Effects of clinical, comorbid, and social determinants of health on brain ageing in people with and without HIV: a retrospective case-control study

Kalen J Petersen, Tina Lu, Julie Wisch, June Roman, Nicholas Metcalf, Sarah A Cooley, Ganesh M Babulal, Rob Paul, Aristeidis Sotiras, Florin Vaida, Beau M Ances

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Department of Neurology (K J Petersen PhD, T Lu, J Wisch PhD, J Roman BA, N Metcalf BS, S A Cooley PhD, G M Babulal PhD, B M Ances MD) **and Department of Radiology** (A Sotiras PhD)**, Washington University School of Medicine, St Louis, MO, USA; Missouri Institute of Mental Health, University of Missouri, St Louis, MO, USA** (R Paul PhD)**; Department of Family Medicine, The University of California, San Diego, CA, USA** (F Vaida PhD)

Correspondence to: Dr Kalen J Petersen, Department of Neurology, Washington University School of Medicine, St Louis, MO 63130, USA **kalen@wustl.edu**

Summary

Background Neuroimaging reveals structural brain changes linked with HIV infection and related neurocognitive disorders; however, group-level comparisons between people with HIV and people without HIV do not account for within-group heterogeneity. The aim of this study was to quantify the effects of comorbidities such as cardiovascular disease and adverse social determinants of health on brain ageing in people with HIV and people without HIV.

Methods In this retrospective case-control study, people with HIV from Washington University in St Louis, MO, USA, and people without HIV identified through community organisations or the Research Participant Registry were clinically characterised and underwent 3-Tesla T_1-weighted MRI between Dec 3, 2008, and Oct 4, 2022. Exclusion criteria were established by a combination of self-reports and medical records. DeepBrainNet, a publicly available machine learning algorithm, was applied to estimate brain-predicted age from MRI for people with HIV and people without HIV. The brain-age gap, defined as the difference between brain-predicted age and true chronological age, was modelled as a function of clinical, comorbid, and social factors by use of linear regression. Variables were first examined singly for associations with brain-age gap, then combined into multivariate models with best-subsets variable selection.

Findings In people with HIV (mean age 44·8 years [SD 15·5]; 78% [296 of 379] male; 69% [260] Black; 78% [295] undetectable viral load), brain-age gap was associated with Framingham cardiovascular risk score (p=0·0034), detectable viral load (>50 copies per mL; p=0·0023), and hepatitis C co-infection (p=0·0065). After variable selection, the final model for people with HIV retained Framingham score, hepatitis C, and added unemployment (p=0·0015). Educational achievement assayed by reading proficiency was linked with reduced brain-age gap (p=0·016) for people without HIV but not for people with HIV, indicating a potential resilience factor. When people with HIV and people without HIV were modelled jointly, selection resulted in a model containing cardiovascular risk (p=0·0039), hepatitis C (p=0·037), Area Deprivation Index (p=0·033), and unemployment (p=0·00010). Male sex (p=0·078) and alcohol use history (p=0·090) were also included in the model but were not individually significant.

Interpretation Our findings indicate that comorbid and social determinants of health are associated with brain ageing in people with HIV, alongside traditional HIV metrics such as viral load and CD4 cell count, suggesting the need for a broadened clinical perspective on healthy ageing with HIV, with additional focus on comorbidities, lifestyle changes, and social factors.

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Introduction

People ageing with HIV exhibit altered brain structure and function compared with those without HIV, including morphological changes detectable on MRI.[1–3] However, group-level differences conceal substantial within-group heterogeneity. Although dementia is increasingly rare because of combination antiretroviral therapy (ART), more subtle forms of cognitive impairment persist in a subset of people with HIV, in some instances diminishing quality of life.[4]

To account for variability in ageing, new models must consider a broader range of health drivers than previous models, which focused mainly on clinical HIV metrics such as viral load. Growing literature quantifies the effect of comorbid disease burden and social determinants of health such as poverty, stress, and social stigma.[5,6] However, relationships between such risk or resilience factors and MRI biomarkers are poorly understood. To address this gap, innovative methods are needed.

Machine learning algorithms can provide unexpected insights into latent patterns in large clinical and neuroimaging datasets, including in people with HIV.[7,8] One of the most fruitful lines of research has involved brain-predicted age, in which models are trained to

Research in context

Evidence before this study

We searched PubMed on Aug 15, 2022 using the search terms ("HIV" or "human immunodeficiency virus") and ("brain", "neurological", "neurocognitive", or "HIV-associated neurocognitive disorder [HAND]") in the title, and ("comorbidity" or "social determinants of health") in the title or abstract, including spelling variants. We included original, peer-reviewed, clinical studies of adults with HIV published between Jan 1, 1996 (combination antiretroviral therapy development) and Aug 15, 2022 (search date), in English. Initial results included 149 studies; two were excluded for paediatric populations, 11 used animal or in vitro methods, and 59 were reviews, meta-analyses, editorials, or case studies. The remaining 77 were published between 2006 and 2022. These studies collectively identified numerous risk factors for changes in brain structure and neurocognitive deficits in people with HIV in the following categories: HIV clinical measures (current or nadir CD4 cell counts, AIDS-defining events, frailty, and viral loads), comorbidities (alcoholism, other substance use, depression and anxiety, co-infection, cardiovascular disease, and metabolic syndrome), plasma biomarkers of inflammation (IL-6 and soluble CD14), antiretroviral toxicity (efavirenz and integrase inhibitors), genetics (haplogroups and single-nucleotide polymorphisms), and demographic or social determinants of health (age, education, employment, and race and ethnicity). Some factors (education, exercise, and mitochondrial haplogroup B) were protective against neurocognitive impairment. In general, studies were focused on single domains of risk; however, a minority of studies used machine learning approaches with multidomain inputs.

