ISCHEMIC HEART DISEASE AND VASCULAR RISK FACTORS ARE ASSOCIATED WITH ACCELERATED BRAIN AGING

Brief title: Cardiac ischemia, vascular risk factors and brain aging

Elisa Rauseo [a,b,*], MSc, MD, Ahmed Salih [a,b c,*], MSc, Zahra Raisi-Estabragh [a,b], MBBS, PhD, Nay Aung [a,b], MBBS, PhD, Neha Khanderia [d], MBBS, Gregory G. Slabaugh [e,f,g], MSc, PhD, Charles R. Marshall [h,i], MRCP, PhD, Stefan Neubauer [l], MD, Petia Radeva [m], Ilaria Boscolo Galazzo, MSc, PhD [c], Gloria Menegaz [c,†], PhD, Steffen E. Petersen [a,b,f,n,†], MSc, MPH, MD, DPhil

[*] **Elisa Rauseo and Ahmed Salih contributed equally to this work**
[†] **Steffen E. Petersen and Gloria Menegaz are joint corresponding authors**

Total word counts: 5000

Affiliations
[a] William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University London, Charterhouse Square, London, EC1M 6BQ, UK
[b] Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, West Smithfield, EC1A 7BE, London, UK
[c] Department of Computer Science, University of Verona, Verona, Italy
[d] Imperial College Healthcare NHS Trust, London, United Kingdom
[e] School of Electronic Eng. & Computer Science, Queen Mary University of London, United Kingdom
[f] Alan Turing Institute, London, UK
[g] Digital Environment Research Institute, Queen Mary University of London, United Kingdom
[h] Preventive Neurology Unit, Wolfson Institute of Population Health, Charterhouse Square, London EC1M 6BQ, UK
[i] Neurology Department, Royal London Hospital, Barts Health NHS Trust, London, E1 1FR, UK
[l] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford NIHR Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust
[m] Dept. Mathematics and Computer Science, University of Barcelona, Barcelona, Spain
[n] Health Data Research UK, London, UK

Funding:
Barts Charity (G-002346) contributed to fees required to access UK Biobank data [access application #2964]. ER and SEP acknowledge support by the London Medical Imaging and Artificial Intelligence Centre for Value Based Healthcare (AI4VBH), which is funded from the Data to Early Diagnosis and Precision Medicine strand of the government's Industrial Strategy Challenge Fund, managed and delivered by Innovate UK on behalf of UK Research and Innovation (UKRI). SEP also acknowledges support from the National Institute for Health Research (NIHR) Biomedical Research Centre at Barts. SEP acknowledges the British Heart Foundation for funding the manual analysis to create a cardiovascular magnetic resonance imaging reference standard for the UK Biobank imaging resource in 5,000 CMR scans (www.bhf.org.uk; PG/14/89/31194). SEP acknowledges support from the SmartHeart EPSRC programme grant (www.nihr.ac.uk; EP/P001009/1). AS is supported by INVITE

program co-financed by the European Union within the Horizon 2020 Programme and by the Regione del Veneto. CRM is funded by a grant from Barts Charity. SN acknowledges support from the Oxford NIHR Biomedical Research Centre. IBG and GM acknowledge support from Fondazione CariVerona (EDIPO project - reference number 2018.0855.2019). NA acknowledges the NIHR Integrated Academic Training programme which supports his Academic Clinical Lectureship post. NA is supported by the Academy of Medical Sciences Starter Grant for Clinical Lecturers (SGL024\1024). ZR-E recognises the NIHR Integrated Academic Training programme which supports her Academic Clinical Lectureship post and was also supported by British Heart Foundation Clinical Research Training Fellowship No. FS/17/81/33318.

Disclosures:
GGS provides consultancy to MindRank AI. CRM has received personal fees from Biogen and GE Healthcare. SEP provides consultancy to Circle Cardiovascular Imaging, Inc., Calgary, Alberta, Canada. The remaining authors have nothing to disclose.

Data availability statement:
This research was conducted using the UK Biobank resource under access application 2964. UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: http://www.ukbiobank.ac.uk/register-apply/.

Acknowledgments: Figures are created with BioRender.com.

Author contributions: ER and AS conceived that idea, conducted the analyses and wrote the manuscript. GM, SEP, IBG and PR supervised, guided the experiments, and revised the manuscript. CRM helped in interpreting the results. All the authors have contributed to the work and read and approved the final manuscript.

