprocessing and analysis scripts, (5) workflow for reproducing figures and tables and (6) directory structure with script functions.

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Author contributions

A.I., A.L., S.M. and H.H. were responsible for conceptualization, formal analysis and writing the original draft. All authors contributed to review and editing. A.L., S.M., H.H., P.B., J.C. and S.D.G. had access to the raw data. All authors had access to all preprocessed data in the study, and the corresponding authors had final responsibility for the decision to submit for publication.

Competing interests

All authors declare no competing interests.

Additional information

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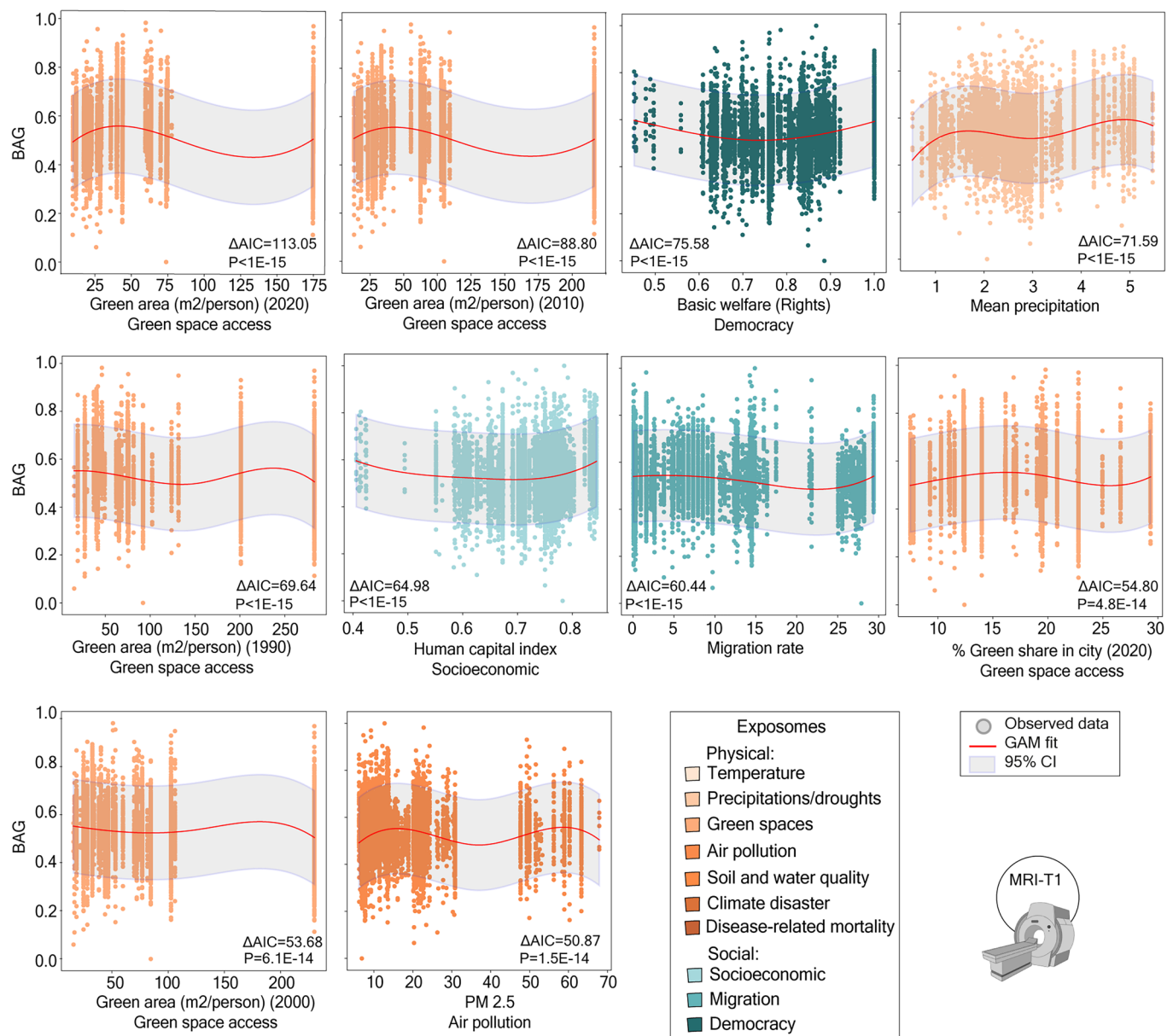
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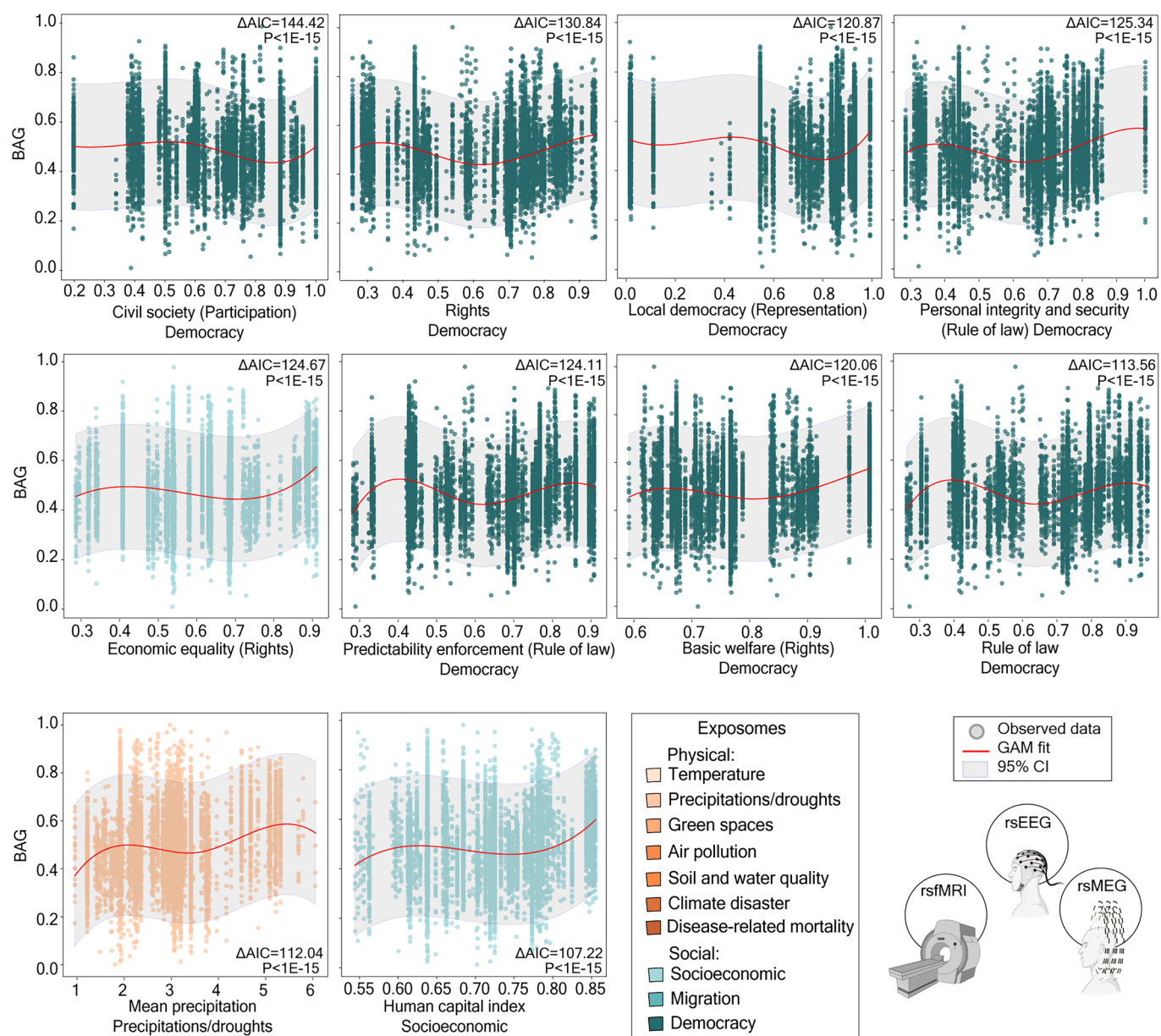
a. Total exposomes: structural BAGs individual GAMs