Added value of this study

This study expands upon existing knowledge in several key ways. First, rather than examining neurocognitive risk factors in isolation, we build cross-modal models that combine clinical, comorbid, and sociodemographic predictors of brain health. Second, these factors are examined in the context of one of the largest single-site neuroimaging datasets of people with HIV and people without HIV. Third, brain-predicted age is quantified with a deep learning method, which produces a highly repeatable, disease-sensitive measure of whole-brain structural integrity. Finally, we examine geospatial data (Area Deprivation Index), which have not previously been compared with brain-predicted age in the context of HIV.

Implications of all the available evidence

Our key findings indicate that brain ageing in people with HIV is best explained by a combination of clinical, social, and comorbid risk factors. Together with the reviewed literature, our findings suggest that clinical care for people with HIV should incorporate a broader view of neurological health, including management of cardiovascular disease and consideration of sociological factors such as environmental stressors, unemployment, and neighbourhood quality of life.

estimate the age of individuals from neuroimaging features. The difference between brain-predicted age and true chronological age is known as the brain-age gap.

Positive brain-age gap (ie, age overestimation) reflects the accumulation of pathology; for example, people with Alzheimer's disease or mild cognitive impairment,[9] schizophrenia,[10] and HIV[11–13] have higher brain-age gap on average than controls. However, studies have largely focused on between-group differences rather than explaining within-group variability. Moreover, they have typically examined the effect of the primary disease rather than the effects of comorbidities and social factors. To meet these challenges, we used a large sample of people with HIV and people without HIV who underwent neuroimaging at a single site and whose clinical profiles and socioeconomic statuses are well characterised.

The aim of this study was to identify current and lifetime factors that explain brain ageing in people with HIV and people without HIV. These groups were first modelled separately, then a joint model was used to identify common factors affecting brain ageing across both populations. The two groups were not compared directly due to large differences in sample size and demographics. The outcome variable in all analyses was the brain-age gap, derived by applying a deep neural network to individual MRIs. The analysis consisted of two methods. First, potential correlates of brain ageing were examined singly, controlling for demographics, with correction for multiple comparisons. Then, multivariate models were built with variable selection.

Although our approach was data-driven, previous findings enabled us to hypothesise specific associations. We predicted that cardiovascular risk[14] and detectable viral load[11] would show positive associations with brain-age gap in people with HIV. On the basis of known relationships between social determinants of health and mortality and morbidity in people with HIV, we predicted that greater neighbourhood socioeconomic deprivation[15] and early life stress[16] would correspond to elevated brain-age gap. By contrast, because education is linked with better neuropsychological functioning in people with HIV,[17] we predicted an inverse association between education achievement and brain-age gap.

Methods

Study design and population

In this retrospective case-control study, participants were drawn from several HIV studies done in a single laboratory for the primary purpose of examining the effects of HIV disease and prevalent health comorbidities

on brain structure and function. Adults with HIV were recruited between Dec 3, 2008, and Oct 4, 2022, from the Washington University in St Louis Infectious Disease Clinic, and people without HIV were identified through community organisations or the Research Participant Registry in the same years. All participants provided written informed consent for study procedures, approved by the Institutional Review Board. All studies from which data were drawn were approved by the Washington University in St Louis Institutional Review Board.

Exclusion criteria were established by a combination of self-reports and medical records. Individuals who met the Diagnostic and Statistical Manual of Mental Disorders fifth edition criteria for current, severe substance use disorder or unmedicated major depressive disorder were excluded from parent protocols because of challenges with study compliance and the potential for confounding effects on neuroimaging. Individuals with depressive symptoms, anxiety, or mild-to-moderate substance use disorders were included to maximise external validity. Other exclusion criteria were incidental psychiatric disorders including schizophrenia and bipolar disorder, or neurological disorders such as epilepsy, traumatic brain injury with prolonged unconsciousness, or active opportunistic brain infections.

For more on **FreeSurfer** see surfer.nmr.mgh.harvard.edu

	People without HIV (N=259)	People with HIV (N=379)	p value
Age, years*	38·3 (17·1)	44·8 (15·5)	<0·0001
Sex†			
Male	129 (50%)	296 (78%)	<0·0001
Female	130 (50%)	83 (22%)	..
Race†	..	..	0·0021
Black or African-American	146 (56%)	260 (69%)	..
White	104 (40%)	111 (29%)	..
Asian	7 (3%)	2 (1%)	..
American Indian or Native American	0	1 (<1%)	..
Multiracial	2 (1%)	4 (1%)	..
Other	0	1 (<1%)	..
Education, years*	14 (2)	13 (2)	<0·0001
Unemployed (including disability)†	28 (11%)	102 (27%)	<0·0001
10-year Framingham risk score*	12·7 (10·8)	17·1 (12·1)	0·0065
Alcohol use (KMSK total)*	6·0 (3·7)	6·9 (4·0)	0·015
Cocaine use (KMSK total)*	0·6 (2·2)	3·3 (5·3)	<0·0001
Tobacco use (KMSK total)*	4·4 (4·8)	6·6 (4·9)	<0·0001
Area Deprivation Index (percentile)*	63·8 (25·0)	73·4 (24·8)	0·0011
Early Life Stress total events*	3·1 (2·8)	3·9 (2·9)	0·0023
WRAT-III reading subtest*	47·1 (7·1)	43·0 (8·7)	<0·0001
Viral load (copies per mL, $\log_{10}$)	..	1·8 (1·1)	..
Undetectable viral load (≤50 copies per mL)	..	295 (78%)	..
Most recent CD4 count (cells per μL)	..	588(312)	..
Nadir CD4 count (cells per μL)	..	224 (200)	..
Hepatitis C infection	..	25 (7%)	..

Data are mean (SD) or n (%). KMSK=Kreek-McHugh-Schluger-Kellogg. WRAT=Wide Range Achievement Test. *Compared between groups with ANOVA. †Compared with χ^2 tests.