Tweet: A large @UK_Biobank imaging study shows associations between prevalent ischemic heart disease, vascular risk factors and accelerated brain aging reflecting structural MRI brain changes. #CardioTwitter @QMULWHRI @eucanshare @smartheartUK

Address for correspondence:

Professor Steffen E. Petersen
William Harvey Research Institute, Queen Mary University London
Charterhouse Square, London, EC1M 6BQ, UK
Telephone: +44(0) 20 7882 6902; Email: s.e.petersen@qmul.ac.uk
Twitter handle: @s_e_petersen

Structured abstract

Background: Ischemic heart disease (IHD) has been linked with poor brain outcomes. The brain magnetic resonance imaging (MRI) derived difference between predicted brain age and actual chronological age (brain-age delta in years, positive for accelerated brain aging) may serve as an effective means of communicating brain health to patients to promote healthier lifestyles.

Objectives: We investigated the impact of prevalent IHD on brain aging, potential underlying mechanisms, and its relationship with dementia risk, vascular risk factors, cardiovascular structure, and function.

Methods: Brain age was estimated in subjects with prevalent IHD (n = 1,341) using a Bayesian ridge regression model with 25 structural (volumetric) brain MRI features and built using UK Biobank participants with no prevalent IHD (n = 35,237).

Results: Prevalent IHD was linked to significantly accelerated brain aging ($p < 0.001$) and that was not fully mediated by microvascular injury. Brain aging (positive brain-age delta) was associated with increased risk of dementia (odds ratio = 1.13, 95% CI [0.04, 1.22], $p = 0.002$) and with vascular risk factors as diabetes, and high adiposity. In the absence of IHD, brain aging was also associated with cardiovascular structural and functional changes typically seen in aging hearts. However, such alterations were not linked with risk of dementia.

Conclusions: Prevalent IHD and coexisting vascular risk factors are associated with accelerated brain aging and risk of dementia. Positive brain-age delta representing accelerated brain aging may serve as an effective communication tool to illustrate the impact of modifiable risk factors and disease supporting preventative strategies.

Condensed abstract

Ischemic heart disease (IHD) has been linked with poor brain outcomes. Brain age estimated from structural brain features and its deviation from actual age (brain-age delta in years, positive for accelerated brain aging) can express individual brain health in neurologically intact adults. Prevalent IHD is associated with accelerated brain aging and increased risk of dementia, that is not fully explained by microvascular injury. Besides shared vascular risk factors, additional disease-related mechanisms might contribute to abnormal aging. Brain-age delta may serve as an effective communication tool to illustrate the impact of modifiable risk factors and disease supporting preventative strategies.

Keywords

Ischemic heart disease, brain aging, cognitive decline, brain health, vascular risk factors

Abbreviations
BMI = body mass index
IHD = ischemic heart disease
LV = left ventricle
LVEF = left ventricle ejection fraction
MAE = mean absolute error
M/V = mass-to-volume ratio
R2 = coefficient of determination
RV = right ventricle
TAC = total arterial compliance
UKB = UK Biobank
WMH = white matter hyperintensity

INTRODUCTION

Although the risk of cognitive decline is primarily driven by age, vascular risk factors and coexisting diseases may augment the risk of age-related brain deterioration (1)(2). Ischemic heart disease (IHD) has been associated with poor brain health independently of the effect of aging itself (3)(4). Several pathways involved in the heart-brain crosstalk have been proposed, albeit the precise pathophysiological mechanisms by which IHD may cause cognitive deterioration remain to be elucidated (5). Cardiac ischemia has been linked with macro- and microstructural brain abnormalities in both white and grey matter even before the onset of clinical symptoms of dementia (6)(7). Detecting and quantifying subtle deviations from age-related brain changes may enable identifying subjects at greater risk of developing cognitive decline, to whom preventive strategies and targeted treatments should be directed.

Recent neuroimaging studies have introduced modelling approaches to estimate individual's brain age based on brain Magnetic Resonance Imaging (MRI) features. The difference between estimated brain age and actual age (delta) reflects deviations from normal aging and may serve as a biomarker for cognitive deterioration (8). An older appearing brain indicating accelerated brain aging (positive delta) has been linked with certain neurological conditions and lifestyle factors in cognitively healthy cohorts (9)(10).

Brain age may represent an effective means of communicating the risk of brain deterioration to patients, just as vascular age can be used to express cardiovascular disease risk (11). It can increase risk awareness and likely promote healthier lifestyles and preventive actions (12).

In this paper, we investigated the impact of prevalent IHD on brain aging and the risk of dementia, possible mechanisms underlying the association, and the role of vascular risk factors, cardiovascular structure, and function using UK Biobank (UKB) data. No previous studies have used this approach to evaluate brain health in large IHD cohorts without pre-

existing neurological conditions. We hypothesize that IHD may be associated with accelerated brain aging, reflecting structural brain changes predisposing to cognitive decline or dementia. The estimated brain age can thus be used to express the individual risk level and motivate IHD patients to improve their health behaviors.