Extended Data Fig. 1 | Individual GAMs for structural BAGs – total exposome.
a. Scatterplots show top-ten individual model GAMs between each exposomal factor and structural BAGs. Solid red lines represent the mean GAM fit; shaded bands indicate 95% confidence intervals. P-values reflect the significance of GAM

predictive accuracy, assessed via two-sided t-test on the prediction-observation slope in held-out data. All models are FDR $P < 0.001$. Scatter plots were generated in Python using Matplotlib. Created in BioRender; Migeot, J. (2026) <https://biorender.com/y73zai8> (MRI device). Related to Fig. 2.

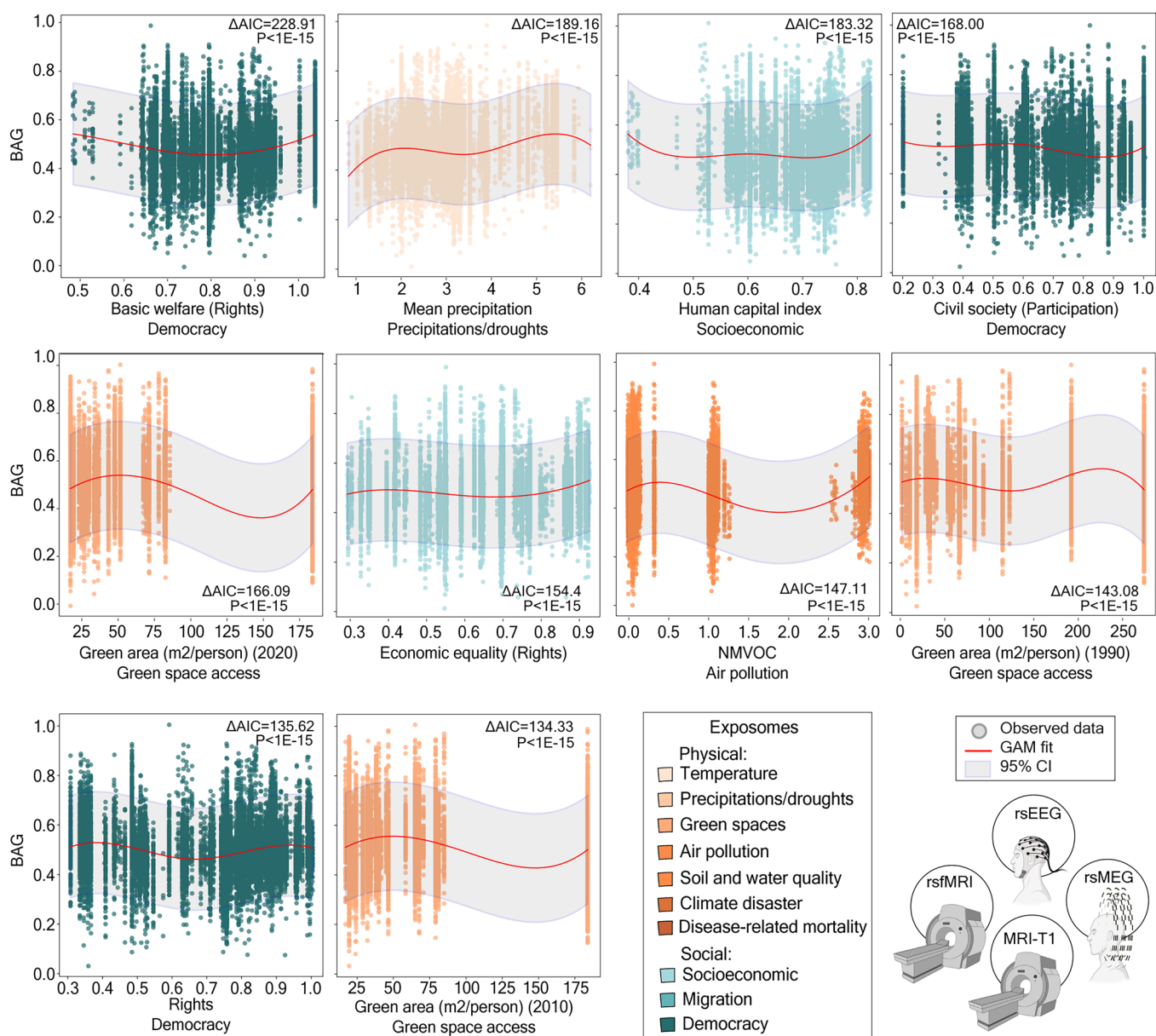
a. Total exposomes: functional BAGs individual GAMs



Extended Data Fig. 2 | Individual GAMs for functional BAGs – total exposome.
a. Scatterplots show top-ten individual model GAMs between each exposomal factor and functional BAGs. Solid red lines represent the mean GAM fit; shaded bands indicate 95% confidence intervals. P-values reflect the significance of GAM

predictive accuracy, assessed via two-sided t-test on the prediction-observation slope in held-out data. All models are FDR $P < 0.001$. Scatter plots were generated in Python using Matplotlib. Created in BioRender; Migeot, J. (2026) <https://biorender.com/rxp5lws> (MRI and EEG device). Related to Fig. 2.

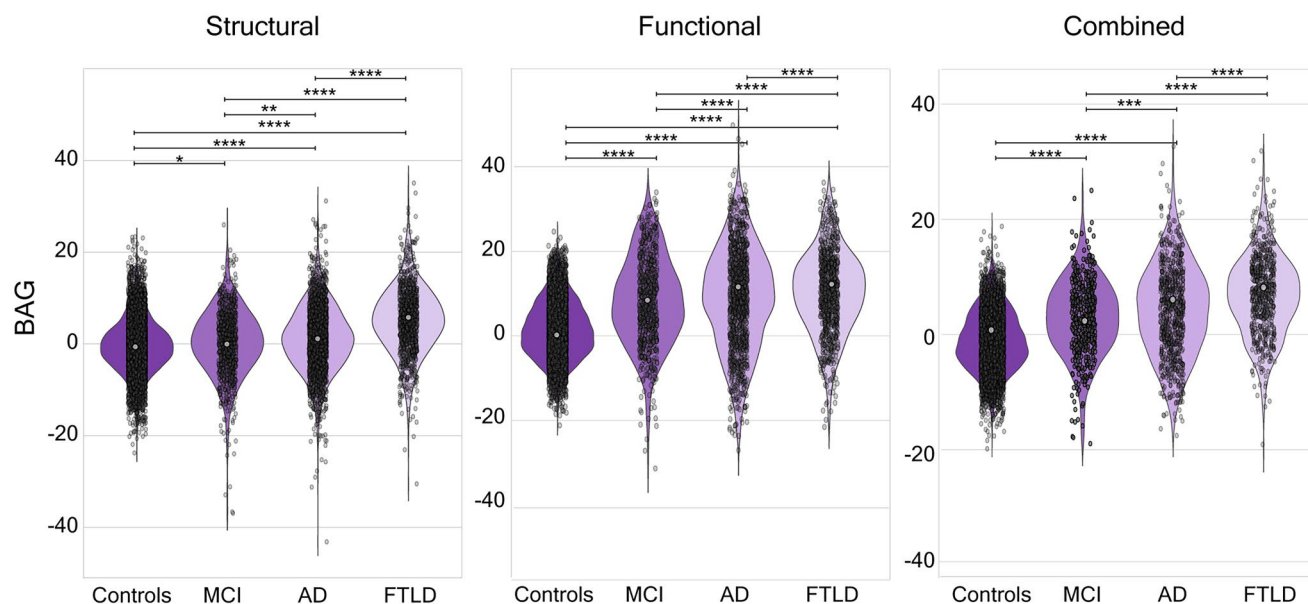
a. Total exposomes: combined BAGs individual GAMs