Table: **Participant characteristics**

Procedures

For people with HIV, viral load was measured by RT-PCR with blood obtained on the day of imaging. Viral loads of more than 50 HIV copies per mL in plasma were considered detectable. CD4 cell counts were measured with flow cytometry, and nadir levels were taken from self-reports or medical records if available. Cardiovascular health was quantified with the 10-year Framingham score, which forecasts individual probability of developing cardiovascular disease,[18] calculated from the following risk factors: age, sex, smoking, systolic blood pressure, high-density lipoprotein, total cholesterol, and blood pressure medications. Lifetime heaviest substance use was quantified with the Kreek-McHugh-Schluger-Kellogg scale for alcohol, tobacco, and cocaine, which corresponds to clinical rating scales such as the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM). Heaviest use was assessed on a semiquantitative 13-point scale based on duration, frequency, and amount of consumption. Cannabis was not examined due to poor data availability. Hepatitis C co-infection was self-reported.

Socioeconomic status was assayed using the Area Deprivation Index, which combines US census tract-level housing, employment, education, and poverty data into a summary metric, with increasing scores indicating greater deprivation.[19] Area Deprivation Indexes were obtained from geospatial coding of residential addresses. The 2015 Area Deprivation Index national ranking was used, as this was the nearest timepoint to the mean visit (June, 2014 [2·6 years]). Educational achievement was quantified by use of the Wide Range Achievement Test reading component; the reading is a better proxy for educational achievement than years of schooling, and attenuates apparent racial discrepancies in neurocognitive test performance, suggesting better sensitivity to socioeconomic effects.[20] Self-reported unemployed status including disability was recorded. Childhood and adolescent stress was measured with the Early Life Stress Questionnaire, summing total adverse events experienced by the age of 17 years.

The MRI scan was done on two 3-Tesla Siemens (Erlangen, Germany) scanners (Prisma, Trio) and included T_1-weighted magnetisation prepared rapid gradient echo (T_1-MPRAGE) structural MRI (repetition time and echo time 2400/3·2 ms, spatial resolution 1×1×1 mm). Minimal pre-processing was applied, including skull-stripping with the FMRIB Software Library Brain Extraction Tool, and linear registration to the 1-mm Montreal Neurological Institute template. To obtain brain structure volumes, FreeSurfer (version 5.3) was run, with manual inspection and correction.

Statistical analysis

DeepBrainNet, a publicly available brain-predicted age model, was trained on 11729 MRI scans from a diverse cohort of normative controls (ages 3–95 years), from 16 imaging databases including multiple scanners and sites.[21] Model accuracy was tested on a previously unseen cohort of 2739 healthy controls. DeepBrainNet was built with the inception-resnet-v2 framework, which has high performance on complex computer vision challenges. DeepBrainNet uses two dimensional (2D) convolutional architecture, including a global maximum pooling layer, a dropout layer to prevent overfitting, and a fully connected 1024-node layer. The network was implemented in TensorFlow and Keras with five-fold cross-validation. Networks were initialised on ImageNet, a dataset of over 14 million hand-annotated images.

DeepBrainNet takes minimally processed T_1-weighted scans as input, with brain extraction and linear registration but no segmentation or warping. Scans are represented as 80 axial slices; to obtain the brain-predicted age, each slice was used as a separate input, and the median age estimate was taken. Brain-age gap was obtained by subtraction of chronological age from DeepBrainNet-predicted age; thus, a positive brain-age gap indicates model overestimation. To ensure that brain-age gap was not dependent on hardware, we tested for statistical differences between scanners.

Interpretation of spatial patterns detected by deep learning algorithms is non-trivial because of network complexity. To obtain a first-order approximation of volumetric features relevant to DeepBrainNet, we correlated normalised FreeSurfer grey and white matter volumes with brain-age gap. Correlation heatmaps for people with HIV and people without HIV were applied to a standard atlas for cortex (Desikan-Killiany), subcortical structures, white matter (including T_1 hypointensities), and cerebrospinal fluid compartments.

Potential predictors of brain-age gap were transformed to mitigate skewness. CD4 cell count and Framingham score were square-root transformed, the Early Life Stress Questionnaire was $\log_{10}$-scaled, and Area Deprivation Index was logit transformed. Cocaine and tobacco use were binarised (user and never user); alcohol use (Kreek-McHugh-Schluger-Kellogg lifetime heaviest use) was continuous. As study participants were over 97% White or Black or African American, approximately consistent with demographics of people with HIV in the St Louis area, race was collapsed into a binary (Black and non-Black). Due to protocol differences between studies conducted over the 13-year timeframe, some missingness was present in the dataset. For a sensitivity analysis with complete observations and the use of least absolute shrinkage and selection operator (LASSO) as additional validation, please see the appendix (p 1).

All statistical analyses were done in R (version 4.1.3). To test whether brain-age gap was associated with clinical, comorbid, and social factors, we performed univariate testing for all predictors separately for people with HIV and people without HIV, controlling for age, sex, and race. 13 predictors were tested: viral load, current CD4 cell count, nadir CD4 cell count, Framingham score, alcohol, tobacco, cocaine, hepatitis C, Area Deprivation Index, early life stress, Wide Range Achievement Test reading, years of education, and employment status. To mitigate false positives, multiple comparisons correction was done by use of Benjamini-Hochberg false discovery rate correction (α=5%).

To build multivariate models of brain ageing in people with HIV and people without HIV, we did multiple linear regression modelling with best-subsets variable selection using the Regsubsets R package. This method involved the fitting of one regression model per combinatorial subset of predictors. Variable selection was done by choosing the model with minimum Mallows' C_p, which is a measure commonly used for selective modelling.[22] Multivariate modelling was done separately for people with HIV and people without HIV, and in the combined cohort, adding HIV serostatus as a predictor.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, writing and interpretation, or the decision to publish.