METHODS

The UKB dataset

The UKB is a large prospective population study following the health and wellbeing of over half a million participants aged 40–69 years recruited from across the UK. The protocol is publicly accessible, and data are made available for researchers through an application process (13). Participants' characteristics, including socio-demographics, lifestyle, environmental factors, medical history, genetics, and physical measures, were collected at the visits. Since 2015, over 48,000 participants underwent imaging studies, including brain and cardiovascular magnetic resonance (CMR) imaging.

Ethics

This study complies with the Declaration of Helsinki. It is covered by the ethical approval for UKB studies from the NHS National Research Ethics Service on 17th June 2011 (Ref 11/NW/0382) and extended on 18 June 2021 (Ref 21/NW/0157). Written informed consent was obtained from all participants.

Study populations

Participants with brain imaging-derived phenotypes (IDP)s available and without any history of mental health, neurological disorders, or dementia that could directly affect cognitive function were selected for our analysis (n= 36,578) (14). Two distinct subsets were then defined (Figure 1). The prevalent IHD group comprised 1,341 subjects with angina, previous myocardial infarction, or any manifestation of IHD not resulting in infarction (Supplemental Table 1). The non-IHD (control) group was composed of the remaining subjects with no

history of IHD at the time of scanning (n= 35,237). This group was further split into training and test sets to define the brain aging model. For the post-hoc association analyses (performed on IHD and non-IHD test-set), we selected only subjects with available values for the exposure variable of interest.

MRI data acquisition

Brain MRI data were acquired using a 3T Siemens scanner (Skyra, VD13A SP4, Siemens Healthcare, Erlangen, Germany) in accordance with a publicly accessible protocol (15). In brief, imaging acquisition included six different sequences, covering structural, diffusion and functional imaging for a total of 35 min scan time per participant. MPRAGE sequence with 1-mm isotropic resolution was used to acquire T1-weighted data, while fluid-attenuated inversion recovery contrast was used for T2-weighted scans (1.05 x 1 x 1 mm resolution).

CMR images were acquired using 1.5 Tesla scanners (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) according to a pre-defined acquisition protocol (16). In brief, the cardiac assessment includes a combination of long-axis cines and a complete short-axis stack covering both the left and right ventricles (LV, RV) acquired using balanced steady-state free precession sequences.

Brain MRI feature extraction

Brain IDPs were extracted from brain MRI and accessible through the UKB showcase (Supplemental Table 2). We selected 25 volumetric features extracted from structural MRI as they were identified among the top informative predictors to model brain age (17)(18). The total volume of white matter hyperintensities (WMH)s (not used to model brain age) was instead used for the post-hoc mediation analysis. A detailed description of processing data is provided in the Supplementary Methods.

CMR parameters

Conventional measures of LV and RV structure and function were extracted using an automated pipeline with inbuilt quality control, previously developed, and validated in a large sample of the UKB (19). Specifically, we analyzed the following parameters: LV and RV volumes in end-diastole and end-systole; LV and RV stroke volumes; LV mass and ejection fraction (LVEF).

Additional cardiac indices able to capture changes in myocardial function in relation to structural chamber remodeling were analyzed, including LV mass-to-volume (M/V) ratio, and LV global function index (LVGFI). M/V ratio was calculated as LV mass divided by LV end-diastolic volume. LVGFI is a validated measure of LV cardiac performance that integrates structural components of adverse myocardial remodeling into LV function assessment for which the formula is described elsewhere (20).

Aortic distensibility and total arterial compliance (TAC) obtained at the imaging visit were considered as indices of arterial health. Aortic distensibility is a measure of local aortic compliance and lower values indicates poor vascular health (21). Aortic distensibility values at the proximal descending aorta were obtained from a previous analysis of a large subset of the UKB imaging studies using a fully automated image analysis pipeline embedded with purpose-designed quality control (22). TAC is an additional descriptor that can be used to estimate arterial function. Greater values, indicating reduced arterial load, have been associated with better cardiovascular outcomes (23). TAC was estimated using LV stroke volume divided by central pulse pressure (24).

Vascular risk factors

Vascular risk factors previously linked with brain health, including hypertension, diabetes, hypercholesterolemia and (current) smoking were considered as exposures. Body mass index (BMI) and waist-hip ratio, two biomedical indices of body adiposity, were also evaluated. We also assessed the role of socio-economic deprivation, expressed as Townsend index, a

measure of material deprivation relative to national averages. The clinical exposures were ascertained using selected UKB fields (Supplemental Table 3).

Statistical analysis

A more detailed description of the statistical analysis is provided in the Supplemental Methods. All analyses were performed using Python 3.8.10 (Python Software Foundation, Delaware USA) and Scikit-learn version 0.23.2. A two-sided p value <0.05 (corrected for multiple tests) was considered statistically significant for all analyses.