Extended Data Fig. 3 | Individual GAMs for combined BAGs – total exposome.
a. Scatterplots show top-ten individual model GAMs between each exposomal factor and combined BAGs. Solid red lines represent the mean GAM fit; shaded bands indicate 95% confidence intervals. P-values reflect the significance of GAM

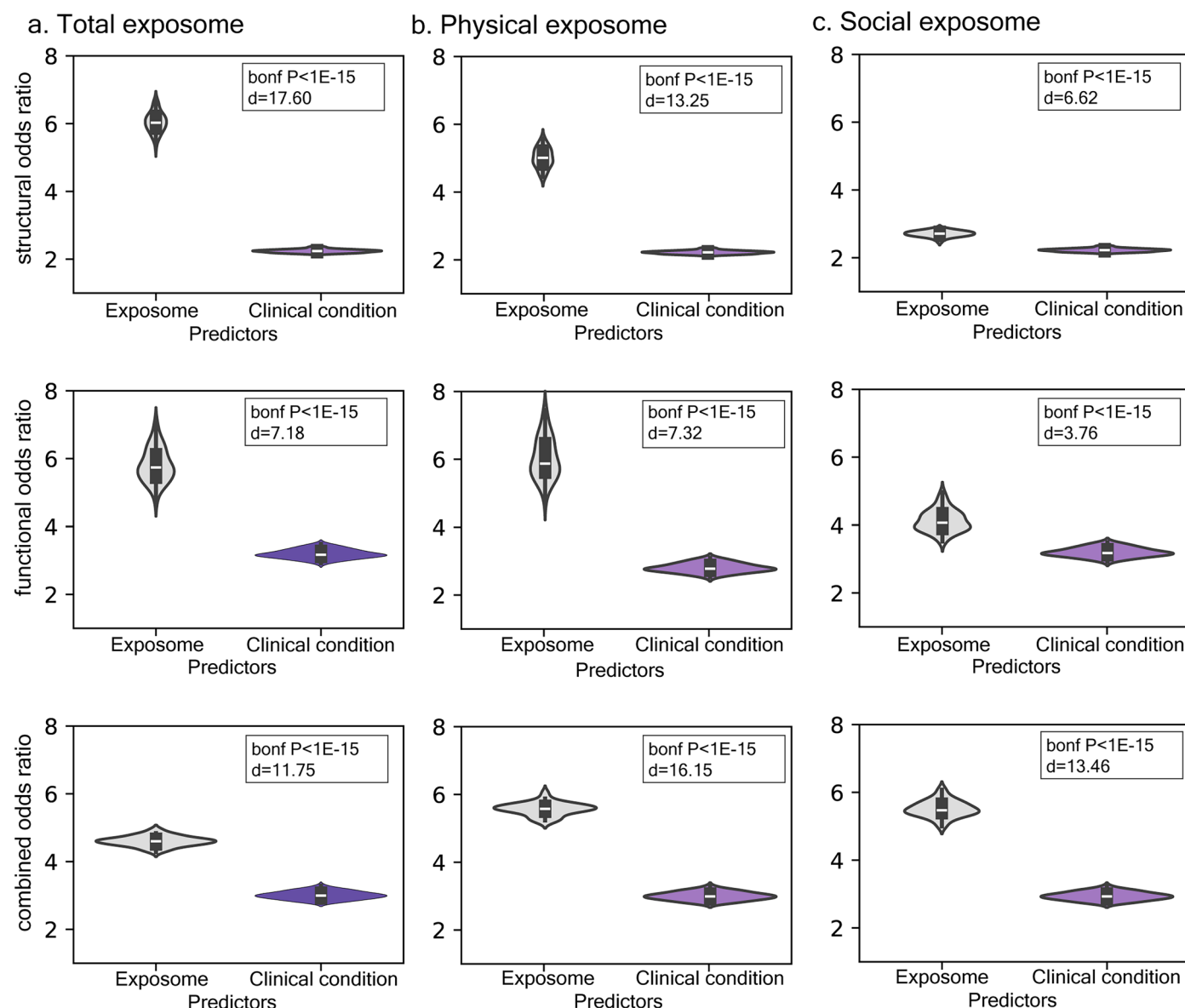
predictive accuracy, assessed via two-sided t-test on the prediction-observation slope in held-out data. All models are FDR $P < 0.001$. Scatter plots were generated in Python using Matplotlib. Created in BioRender; Migeot, J. (2026) <https://biorender.com/rskoaw4> (MRI and EEG device). Related to Fig. 2.

a. BAGs across groups



Extended Data Fig. 4 | BAGs differences between groups. a. Violin plots for the distribution of prediction gaps by group. Statistical comparisons were calculated using two-sided subsample permutation testing without multiple comparisons, and with 5,000 algorithm iterations and FDR corrected P values. White dots

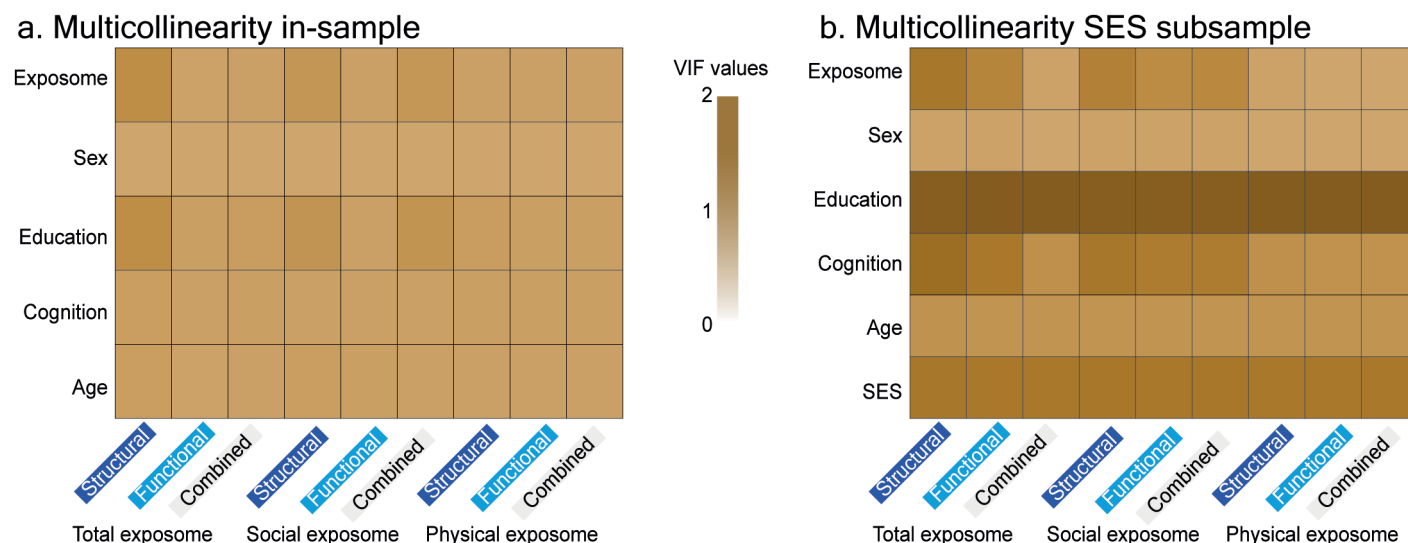
indicate mean values. Expected significant differences between groups were observed for structural, functional and combined BAGs (healthy controls > MCI > AD > FTLD). **** FDR $P < 1E-15$; *** FDR $P = 9E-04$; ** FDR $P = 0.002$; * FDR $P = 0.013$. Related to Fig. 2.