See Online for appendix

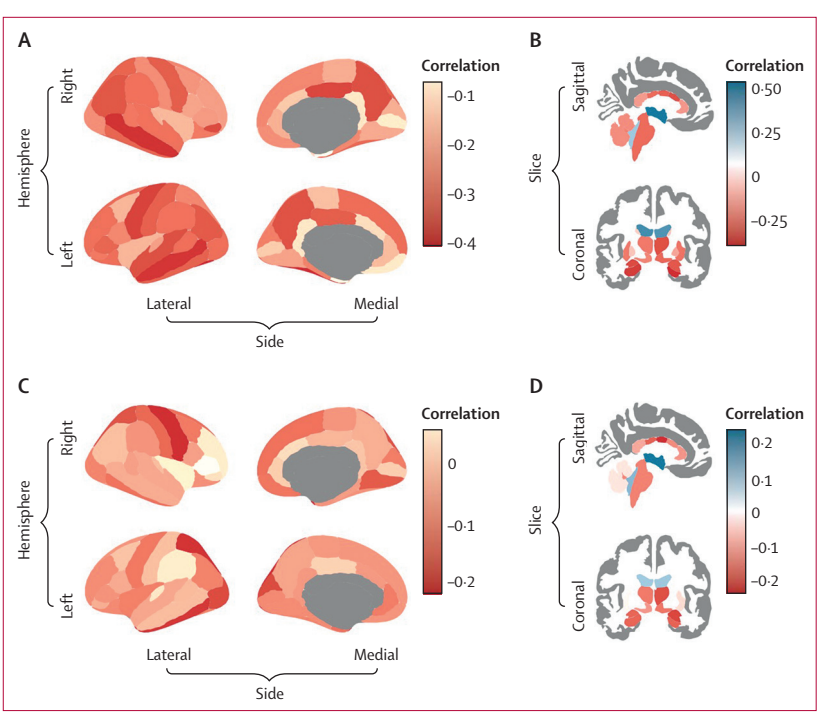

Figure 1: **Spatial correlation map of brain-age gap and volumetric features**

To estimate the importance of volumetric features in the derivation of the brain-age gap by the convolutional neural network DeepBrainNet, correlations between brain-age gap and FreeSurfer volumes were calculated for people with HIV (A, B) and people without HIV (C, D). All significant positive correlations (blue) were for ventricular cerebrospinal fluid compartments and for T_1 white matter hypointensities (not shown), whereas the strongest negative correlations were subcortical in the hippocampus (bilateral), amygdala (bilateral), brainstem, and corpus callosum.

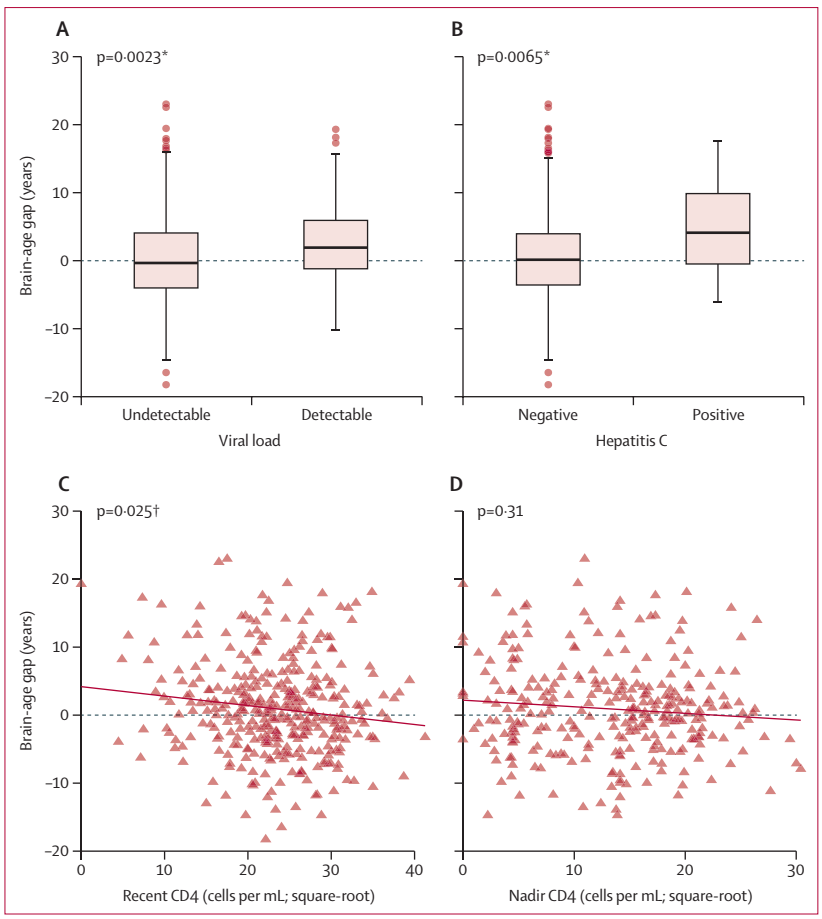

Figure 2: **HIV-specific predictors of brain ageing**
Univariate associations between potential predictors of brain ageing and DeepBrainNet-derived brain-age gap (ie, the difference between model-estimated age and chronological age). Four factors were considered only in people with HIV: plasma HIV viral load (A), hepatitis C co-infection (B), current plasma CD4 cell counts (C), and lifetime nadir CD4 cell count (D). *Significant at p<0·05 after false discovery rate correction. †Significant at precorrected p<0·05.

Results

People with HIV were older and more likely to be male and Black than those without HIV (table). These core demographics were included as covariates in all analyses.

In people with HIV, 10-year Framingham scores, and lifetime alcohol, cocaine, and tobacco use were greater than in people without HIV (table). People with HIV lived in neighbourhoods with greater socioeconomic disadvantage as measured by the Area Deprivation Index, experienced more early life stressors, and had lower educational achievement on the Wide Range Achievement Test reading subtest. For people with HIV, mean viral load was 63·1 copies per mL, and mean CD4 T-cell counts were 588·0 cells per µL, with a mean nadir of 224·3 cells per µL. Of 379 people with HIV, 25 reported a history of hepatitis C.