Briefly, to assess whether IHD was associated with faster brain aging, whether it, in turn, was linked with dementia risk, and to investigate potential mechanistic links and risk factors involved in the association, we used a staged approach, which can be summarized as follow.

Brain age estimation

Brain age was estimated using Bayesian Ridge regression model as it was shown to provide competitive performance (25). In the model, 25 brain IDPs were the independent variables while the chronological age was the dependent variable. The actual age was demeaned (shifted to have zero mean) before fitting it into the model to have a centered version of the outcome (8). Sex, education level, height, and volumetric scaling from T1 head image to standard space were used as confounds as they can significantly affect the outcome. The confounds were regressed from the features using a linear regression model prior to modeling brain age. The model performance was assessed using the Mean Absolute Error (MAE) and the coefficient of determination (R2). MAE in brain age studies is interpreted as the deviation between predicted brain age and the chronological age expressed in years, with higher values indicating older appearing brains. R2 represents the proportion of variance in the predicted brain age explained by the used features in the model.

The brain aging model was first built based on participants with non-IHD by splitting the data into two subsets (training set, 80%; testing set, 20%). After removing the age-dependency

bias (as described in the supplemental materials), we calculated brain-age delta by subtracting the chronological age from the predicted brain age in the test datasets, with positive values (expressed in years) indicating accelerated brain aging. Pearson correlation was also calculated between actual age and brain-age delta, before and after bias correction.

Next, brain age was estimated on IHD subjects using the previously trained model to assess the deviation of the brain-age delta from the reference (non-IHD) population. IHD and non-IHD groups were thus compared in terms of model performance, and difference in mean brain-age delta, the latter considered as a measure of apparent brain aging (8).

Brain age and risk of dementia

Logistic regression was used to analyze the relationship between brain-age delta and incident dementia (Supplemental Table 4). The model was adjusted for age, sex, and education level. As the number of incident events was low in comparison to non-events, to account for imbalance data potentially affecting the model, we repeated the association analysis after using propensity score matching based on age and sex.

Mediation effects of WMH on IHD and brain age

To study potential mechanistic links, we performed a mediation analysis to test to which extent WMH, a marker of cerebrovascular injury, mediated the impacts of IHD on brain aging (indirect effect). The ordinary least squares regression was used to study the associations (described in terms of effect) between the variables (IHD, WMH as mediator, brain-age delta). The model was adjusted for age, sex, and education.

Association of brain age with vascular risk factors and imaging parameters

A linear regression model in both IHD and non-IHD (test-set) groups was used to assess the role of vascular risk factors and imaging parameters in advancing brain age. The model was adjusted for the same confounds used for brain aging model plus age. In the analysis we used unstandardized measures to reveal the effect (beta value) of changing one unit in the

exposure on the brain-age delta. Specifically, changing the exposures may lead to increasing or decreasing in brain-age delta (estimated in years) based on the direction of the association (positive vs negative beta value).

As we found significant associations between certain imaging parameters and brain aging only in non-IHD subjects, we studied whether these metrics were linked with incident dementia in this group using logistic regression. The model was adjusted for age and sex.

RESULTS

Baseline characteristics of the study populations

People with IHD were on average older than the controls (59.2 ±6.3 vs 54.6 ± 7.4 years; $p < 0.05$), albeit the age range was similar in the two cohorts (40-70 years, Supplemental Figure 1). The diseased subjects were more likely to be males than those without the disease (71.4% vs 46.3%, respectively; $p < 0.05$) (Table 1), with a greater burden of risk factors and worse cardiovascular health indices (Table 2). IHD subjects had significantly lower volumes of most brain structures and increased volume of WMH than those without the disease (Supplemental Table 5).

Estimated brain age in IHD

In non-IHD subjects (test-set), the model showed a mean difference between the chronological age and predicted brain age (MAE) of 4.69 years (Table 3). When applying the model to the IHD group, a greater deviation of predicted brain age from actual age was observed (MAE = 6.96 years) indicating older appearing brain. A significant difference in mean brain-age delta values between the two cohorts was also found ($p < 0.001$) confirming that the IHD subjects had significantly higher brain age than those without the disease.

The difference between the two groups was further confirmed by R2, with a negative value in IHD indicating that the prediction in this group was worse than the mean prediction

(Supplemental Figure 2). Such negative value was mentioned in the scikit-learn documentation and reported in previous brain aging studies (30).

The correlation value between brain-age delta and actual age in both cohorts decreased to close to zero after the estimated brain age was corrected from bias. This indicates that the correction steps were performed correctly, and the derived brain-age delta was free from age dependency. That was notably observed in the IHD cohort (Supplemental Table 6).