Extended Data Fig. 5 | Exposome vs clinical condition: odds ratios comparison.

a. Violin plots show the distribution of odds ratios obtained from logistic models using either exposome factors (gray) or clinical condition (purple) as predictors of accelerated aging (binary outcome: accelerated vs. delayed). Panels depict results for **(a)** total, **(b)** physical, and **(c)** social exposomes across structural, functional, and combined modalities ($n = 100$ per combination). Across all domains, exposome-based models yielded significantly higher odds ratios

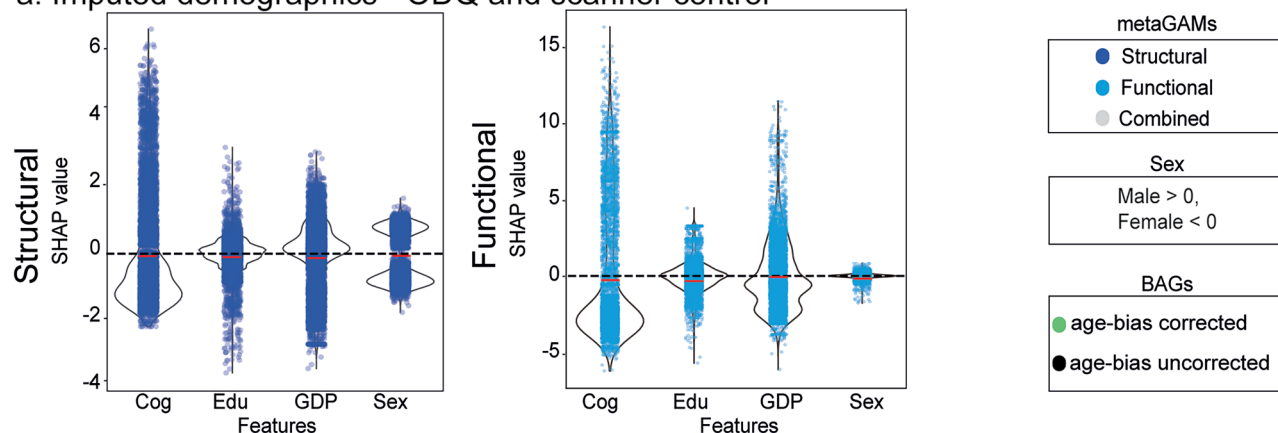
than clinical-condition-based models (two-sided permutation tests; 5,000 permutations; Bonf $P < 1E-15$; Cohen's $d = 3.76-17.6$), indicating that exposomal burden exerts a stronger and more consistent influence on the likelihood of accelerated brain aging. Box centers represent median values; white lines denote means; box limits indicate interquartile ranges (Q1–Q3), and whiskers represent minimum and maximum observed values. Related to Fig. 3.



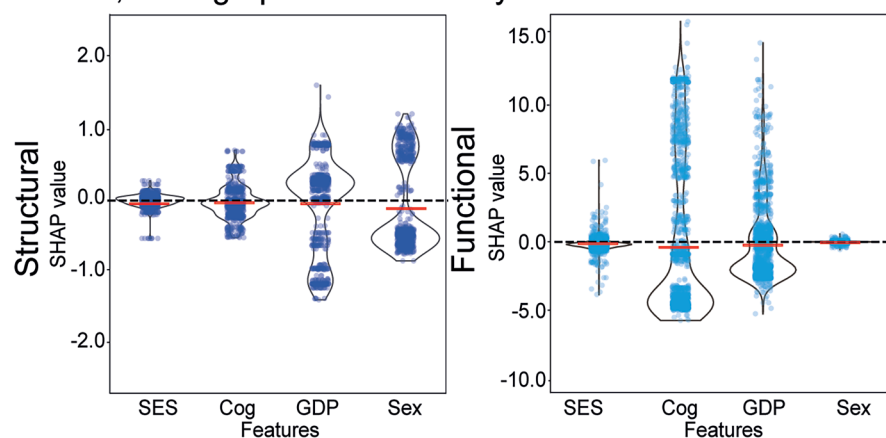
Extended Data Fig. 6 | Variance inflation factors for exposome and demographic/cognitive variables. Variance inflation factor (VIF) values assessing multicollinearity among covariates in **(a)** the in-sample dataset and **(b)** the SES subsample. Each panel displays VIFs for exposome indices (total, social, and

physical) across structural, functional, and combined brain age gap models. Variables include exposome, sex, years of education, cognitive score, age, and individual socioeconomic status (SES; in panel b only). All VIF values were below 1.82, confirming minimal multicollinearity among predictors. Related to Fig. 3.

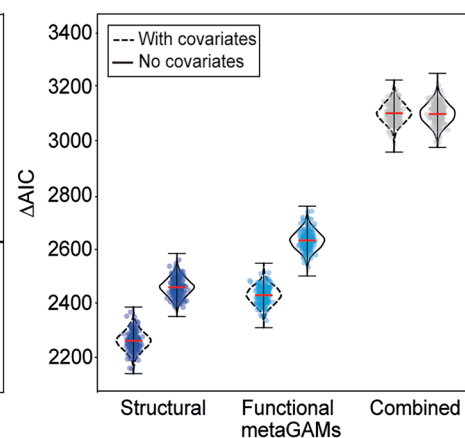
a. Imputed demographics - ODQ and scanner control