DeepBrainNet predicted participant age from T_1-weighted images with a mean absolute error of 5·7 years (5·5 years for people without HIV; 5·8 years for people with HIV). After linear bias correction (ie, regression of chronological age from the brain-age gap), mean absolute error was reduced to 5·3 years. Brain-age gap was not different between T_1-weighted images from Prisma and Trio scanners (p=0·20). Regardless of serostatus, all significant associations in spatial heatmaps (figure 1) for grey and white matter regions were negative (ie, greater brain-age gap correlated with smaller volume), whereas significant positive associations (greater brain-age gap with larger volumes) were limited to CSF compartments (lateral ventricles—eg, r=0·15–0·52) and T_1 white matter hypointensities (r=0·36 for people with HIV; r=0·12 for people without HIV).

Among HIV-specific variables (figure 2; appendix p 4), detectable viral load (p=0·0023) and hepatitis C co-infection (p=0·0065) were significantly positively associated with brain-age gap. CD4 cell count was negatively associated (p=0·025) but fell short of significance after false discovery rate adjustment. Other predictors were examined in both serostatus groups (figure 3). Framingham score, quantifying cardiovascular risk, was significantly positively associated with brain-age gap in people with HIV (p=0·0034) but not people without HIV (p=0·097), although the direction of effect was the same. Educational achievement (Wide Range Achievement Test reading; p=0·016) and educational duration (p=0·033) were negatively associated with brain-age gap, indicating potential predictors of resilience, but these did not survive false discovery rate correction. Unemployed status was associated with greater brain-age gap only in people with HIV (p=0·0019).

To create multivariate brain-age gap models for people with HIV and people without HIV, regression with best-subsets selection was used. The best model for people with HIV (figure 4) included Framingham score (p=0·0019; β=1·43), hepatitis C (p=0·073; β=3·90), and unemployment (p=0·020; β=3·21). The best model for people without HIV (figure 4) included alcohol use (p=0·0041; β=0·40), early life stress (p=0·047; β=–3·27) and Wide Range Achievement Test reading (p<0·0001; β=–0·304), with a non-significant term for unemployment (p=0·79; β=0·327). Finally, the best model for the combined cohort (people with HIV and people without HIV; figure 5) included Framingham score (p=0·0039; β=1·06), hepatitis C (p=0·037; β=3·84), Area Deprivation Index (p=0·033; β=0·684), and unemployment (p=0·00010), with retained non-significant terms for male sex (p=0·078; β=2·11) and alcohol use (p=0·090; β=0·224).

Sensitivity analysis with the complete-observation subset, with best-subsets selection and LASSO regression, yielded consistent findings and is discussed in the appendix (p 2). In five-fold cross-validation, the best-subsets model predicted brain-age gap for people in the complete-observations subset with a root-mean-square error of 6·72 years and a Pearson's r=0·44.