Association of brain age with incident dementia

One unit increase in brain-age delta was associated with an increase of 13% in the odds of dementia occurring (OR = 1.13, 95% CI [0.04, 1.22], p = 0.002). Such association remained significant after accounting for imbalance between the two groups (dementia vs non-dementia) (OR = 1.15, 95% CI [1.01, 1.33], p = 0.04) (Table 4).

Mediation effects of WMH on IHD and brain age

The association of IHD diagnosis with brain-age delta can be explained as a direct effect, due to the disease itself, an indirect effect mediated by WHM, and a total effect, which is the result of both (Figure 2).

Unadjusted model showed that IHD had significant effects on brain-age delta both directly and indirectly ($p < 0.001$). However, the direct effect of IHD on brain aging was far larger than through WMH as mediator (beta values: 6.41 vs 0.11, respectively).

When adjusted for covariates, the direct effect remained similar in size and significant (beta value=6.62, $p < 0.0001$), whilst the mediation effect of WMH became nonsignificant.

Association of brain age with vascular risk factors

Increasing brain-age delta was significantly associated with a history of diabetes in both groups. However, such effect was greater in IHD (beta values up to 2.1 years in IHD vs 1.3 years in controls).

In IHD, faster brain aging was also significantly linked with increased adiposity (larger waist-hip ratio and increased BMI). The greatest association was found with waist-hip ratio, where for one unit increase of such value, there was an increase in estimated brain age of up to 8.02 years from normal aging (as indicated by the beta value) (Table 5). A similar trend was observed in control subjects, albeit the associations were not significant.

The estimated contribution of diabetes and increased adiposity on the acceleration of brain aging was overall greater in the presence of IHD (up to 10.2 years in IHD vs 3 years in controls, when summing up their beta values). The different effect size of vascular risk factors on brain aging in the two cohorts is shown in Figure 3.

Association of brain age with CMR parameters

In non-IHD subjects, increasing brain-age delta was significantly associated with smaller LV and RV volumes, and lower indices of cardiac function, LV mass, aortic distensibility and TAC values. Similar direction of associations was found in the IHD cohort for all imaging metrics, albeit not statistically significant (Table 6). None of the CMR metrics were significantly associated with the risk of dementia (Supplemental Table 7).

DISCUSSION

In this study we estimated the brain age of IHD subjects from the UKB using volumetric brain features extracted from MRI data. We found that subjects with IHD showed, on average, a more advanced brain age than their chronological age, with their brains appearing significantly older than those without the disease. Accelerated brain aging was also linked with increased risk of dementia. WMH, a marker of cerebrovascular injury, did not significantly mediate the effects of IHD on brain aging, suggesting that other mechanisms related to the disease itself were involved in the association. IHD, diabetes and increased adiposity were associated with even faster brain aging. Overall, these findings suggest that

IHD-related mechanisms and vascular risk factors concur to accelerate biological brain aging and so the risk of developing dementia.

IHD and brain health

Although our results cannot be directly compared with previous studies given the different approaches used to evaluate the impact on brain structures, they are consistent with existing research and confirm the association between IHD and poorer brain health (4). There is evidence to support faster cognitive deterioration in the years following the diagnosis of IHD than before, suggesting possible disease-related mechanisms implicated in the association (26).

We observed that IHD subjects had early structural brain changes in the form of brain atrophy and increased WMHs than their peers. WMHs reflect underlying cerebral small vessel disease, a form of vascular dysfunction which may occur both in the brain and the heart, leading to different clinical manifestations, including ischemia, cognitive dysfunction, and dementia (27)(28). However, we observed that the vascular contributions to brain aging in IHD, as expressed by WMHs, were nearly insignificant. Instead, it was mainly a direct effect of the disease to drive the association. These results confirm the strong association between IHD and brain deterioration, and that such relationship is not fully explained by WMHs (7)(6).

Our findings suggest that IHD contributes to brain aging through several disease-related mechanisms that this marker of cerebrovascular injury could not capture. Among the mechanisms involved are direct ischemic brain injury, blood-brain barrier alterations, and various biological pathways, including oxidative stress, immune responses, and endothelial dysfunction (5). Future studies using more sensitive measures of brain microstructural changes are needed to establish the exact pathophysiological pathways linking IHD, brain aging, and cognitive decline in the long term.

The role of coexisting vascular risk factors in brain aging

Vascular risk factors can augment the risk of dementia both through an increased risk of cardiac and cerebrovascular diseases and as independent risk factors (2). These potentially modifiable conditions promote systemic atherosclerosis which may directly affect brain and cardiovascular health (6). When IHD and vascular risk factors coexist, the negative effects on cerebral autoregulation and brain perfusion might be further enhanced thus resulting in accelerating brain aging. In this view, concomitant IHD may be seen as a more advanced, symptomatic end-organ vascular disease and as a surrogate marker of clinically significant atherosclerosis affecting the brain (7).