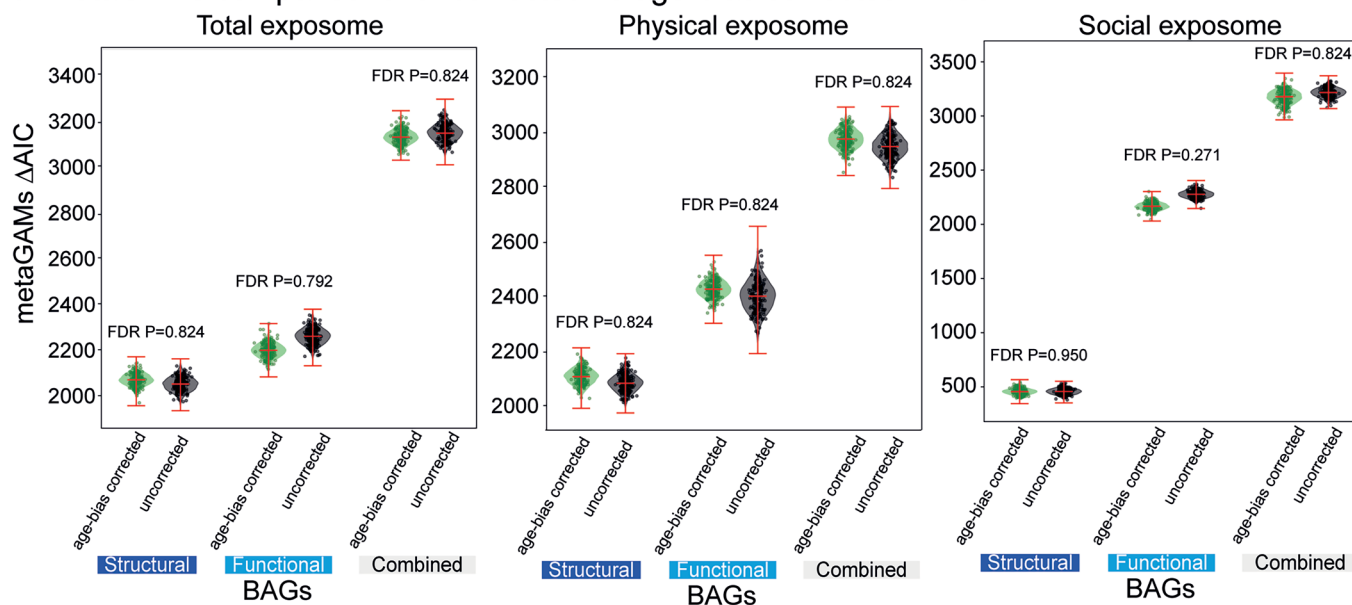
b. SES, demographics and country-level GDP



c. MetaGAMs covariation SES



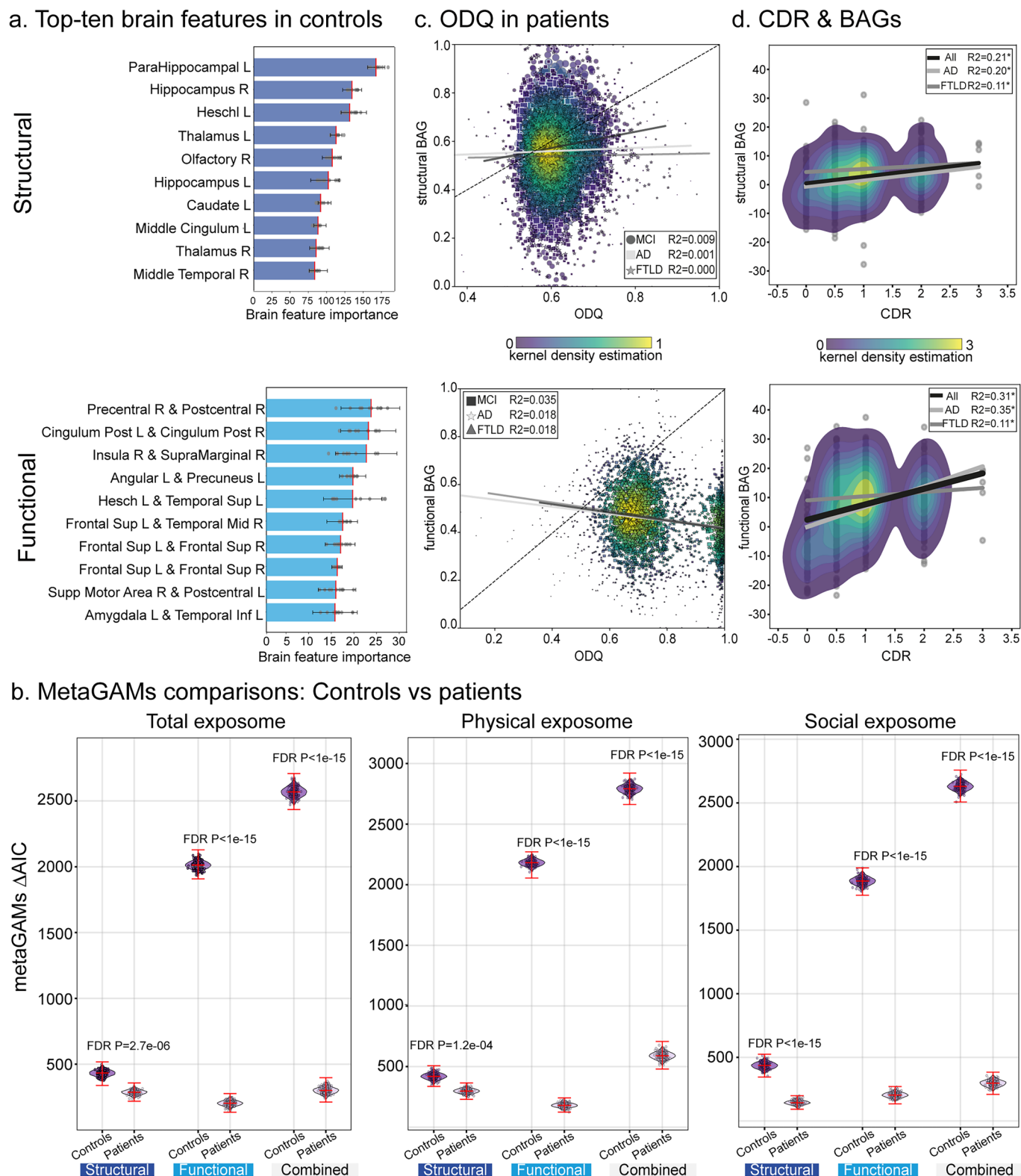
d. MetaGAMs comparisons: uncorrected vs age-bias corrected BAGs



Extended Data Fig. 7 | See next page for caption.

Extended Data Fig. 7 | Sensitivity analyses: Robustness across individual variables and methodological adjustments. (a) SHAP results with imputed education and cognition. SHAP sensitivity analyses were re-run with imputed values for education (16.4% imputed) and cognition (36.7% imputed). GDP data were complete except for Cuba (see missingness details per modality in Supplementary Table 42 and handling strategy and summary Supplementary Table 43). Results remained consistent with non-imputed analyses. (b) Participant demographics and country level GDP effects. Individual SES effects on brain clocks were tested with XGBoost models, including other individual (sex and cognition) and aggregate (country-level GDP) variables. Lower SES was associated with worse outcomes, along with lower cognitive scores, and female sex (T1 model), and lower GDP and cognitive scores (functional model). Shapley additive explanations (SHAP) values indicate the direction and magnitude of each feature's contribution. Violin plots show SHAP

distributions; dots represent participants. (c) MetaGAMs covariation. The effects of total exposome metaGAMs on accelerated brain aging in the subsample with SES remained after controlling for covariates. Violin plots show bootstrapped effect sizes; dots are samples ($n = 5,000$), red lines are the mean ΔAIC , black lines indicate 95% confidence intervals. (d) DeltaAIC differences between metaGAMs derived from uncorrected and age-bias corrected BAGs. Violin plots showing the distribution of bootstrap metaGAM ΔAIC values ($n = 5,000$) by BAG condition in the total sample. Statistical comparisons were calculated using two-sided subsample permutation testing without multiple comparisons, and with 5,000 iterations and FDR P values. Data are presented as mean ΔAIC values $\pm$ 95% confidence intervals (red lines). No significant differences between BAG conditions were observed for structural, functional and combined BAGs across total, physical and social exposomes (all FDR P > 0.001), supporting the stability of exposome-related findings regardless of age-bias correction. Related to Fig. 2.