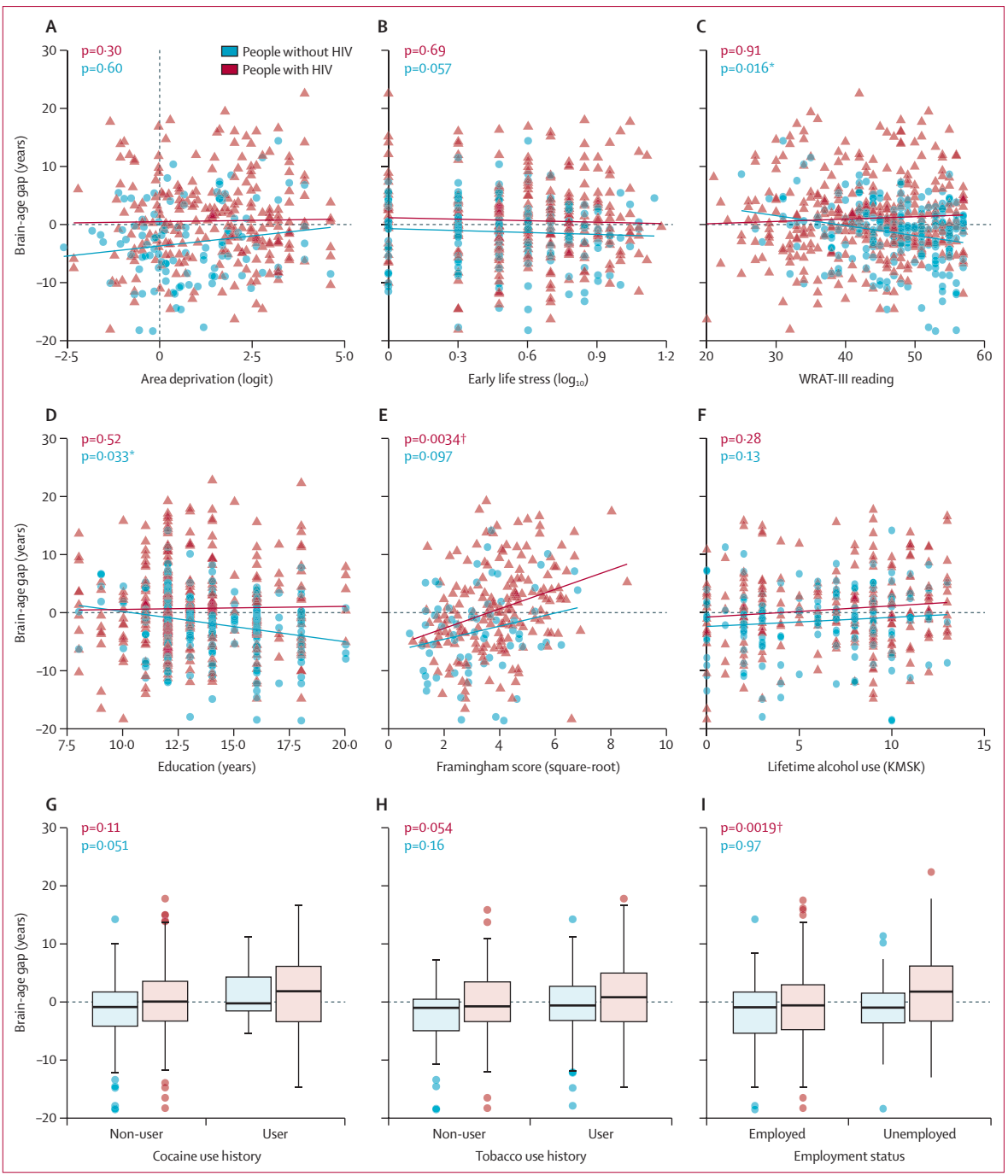

Figure 3: **Predictors of brain ageing for people with and without HIV**
Univariate associations between potential predictors of brain ageing and DeepBrainNet-derived brain-age gap. Nine factors were examined for both people with and without HIV: Area Deprivation Index (A), early life stressors (B), educational achievement (C), educational duration (D), Framingham cardiovascular risk (E), alcohol (F), cocaine (G), tobacco (H), and employment status (I). KMSK=Kreek-McHugh-Schluger-Kellogg. WRAT-III=Wide Range Achievement Test. *p<0·05. †Significant at p<0·05 after false discovery rate correction.

Discussion

By use of neuroimaging, machine learning, and model selection, we have shown that a combination of clinical measures, comorbidities, and social determinants of health are associated with brain-predicted age in people with HIV and people without HIV. Cardiovascular disease burden, detectable HIV viral load, and hepatitis C co-infection were identified as the strongest univariate correlates of brain-age gap in people with HIV. Additionally, the effects of social factors such as

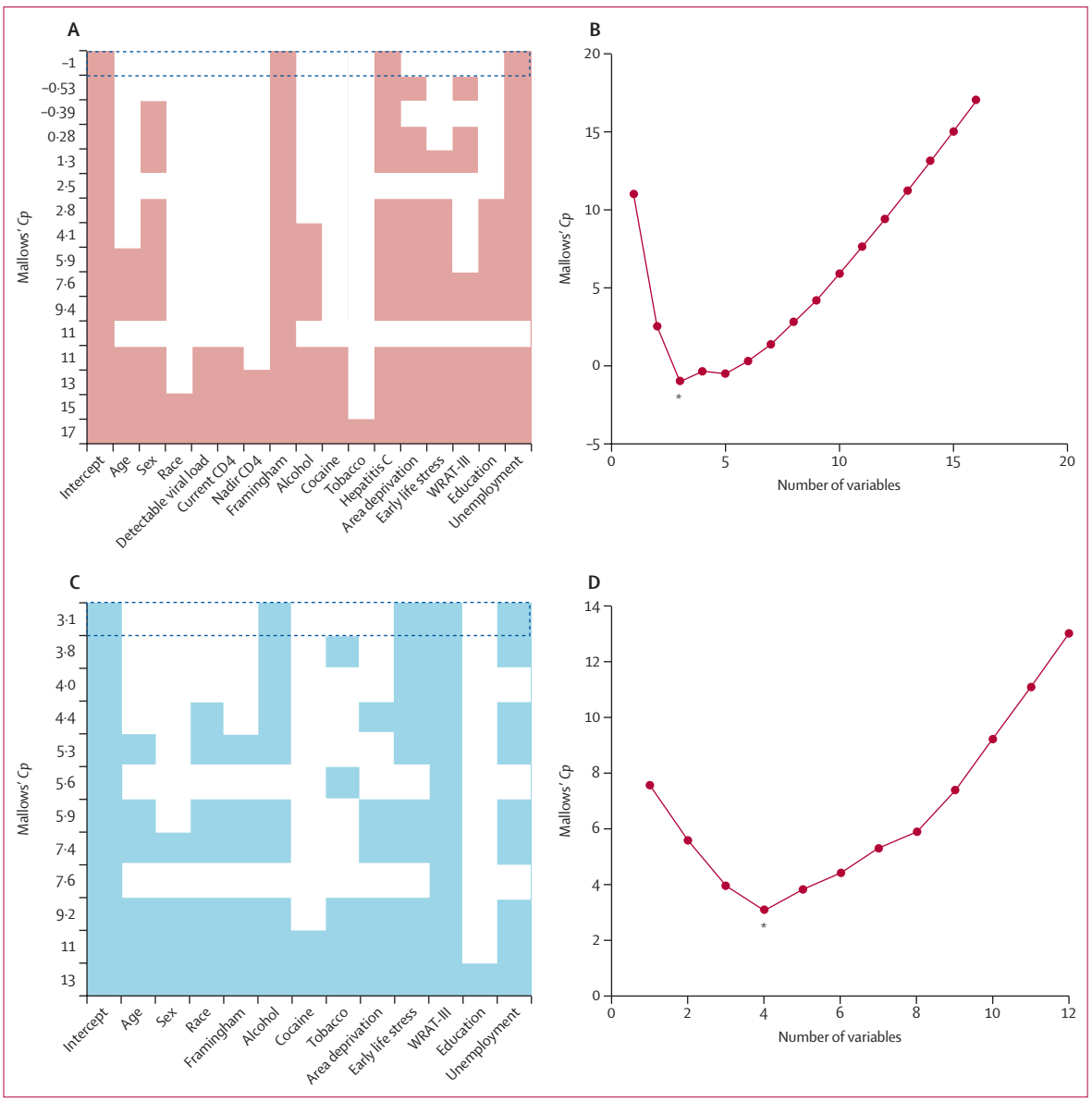

Figure 4: **Multivariate prediction of brain-age gap in people with and without HIV**
To identify predictor subsets that best explain the variability in the brain-age gap for people with HIV (A, B) and people without HIV (C, D), best-subsets variable selection was done with Mallows' C_p as selection criterion. Left panels (A, C) display the best result (lowest C_p) for each number of predictors; shaded panels indicate that the predictor in that column was included. The selected model (highlighted row) for people with HIV included Framingham cardiovascular risk, hepatitis C, and unemployed status. The model for people without HIV included alcohol use, early life stress, Wide Range Achievement Test reading score, and unemployed status. *Right panels (B, D) show model fit across the number of predictors, in which the minimum C_p is obtained with three predictors for people with HIV and four predictors for people without HIV. WRAT-III=Wide Range Achievement Test.

unemployment and area socioeconomic deprivation were identified in multivariate regression. Differences in significant variables between univariate and multivariate analyses could have several causes. For example, two predictors with high colinearity, accounting for shared variance in the response variable, could both show significant effects on brain-age gap in independent univariate tests, but not in a multivariate model.