Similarly, we observed that increased adiposity and diabetes were associated with significantly faster brain aging in presence of IHD. This indicates that the impact of such factors on brain structures is amplified when there is a coexisting diagnosis of IHD with a synergistic effect of vascular and ischemic-related processes on disease progression.

Diabetes played a significant role in brain aging even in the absence of IHD, confirming that this condition is one of the strongest risk factors for dementia (29). We also found a very strong association between indices of adiposity and brain aging in IHD. A higher waist-hip ratio, a measure of abdominal obesity, was associated with the greatest increase in brain aging. This suggests that central adiposity as an indicator of visceral fat might be the component that mainly contributes to accelerating brain aging in the presence of IHD. Visceral adipose tissue inducing insulin resistance and increased systemic inflammation might play a key role in causing vascular endothelial dysfunction and eventually subclinical brain damage (30). Thus, we hypothesize that coexisting IHD and increased central adiposity might represent a condition of higher vascular risk burden. In this view, several factors might interact and lead to a greater risk of structural and vascular cerebral changes potentially resulting in more accelerated brain aging.

The role of cardiovascular hemodynamics in brain aging

In the absence of IHD, we found significant associations between accelerated brain aging and cardiovascular changes typically seen in aging hearts: smaller ventricular volumes, reduced LV global performance, and poorer aortic compliance. However, such alterations did not translate into an increased risk of dementia. These changes in cardiovascular hemodynamics likely reflect the coupling of ventricular and vascular stiffening processes over the lifetime, which can occur even in the absence of explicit cardiovascular conditions, with a potential impact on brain health before the onset of cognitive impairment (31)(14).

None of the CMR measures analyzed was significantly linked with brain aging in IHD. Although that can be due to the smaller number of IHD subjects, other types of cardiac changes, likely ischemia-related and not captured by conventional indices of cardiac function and structure might play a role in the association with brain aging. Further studies using advanced imaging metrics (32) and integrating a more comprehensive assessment of the extent of myocardial ischemia are thus needed to shed light on the complex relationship between IHD and brain aging.

Clinical implications

Our findings highlight the importance of preventing IHD and promoting healthier behaviours to delay brain deterioration and possible dementia. Brain age can be considered an attractive communication tool to inform patients about their risk status and the toll of vascular risk factors on the brain's health. Communicating the risk in age has been shown to increase risk perceptions and to provide greater emotional impact, such as further motivating patients to make lifestyle changes (12). That can be particularly useful for young individuals, who may perceive their absolute short-term risk as too low to be emotionally impactful due to their young age (33). Emotional reactions can play a role in rational behavior by influencing the perception of risk in a more intuitive, rapid, and understandable way than cognitive

evaluations (34). However, future prospective trials demonstrating the effectiveness of using brain age for communicating risk information are needed before recommending such an approach in clinical practice.

Study limitations

We used volumetric brain features to estimate brain age as they were previously identified among the top informative predictors. However, including multiple imaging modalities might probably lead to better model performance.

The number and type of brain IDPs used in the model can affect the estimated value of brain-age delta. However, our purpose was to use this parameter to illustrate the differences in brain aging rate between IHD vs non-IHD rather than propose a quantification of aging itself.

Additional factors, including genetics and early brain developments, can likely influence brain structures. Future studies based on longitudinal imaging data could help determine such factors' role in the individual change trajectories of brain aging.

The average actual age of IHD and non-IHD differed significantly. However, we applied an age-bias correction method that eliminated the effects of age from the estimated brain age delta.

We assessed the effect of certain previously validated exposures linked to brain health. Additional covariates, including biological, psychological, and behavioral parameters, were not evaluated. That was done to avoid model overfitting, potentially decreasing the sensitivity to real effects. Differences in sample size, age range and methods used to select covariates and brain features might explain some discrepancies between the current and previous brain aging results on UKB.

Although the direction of associations between exposures and brain-age delta might indicate the potential impact of the exposure itself on brain aging (accelerating vs decelerating), these results do not allow for causal inference. We cannot infer temporal relationships between

brain aging and exposures as this is a cross-sectional study. Future longitudinal investigations using serial brain and CMR data linked with clinical outcomes might evaluate the effect of having an older appearing brain in the long term.

CONCLUSIONS

Prevalent IHD is associated with accelerated brain aging and increased risk of dementia, that is not fully explained by microvascular injury. Besides shared vascular risk factors, additional disease-related mechanisms might contribute to abnormal aging. Using brain age to communicate the risk levels for cognitive deterioration may increase patients' awareness and improve their adherence to therapies and lifestyle changes.

PERSPECTIVES

Competency in medical knowledge

Our findings highlight the importance of looking for early signs of poorer brain health in the form of subtle (volumetric) changes in brain structures in subjects with prevalent IHD and vascular risk factors.