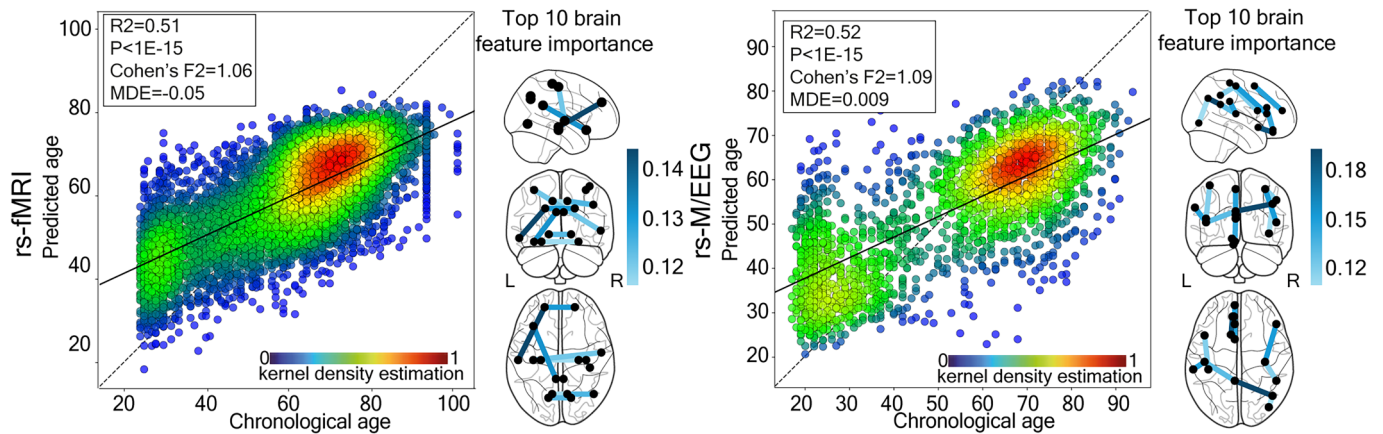


Extended Data Fig. 8 | See next page for caption.

Extended Data Fig. 8 | Sensitivity analyses: Robustness across health, disease, and imaging quality. (a) Brain features in healthy controls BAG models. Top-ten brain areas contributing to healthy controls BAGs in structural ($n = 7,627$, $R^2 = 0.75$, $F^2 = 2.94$, $MDE = 0.02$) and functional ($n = 6,692$, $R^2 = 0.41$, $F^2 = 0.69$, $MDE = -0.04$; all $P < 0.001$) models. Feature importance was derived from SHAP (Shapley additive explanations). Data are presented as mean SHAP values (red line) with 95% confidence intervals (black error lines), derived across $n = 10$ outer fold samples (dots). (b) DeltaAIC differences between controls and patients metaGAMs. Violin plots showing the distribution of bootstrap metaGAM's ΔAIC by subsample. Statistical comparisons were calculated using two-sided subsample permutation testing without multiple comparisons and with 5,000 algorithm iterations and FDR P values. Expected significant differences between subsamples were observed for structural, functional and combined BAGs

(Healthy controls > patients) across total, physical and social exposomes (all $FDR P < 0.001$). (c) ODQ in clinical conditions. Association between ODQ and BAGs in structural and functional models. Linear regressions used permutation testing (10,000 repetitions) to assess significance. BAG values were randomly permuted to generate a null distribution of regression slopes for FDR P value calculations. No significant associations were found. (d) Disease severity and BAGs in patients with dementia. Linear regressions using permutation testing (100,000 iterations) were run to target the association between CDR scores and structural and functional BAG values across patients. Each line denotes the fitted linear trend within patient subgroups (AD, FTLD) and all patients together. In both modalities, higher CDR scores were associated with increased BAGs across conditions. Kernel density contours indicate the distribution of BAG values across the CDR spectrum. * indicates $P FDR < 0.001$. Related to Fig. 2 and Fig. 4.

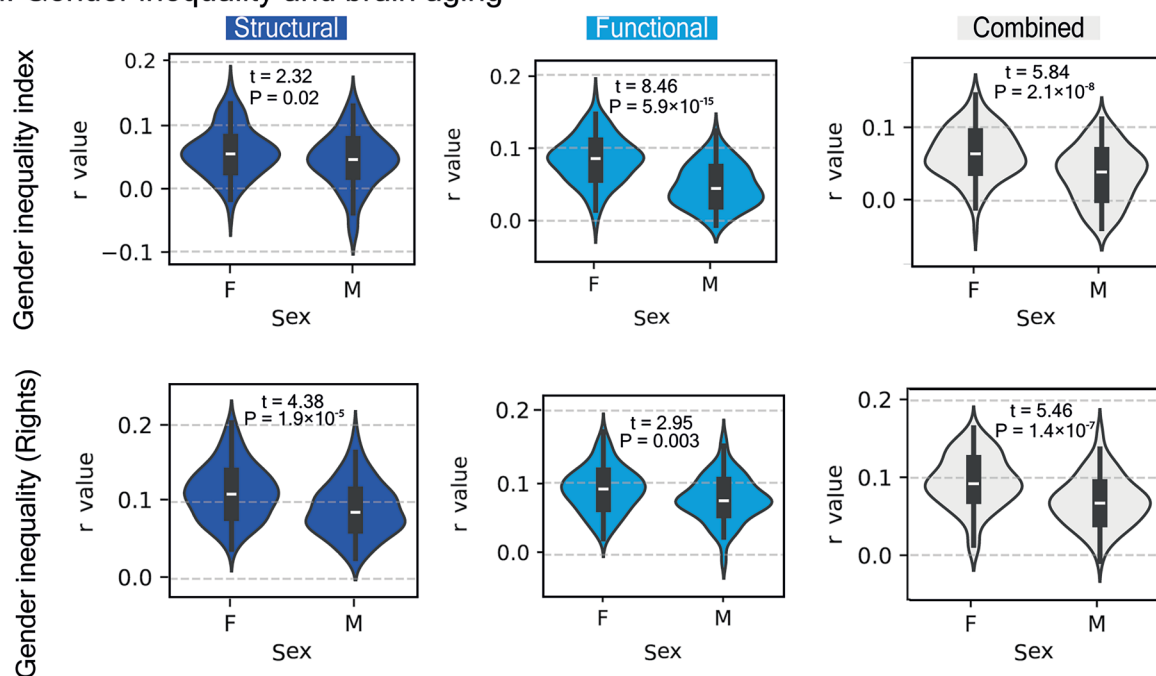
a. BAGs & fMRI - M/EEG brain features



Extended Data Fig. 9 | Separate BAGs for rsfMRI and rsM/EEG. a. Scatterplots show model accuracy for predicted brain age versus chronological age using functional rsfMRI (left panel) and functional rsEEG/MEG (right panel) in-sample data. Brain plots indicate the top-10 most important brain features ranked by

Shapley additive explanations (SHAP) values for each model. Reported P-values ($P<1E-15$) are two-sided and derived from a t-test on the regression slope coefficient; no adjustments for multiple comparisons were applied. Related to Fig. 2.

a. Gender inequality and brain aging



Extended Data Fig. 10 | Sex-specific associations between gender inequality and brain aging. a, Violin plots display the distribution of correlation coefficients (r values) between brain age gaps (BAGs) and gender inequality measures (gender inequality index and inverse gender equality (rights)) computed separately for females and males. Each panel represents the correlation pattern across structural, functional, and combined BAGs.