Brain-age gap was also modelled in people without HIV. Because our primary goal was to explain within-group variability in brain ageing rather than test for between-group differences, and due to sample size and demographic differences, we elected not to do head-to-head comparisons between HIV serostatus groups. Best-subsets selection produced a multivariate model for people without HIV that included significant terms for alcohol use, early life stress, and Wide Range

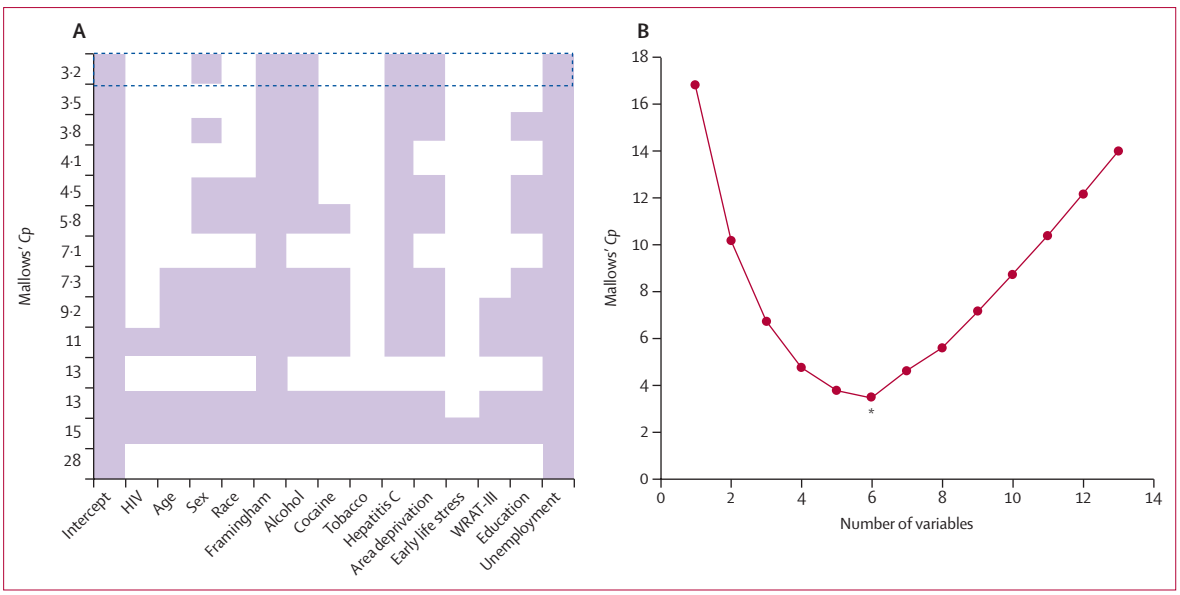

Figure 5: **Multivariate predictors of brain ageing in combined cohort of people with and without HIV**
Best-subsets selection was also done to model the brain-age gap for people with HIV and without HIV. (A) Best result (lowest C_p) for each number of predictors; shaded purple panels indicate that the predictor in that column was included. The final model (top row) included male sex, Framingham risk score, lifetime alcohol use, hepatitis C, area deprivation index, and unemployment. (B) Model fit across the number of predictors, in which the minimum C_p is obtained with six predictors (*). WRAT-III=Wide Range Achievement Test.

Achievement Test reading subscale. The Wide Range Achievement Test showed a significant inverse relationship with brain-age gap, indicating that educational achievement might be a resilience factor for brain ageing. Finally, modelling people with HIV and people without HIV together implicated Framingham score, alcohol use, Area Deprivation Index, unemployment, male sex, and hepatitis C with older-appearing brain phenotypes. Notably, HIV itself was not significantly associated with brain-age gap when modelling these other factors, suggesting the relative importance of non-HIV drivers of brain ageing in the combination ART era.

Substantial evidence now implicates non-HIV risk and resilience factors in ageing effects for people with HIV.[23,24] Health disparities between people with HIV and people without HIV partly reflect the legacy of early uncontrolled infection, but these residual effects alone are insufficient to explain the persistence of neurocognitive impairment among people with well controlled HIV.[25] As a result, comorbidities and social determinants of health are increasingly salient features in people with HIV with suppressed viral loads, immune reconstitution, and the expectation of longevity.

People with HIV have increased average brain-age gap relative to seronegative peers; however, available data indicate that within-group variability in brain ageing exceeds between-group differences, and accounting for heterogeneity is crucial.[12,14] In this study, we approach the question of brain ageing using an array of multimodal predictors, including clinical measures, comorbid disease burden, and social determinants of health. A novel aspect of this study is the incorporation of geospatial data on neighbourhood characteristics into MRI data analysis.

The first group of factors that could affect brain ageing are direct effects of HIV. We examined four key variables: viral load, current CD4 lymphocytes, nadir CD4 count, and hepatitis C co-infection. Detectable viral load was significantly associated with elevated brain-age gap, consistent with a large literature implicating viral suppression and immune re-constitution in preserved neurocognitive function.[26] Hepatitis C was associated with approximately 4 years of added brain-age gap in people with HIV, suggesting that the pathological effects of HIV and hepatitis C have additive effects on brain health.[27] Thus, achieving control of both viruses is likely to be important for healthy brain ageing.