Translational outlook 1

Brain age can help identify IHD subjects at higher risk of developing cognitive deterioration who may benefit from early and more aggressive treatment and preventative interventions.

Translational outlook 2

Brain age can be used to efficiently communicate the risk of brain deterioration to patients and promote healthy behaviors.

Translational outlook 3

Given the projected increase of prevalent IHD and dementia due to global population aging, there is a need for insights into causal mechanisms underlying heart-brain interactions and early signs of cognitive impairment before overt symptoms.

REFERENCES

1. Wrigglesworth J., Ward P., Harding IH., et al. Factors associated with brain ageing - a systematic review. BMC Neurol 2021;21(1):1–23. Doi: 10.1186/s12883-021-02331-4.
2. Gorelick PB., Scuteri A., Black SE., et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2011;42(9):2672–713. Doi: 10.1161/STR.0B013E3182299496.
3. Singh-Manoux A., Sabia S., Lajnef M., et al. History of coronary heart disease and cognitive performance in midlife: the Whitehall II study. Eur Heart J 2008;29(17):2100–7. Doi: 10.1093/EURHEARTJ/EHN298.
4. Deckers K., Schievink SHJ., Rodriquez MMF., et al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PLoS One 2017;12(9):e0184244. Doi: 10.1371/journal.pone.0184244.
5. Qiu C., Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nat Rev Cardiol 2015;12(5):267–77. Doi: 10.1038/nrcardio.2014.223.
6. Van Dijk EJ., Prins ND., Vrooman HA., Hofman A., Koudstaal PJ., Breteler MMB. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. Stroke 2008;39(10):2712–9. Doi: 10.1161/STROKEAHA.107.513176.
7. Zheng L., MacK WJ., Chui HC., et al. Coronary Artery Disease is Associated with Cognitive Decline Independent of MRI Changes in Cognitively Normal Elderly. J Am

Geriatr Soc 2012;60(3):499. Doi: 10.1111/J.1532-5415.2011.03839.X.

8. Smith SM., Vidaurre D., Alfaro-Almagro F., Nichols TE., Miller KL. Estimation of brain age delta from brain imaging. Neuroimage 2019;200(February):528–39. Doi: 10.1016/j.neuroimage.2019.06.017.

9. Cole JH. Multimodality neuroimaging brain-age in UK biobank: relationship to biomedical, lifestyle, and cognitive factors. Neurobiol Aging 2020;92:34–42. Doi: 10.1016/j.neurobiolaging.2020.03.014.

10. Cole PhD JH., Raffel MD J., Friede PhD T., et al. Longitudinal Assessment of Multiple Sclerosis with the Brain-Age Paradigm. Ann Neurol 2020;88(1):93–105. Doi: 10.1002/ANA.25746.

11. Groenewegen KA., Den Ruijter HM., Pasterkamp G., Polak JF., Bots ML., Peters SAE. Vascular age to determine cardiovascular disease risk: A systematic review of its concepts, definitions, and clinical applications. Eur J Prev Cardiol 2016;23(3):264–74. Doi: 10.1177/2047487314566999.

12. Soureti A., Hurling R., Murray P., Van Mechelen W., Cobain M. Evaluation of a cardiovascular disease risk assessment tool for the promotion of healthier lifestyles. Eur J Cardiovasc Prev Rehabil 2010;17(5):519–23. Doi: 10.1097/HJR.0B013E328337CCD3.

13. UK Biobank: Protocol for a large-scale prospective epidemiological resource. March 2007. Available at: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf. Accessed December 1, 2021.

14. Salih A., Boscolo Galazzo I., Raisi-Estabragh Z., et al. Brain age estimation at tract group level and its association with daily life measures, cardiac risk factors and genetic variants. Sci Rep 2021;11(1). Doi: 10.1038/S41598-021-99153-8.

15. Smith M., Alfaro-Almagro F., Miller K. UK Biobank Brain Imaging Documentation.

December, 2020. Available at: https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf. Accessed December 1, 2021.

16. Petersen SE., Matthews PM., Francis JM., et al. UK Biobank's cardiovascular magnetic resonance protocol. J Cardiovasc Magn Reson 2016. Doi: 10.1186/s12968-016-0227-4.

17. Xifra-Porxas A., Ghosh A., Mitsis GD., Boudrias MH. Estimating brain age from structural MRI and MEG data: Insights from dimensionality reduction techniques. Neuroimage 2021;231:117822. Doi: 10.1016/j.neuroimage.2021.117822.

18. Ning K., Zhao L., Matloff W., Sun F., Toga AW. Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. Sci Rep 2020;10(1). Doi: 10.1038/s41598-019-56089-4.