Sex differences were assessed using two-sided t-tests on correlation coefficients ($n = 100$ per sex), without adjustment for multiple comparisons. Statistical tests (shown above each plot) indicate significantly stronger positive associations in females (all $P < 0.01$), suggesting that higher gender inequality is more tightly linked to accelerated brain aging in women than in men. Related to Fig. 2.

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- | | |
|-------------------------------------|--|
| n/a | Confirmed |
| ☐ | ☒ The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ A description of all covariates tested |
| ☐ | ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☐ | ☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	The sample comprised 18,701 participants across 34 countries and six continents, including healthy controls, participants diagnosed with probable Alzheimer’s disease, participants who fulfilled criteria for frontotemporal lobar degeneration (FTLD), and participants that met the Petersen criteria for mild cognitive impairment (MCI). MRI, fMRI, and M/EEG data collection and diagnostics followed standardized procedures. All datasets adhered to the Declaration of Helsinki, with informed consent and IRBs ethics approvals. The exposome datasets come from sources that are either publicly available for direct download or accessible upon request.
Data analysis	Analyses were conducted in MATLAB (vR2022a), Python (v3.8) and R (v4.4.2). Specific packages included: Imaging preprocessing: CAT12 (v2.9), CONN toolbox (v22), fMRIPrep toolbox (v22.0.2), MRIQC software (v24.1.0), Nilearn library (v0.10.0), Machine learning: scikit-learn (v1.5.1), XGBoost (v2.1.3). Statistical analysis: numpy (v1.26.4), pandas (v2.2.2), scipy (v1.11.4), readxl (v1.4.3), dplyr (v.1.1.4), MatchIt (v4.6.0). Visualization: circlize (v0.4.16), geopandas (v1.0.1), matplotlib (v3.7.5, v3.10.0), MRICron (V1.0.20201102), and seaborn (v0.13.2).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Preprocessed BAGs and exposome values are provided online (<https://osf.io/yagdh>). The brain datasets used in this study are available from different sources (Supplementary Tables). The MRI-T1, rsfMRI, rsM/EEG datasets comprise sources: (1) currently publicly available for direct download after registration, (2) available after contacting the researcher or (3) accessible after IRB approval of formal data-sharing agreement in a process that can last up to 12 weeks, depending on the nature of the request and compliance with institutional guidelines. The exposome datasets come from sources that are either publicly available for direct download or accessible upon request (Supplementary Table 1 and Supplementary Table 2).

Preprocessing and analysis codes with their associated README files are freely available on Open Science Foundation repository: <https://osf.io/yagdh>.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender

We considered female sex as a risk factor for accelerated aging and included sex-stratified analyses. All methods adhered to the Declaration of Helsinki, with informed consent and ethics approvals. We included 18,701 participants (57.81% females).

Reporting on race, ethnicity, or other socially relevant groupings

We did not use any socially relevant or socially constructed categorization.

Population characteristics

This study included 18,701 participants (Table 1). Main analyses were run with an in-sample dataset. An external cross-validation was run with an independent out-of-sample dataset. The in-sample dataset comprised 14,170 participants (12,120 with MRI-T1, 7,021 with rsfMRI and 2,594 with rsM/EEG). Of these, 9,197 were healthy controls (HC), 2,705 were diagnosed with probable Alzheimer's disease (AD), 1,176 fulfilled criteria for frontotemporal lobar degeneration (FTLD), and 1,132 met the Petersen criteria for mild cognitive impairment (MCI) (Supplementary Table 32). The out-of-sample dataset comprised 4,531 subjects (4,275 with MRI-T1, 3,842 with functional data) including 3,693 HC, 368 AD, 72 FTLD and 398 MCI (Supplementary Table 25). Out-of-sample datasets were allocated based on their later availability in the data collection timeline. Detailed data about diagnostic status, country of residence, year of brain data acquisition (range: 2000-2025) were acquired for each participant. Demographic and cognitive data (Table 1) were obtained for each participant when available, including age (M=54.3, SD=21.68, range: 17-100 comparable or larger to other brain age studies in aging), sex (57.81% female, 42.19% male), years of education (M=13.16, SD=4.54) which included total formal schooling across all levels (primary, secondary, high school, and post-secondary/tertiary education), and a general cognitive score (0-100) derived from harmonized scores between the Addenbrooke's Cognitive Examination III (ACE-III), the Mini-Mental State Examination (MMSE), or the Montreal Cognitive Assessment (MoCA) scales. MMSE and MoCA scores were re-scaled from 0-30 to 0-100, and then all three scales averaged to create a single cognitive score per participant. Sex information was determined by self-report. Individual-level socioeconomic status (SES) measures were available in a subsample (n = 2,931; see distribution across datasets in Supplementary Figure 2). No information regarding gender was inquired. All datasets adhered to the Declaration of Helsinki, with informed consent and IRBs ethics approvals.

Recruitment

MRI, fMRI, and M/EEG data collection and diagnostics followed standardized procedures. All datasets adhered to the Declaration of Helsinki, with informed consent and IRBs ethics approvals. The exposome datasets come from sources that are either publicly available for direct download or accessible upon request.

Ethics oversight

The local institutions that contributed MRI-T1, rsfMRI and/or rsM/EEG data to this study approved the acquisitions and protocols with informed consent from participants in accordance with the Declaration of Helsinki (Supplementary Table 33). The overall study was approved by the ReDLat consortium under multiple Institutional Review Boards (FWA00028264, FWA00001035, FWA00028864, FWA00001113, FWA00010121, FWAA00014416, FWA00008475, FWA00029236, FWA00029089, and FWA00000068). Data collection and analysis posed no risks concerning stigmatization, incrimination, discrimination, animal welfare, environmental, health, safety, security or personal concerns. No transfer of biological materials, cultural artifacts or traditional knowledge occurred.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No a priori sample size calculation was performed, as the study was exploratory and multivariate in nature, employing machine learning (LightGBM) and generalized additive models (GAMs/metaGAMs) to analyze associations between brain age gaps (BAGs) and multidimensional exposome factors. Instead, we leveraged the largest available dataset from the global collaborating initiatives, totaling 18,701 individuals from 34 countries. The large sample size enabled robust estimation of brain age models and enhanced generalizability across geographic regions. The adequacy of sample size was empirically validated through nested bootstrap-based cross-validation, meta-modeling, and consistent performance across multiple diagnostic and regional subgroups.
Data exclusions	No data was excluded
Replication	We reported R^2 , Mean Directional Error (MDE), Cohen's f^2 measured effect sizes, and Shapley additive explanations (SHAP) was used to evaluate ROI-level feature importance. For statistical analyses, we reported the corresponding statistic, fdr-corrected p-values, and effect sizes. Nonlinear associations between exposomal factors and brain age gaps were assessed using generalized additive models (GAMs), which modelled each predictor separately and were benchmarked against null models (an intercept-only regression that predicts all observations using the sample mean) using the Akaike information criterion (AIC). To capture joint effects of all the exposomal factors, we aggregate their GAM-derived outputs into second-level meta-analytic models (metaGAMs) using gradient-boosted algorithms coping with complex nonlinear interactions. GAMs and metaGAM model performance was compared using the delta AIC (ΔAIC) values (relative fit of each model against a null model; higher values indicate better performance). For epidemiological metrics, we reported Odds ratios. For sensitivity analyses, we calculated a longitudinal brain aging and cognitive rate of change (deltaBAG and deltaCognition) in a longitudinal subsample (n = 1,578) to then run GAMs and metaGAMs analyses.
Randomization	This is a primarily observational, cross-sectional, quantitative study designed to examine the exposome impact in brain aging across samples. Therefore, samples allocation was not random. Randomization was not applicable. They were grouped by country ; and by diagnosis (healthy controls, frontotemporal lobe degeneration, Alzheimer's disease, mild cognitive impairment).
Blinding	Blinding was not necessary for this study because it used pre-existing data from neuroimaging repositories and centers, and physical and social exposomal factor's datasets, with no direct participant interaction or potential for intervention bias.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a

Magnetic resonance imaging

Experimental design

Design type	structural, resting-state fMRI, EEG or MEG
Design specifications	one MRI/fMRI/EEG/MEG session per subject
Behavioral performance measures	n/a; active fMRI or M/EEG tasks were not used in this study.