The strongest and most consistent brain-age gap association was with Framingham cardiovascular risk score. The modelled difference in brain-age gap between individuals at minimum (<2%) and maximum (>60%) cardiovascular risk in this study was over 10 years. In univariate modelling, this association was significant in people with HIV; however, the effect size was similar in people without HIV, marking cardiovascular disease as a good candidate for a general brain ageing risk factor. However, it remains especially relevant for people with HIV who have increased vascular disease compared with the general population.[28] These findings suggest that maintenance of normal blood pressure and cholesterol could be crucial for people with HIV who

have established viral control but remain vulnerable to cardiovascular disease.

Substance use disorders are also more prevalent among people with HIV than among the general population, and the effects of a history of drug misuse must be considered when studying neurocognitive deficits.[29] Previous work has linked drug use with brain structural and functional changes in people with HIV, but associations with brain-age gap have not been characterised. In multivariate analysis of people without HIV, we found a positive association between brain-age gap and alcohol use, potentially indicating that neurotoxic effects of heavy consumption influence MRI-based brain age. The absence of a similar effect in people with HIV could be a function of the colinearity between alcohol use and other factors (eg, cardiovascular disease) for which stronger links were found.

One unexpected finding was the detection of a protective effect of educational achievement in people without HIV alone, in contrast with years of formal education, which showed no significant association. The Wide Range Achievement Test reading score had a significant negative correlation with brain-age gap in multivariate analysis, such that for each point of improvement on the Wide Range Achievement Test, the mean brain-predicted age was reduced by 0·45 years. The apparent absence of this effect in people with HIV is challenging to interpret but might indicate that the enhanced cognitive reserve conferred by quality of education might not be fully realised in people with HIV who experience clinical and social stressors related to lower rungs on the hierarchy of needs (ie, those related to safety, food security, or other basic needs).

Social determinants of health were given consideration in this study as economic instability and social marginalisation disproportionately affect people with HIV. In addition to education, we examined three major social factors: childhood stress, residential neighbourhood quality from geospatially derived Area Deprivation Index, and unemployment status. Although neither the Early Life Stress Questionnaire or Area Deprivation Index were associated with brain-age gap, Area Deprivation Index had positive associations with brain-age gap in the combined cohort model. Finally, unemployment status showed a strong linkage with increased brain-age gap in people with HIV, although causality remains unclear because neurocognitive impairment associated with accelerated brain ageing might precede loss of employment.

Anatomically, the brain-age gap was interpreted by correlation with FreeSurfer volumes. Although this approach does not capture all the complex patterns identified by the neural network, it provides an approximation of relevant features. Results were congruent with literature on brain structure and ageing: positive associations with brain-age gap were confined to CSF compartments and T_1 white matter hypointensities, whereas the strongest negative correlations were in subcortical structures that atrophy with age, particularly amygdala, hippocampus, and corpus callosum.[30] These results suggest that DeepBrainNet identifies ageing-relevant imaging features.

Some limitations should also be noted. The use of over 10 years of participant data resulted in some differences in the measures collected, producing a degree of data incompleteness. To mitigate confounding effects of missing values, we did a sensitivity analysis in the subset of people with HIV with complete data. Results thus obtained closely matched those derived from the full dataset, indicating that missing data were unlikely to drive results.

Use of self-reported data is another limitation. For example, self-reported hepatitis C prevalence in people with HIV (7%) was lower than expected, suggesting unawareness of infection in some participants. However, despite likely underestimation of co-infection, we nonetheless detected a substantial effect on brain-age gap (4·0 years increase) in people with HIV with hepatitis C. Hepatitis C serostatus was not assessed in people without HIV. Additionally, our sample represented almost exclusively people who self-identified as Black or White, but not other racial or ethnic groups. Furthermore, people with HIV and people without HIV were significantly different on self-identified race, sex, and age, limiting the comparability of serostatus groups.

The use of best-subsets variable selection runs some risk of overfitting since all possible predictor combinations are modelled. This weakness is partly mitigated by use of Mallows' C_p, a selection criterion, which penalises models with numerous predictors.[22] For further validation, we also did variable selection with LASSO regression, an alternative method that uses coefficient shrinkage to eliminate weaker predictors. Again, results corresponded well to the main analysis, suggesting that findings are robust to overfitting and insensitive to methodology.

Taken together, these results paint a nuanced picture of ageing with HIV. Traditional clinical variables such as viral load and T-cell counts affect neuropathology; however, non-HIV drivers of health such as comorbid diseases and socioeconomic status are growing in importance. Together, such factors could account for heterogeneity in neurocognitive outcomes in older people with HIV and people without HIV. Identification of brain-ageing correlates could lead to a broadened perspective on health for people ageing with chronic infectious disease while navigating challenging and often adverse socioeconomic landscapes.

Contributors

KJP and BMA did the conceptualisation of the study. KJP and TL did the formal analysis and data visualisation. KJP, JR, and SAC verified the data. JR, NM, SAC, and JW were responsible for data curation and software development. KJP wrote the original draft of the manuscript. KJP, SAC, GMB, RP, AS, FV, and BMA edited the manuscript.

Declaration of interests
KJP, SAC, FV, JW, JR, TL, and NM have no financial relationships to report. BMA received support for the present work from the National Institutes of Health, the Paula and Rodger Riney Fund, Daniel J Brennan, MD Fund, and participated in a data safety monitoring board for vascular contributions to cognitive impairment and dementia. RP received support from the National Institutes of Health. GMB received support from the National Institutes of Health and the BrightFocus Foundation and participated in a data safety monitoring board for RF1AG061900 - SEABIRD. AS received research support from the National Institutes of Health and the BrightFocus Foundation and has received compensation for serving as a grant reviewer at BrightFocus. AS has a patent issued on "Method and Device for Efficient Parallel Message Computation for Map Inference" and owns equity in TheraPanacea.

Data sharing
De-identified individual participant data, including imaging summary metrics but not original MRI scans, will be made available upon reasonable request to the corresponding author. Data will be shared over the HIPAA-compliant Box service.

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