Acquisition

Imaging type(s)	Structural 3D-T1 weighted for MRI, and resting-state sequences for fMRI and M/EEG
Field strength	1.5 and 3 tesla
Sequence & imaging parameters	Multiple scanners were involved. Sequence & imaging parameters were reported in Supplementary information (Supplementary Table 30, Supplementary Table 32, Supplementary Table 34)
Area of acquisition	whole-brain scans
Diffusion MRI	☐ Used ☒ Not used

Preprocessing

Preprocessing software	Preprocessing standard and harmonized pipelines were consistently applied across datasets. MRI-T1 preprocessing followed standard voxel-based morphometry CAT12 toolbox (v2.9, https://neuro-jena.github.io/cat/) pipelines in Matlab R2022a. RsfMRI preprocessing was conducted using the fMRIPrep toolbox (v22.0.2, https://fmriprep.org/). CONN22 toolbox was used for additional steps. To reduce dimensionality, time series were extracted with Nilearn library (v0.10.0) in Python (v3.8, Python Software Foundation) based on the AAL116 atlas rsEEG and rsMEG preprocessing used a convergent pipeline as done previously for brain age estimations. For both modalities, source localization was performed using standardized Low-Resolution Electromagnetic Tomography (sLORETA) to estimate current densities from five/minute preprocessed data at predefined virtual sensors located in a reference brain (MNI 305, Brain Imaging Centre, Montreal Neurological Institute).
Normalization	All neuroimaging data were normalized or standardized using modality-specific procedures. For structural MRI (T1), non-linear spatial normalization to MNI space (1.5 mm isotropic resolution) was conducted using the CAT12 toolbox, based on tissue segmentation and deformation field application. Gray matter volumes were extracted from 116 AAL-defined ROIs and normalized by total intracranial volume. Resting-state fMRI data were normalized to MNI152 space using fMRIPrep (v22.0.2), which applies non-linear transformations via FSL to ensure inter-subject alignment. For resting-state EEG and MEG, source localization was performed using sLORETA, which maps sensor-level data to MNI305 space via a standardized inverse solution. Time series were extracted from 82 AAL90 ROIs and z-scored within each dataset to reduce site-related variability.
Normalization template	Standard MNI152 for MRI and MNI 305 for M/EEG
Noise and artifact removal	We applied modality-specific procedures to remove artifacts and structured noise. For rsfMRI data, preprocessing was performed using fMRIPrep v22.0.2, which includes motion correction, susceptibility distortion correction, skull stripping, spatial normalization, and estimation of confounding signals (e.g., motion parameters, white matter, and CSF signals). Additional denoising steps included linear regression of nuisance variables (white matter, CSF, and realignment parameters), scrubbing of high-motion volumes, and band-pass filtering (0.008–0.09 Hz), implemented via the CONN22 toolbox. For rsEEG and rsMEG data, preprocessing pipelines were harmonized across modalities and optimized for connectivity analyses. Data were filtered (0.5–40 Hz) using an 8th-order zero-phase Butterworth filter and resampled to 512 Hz. Artifact removal targeted ocular, cardiac, and muscular artifacts using Independent Component Analysis (ICA), supported by ICLabel and EyeCatch. Bad channels were replaced using weighted spherical interpolation. EEG was re-referenced to the average and aligned to REST; MEG followed analogous steps.
Volume censoring	We did not use volume censoring.

Statistical modeling & inference

Model type and settings	We used both predictive and inferential multivariate models. Brain age was estimated using LightGBM (gradient-boosted decision trees), trained on 116 gray matter volumes from T1-weighted MRI (AAL116), and functional connectivity matrices from resting-state fMRI (AAL116) and rsEEG/rsMEG (AAL90). A third combined model averaged the structural and functional
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predictions. Model optimization was performed via nested 10-fold cross-validation with grid search for hyperparameters. SHAP values were used to evaluate feature contributions.

Subsequently, generalized additive models (GAMs) were used to examine nonlinear associations between exposomal factors and brain age gaps (BAGs). Model fit was assessed via delta AIC (ΔAIC). To assess joint effects, we implemented metaGAMs based on LightGBM using GAM-derived predictors.

Effect(s) tested

The primary effects tested were the associations between individual exposomal variables (environmental, socioeconomic, and political indicators) and BAGs across structural, functional, and combined modalities. GAMs tested the effect of each exposomal variable independently, modeling nonlinear effects. MetaGAMs tested the cumulative influence of multiple exposomal predictors simultaneously.

We also tested whether exposome burden predicted the likelihood of accelerated brain aging using logistic regression models to estimate odds ratios, adjusted for demographics and clinical condition. Additional comparisons were performed between clinical groups (AD, FTL, MCI, HC) using two-sided permutation tests (5,000 iterations) to assess BAG differences across diagnostic categories.

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s) 116 regions of interest (ROIs) from the Automated Anatomical Labeling (AAL) atlas for MRI; 82 ROIs from the 90-regions AAL atlas for M/EEG.

Statistic type for inference

(See [Eklund et al. 2016](#))

No voxel-wise or cluster-wise inference was performed. All statistical analyses were conducted at the regional level using ROI-based features. Brain features included 116 gray matter volumes from the AAL116 atlas (T1-MRI) and functional connectivity matrices based on AAL116 (fMRI) or AAL90 (M/EEG). For functional connectivity, parcellated time series were used to compute high-order functional interactions across brain regions using the organizational information (Ω or O-info) metric. Inference was based on generalized additive models (GAMs) and metaGAMs to test associations between exposomal predictors and brain age gaps (BAGs). Model comparisons relied on delta AIC (ΔAIC) values.

Correction

To address the multiple comparisons problem, we employed permutation tests with 5,000 iterations and applied Benjamini-Hochberg FDR correction to p-values within models. The permutation procedure randomly reassigned group labels while preserving the original sample sizes, generating an empirical null distribution against which our observed test statistics were compared. This method effectively controlled the family-wise error rate across all comparisons.

Models & analysis

n/a | Involved in the study

- ☐ ☒ Functional and/or effective connectivity
☒ ☐ Graph analysis
☐ ☒ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

We computed high-order functional interactions from parcellated resting-state time series using the organizational information (Ω or O-info) metric—a multivariate extension of mutual information. Functional connectivity between regions were the features used to calculate functional brain clock models later.

Multivariate modeling and predictive analysis

We trained LightGBM (gradient boosting) brain clock models to predict chronological age from structural (gray matter volumes) and functional features (O-info-based high-order connectivity values). A third combined model averaged predictions from both modalities. Data were harmonized across sites and normalized using a min-max scaler. Model performance was optimized using nested 10-fold cross-validation with grid search for hyperparameters (learning rate, max depth, number of estimators), and evaluated using R^2 , mean deviation error, Cohen's f^2 , and permutation testing (5,000 iterations). ROI-feature relevance was interpreted using SHAP values.