19. Bai W., Sinclair M., Tarroni G., et al. Automated cardiovascular magnetic resonance image analysis with fully convolutional networks 08 Information and Computing Sciences 0801 Artificial Intelligence and Image Processing. J Cardiovasc Magn Reson 2018;20(1). Doi: 10.1186/s12968-018-0471-x.

20. Mewton N., Opdahl A., Choi EY., et al. Left ventricular global function index by magnetic resonance imaging - A novel marker for assessment of cardiac performance for the prediction of cardiovascular events: The multi-ethnic study of atherosclerosis. Hypertension 2013;61(4):770–8. Doi: 10.1161/HYPERTENSIONAHA.111.198028.

21. Resnick LM., Militianu D., Cunnings AJ., Pipe JG., Evelhoch JL., Soulen RL. Direct Magnetic Resonance Determination of Aortic Distensibility in Essential Hypertension. Hypertension 1997;30(3):654–9. Doi: 10.1161/01.HYP.30.3.654.

22. Biasiolli L., Hann E., Lukaschuk E., et al. Automated localization and quality control of the aorta in cine CMR can significantly accelerate processing of the UK Biobank

population data. PLoS One 2019;14(2). Doi: 10.1371/JOURNAL.PONE.0212272.

23. Lilly SM., Jacobs D., Bluemke DA., Duprez D., Zamani P., Chirinos J. Resistive and pulsatile arterial hemodynamics and cardiovascular events: The multiethnic study of atherosclerosis. J Am Heart Assoc 2014;3(6). Doi: 10.1161/JAHA.114.001223.

24. UK Biobank Pulse wave analysis and aortic pressure. October 2015. Available at: https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/vicorder_explan_doc.pdf. Accessed December 1, 2021.

25. Salih A., Galazzo IB., Jaggi A., et al. Multi-modal Brain Age Estimation: A Comparative Study Confirms the Importance of Microstructure. Math Vis 2021:239–50. Doi: 10.1007/978-3-030-73018-5_19.

26. Xie W., Zheng F., Yan L., Zhong B. Cognitive Decline Before and After Incident Coronary Events. J Am Coll Cardiol 2019;73(24):3041–50. Doi: 10.1016/J.JACC.2019.04.019.

27. Moroni F., Ammirati E., Hainsworth AH., Camici PG. Association of White Matter Hyperintensities and Cardiovascular Disease. Circ Cardiovasc Imaging 2020;13:10460. Doi: 10.1161/CIRCIMAGING.120.010460.

28. Berry C., Sidik N., Pereira AC., et al. Small-vessel disease in the heart and brain: Current knowledge, unmet therapeutic need, and future directions. J Am Heart Assoc 2019;8(3). Doi: 10.1161/JAHA.118.011104.

29. Ng JB., Turek M., Hakim AM. Heart disease as a risk factor for dementia. Clin Epidemiol 2013;5(1):135–45. Doi: 10.2147/CLEP.S30621.

30. Lampe L., Zhang R., Beyer F., et al. Visceral obesity relates to deep white matter hyperintensities via inflammation. Ann Neurol 2019;85(2):194–203. Doi: 10.1002/ana.25396.

31. Sabayan B., van Buchem MA., Sigurdsson S., et al. Cardiac hemodynamics are linked

with structural and functional features of brain aging: the age, gene/environment susceptibility (AGES)-Reykjavik Study. J Am Heart Assoc 2015;4(1):e001294. Doi: 10.1161/JAHA.114.001294.

32. Rauseo E., Izquierdo Morcillo C., Raisi-Estabragh Z., et al. New Imaging Signatures of Cardiac Alterations in Ischaemic Heart Disease and Cerebrovascular Disease Using CMR Radiomics. Front Cardiovasc Med 2021;8:1209. Doi: 10.3389/fcvm.2021.716577.

33. Fair AKI., Murray PG., Thomas A., Cobain MR. Using hypothetical data to assess the effect of numerical format and context on the perception of coronary heart disease risk. Am J Heal Promot 2008;22(4):291–6. Doi: 10.4278/061030140R2.1.

34. Timmermans DRM., Ockhuysen-Vermey CF., Henneman L. Presenting health risk information in different formats: The effect on participants' cognitive and emotional evaluation and decisions. Patient Educ Couns 2008;73(3):443–7. Doi: 10.1016/j.pec.2008.07.013.

Figure legends (titles and captions)

Figure 1. Study population selection

IDPs = imaging-derived phenotypes, IHD = ischemic heart disease, WMH = white matter hyperintensity.

Figure 2. Mediation of effects of IHD on brain-age delta

Unadjusted (A) and adjusted models (B). The (beta) values indicate the effect size. IHD = ischemic heart disease, WMH = white matter hyperintensity. * *The association is statistically significant ($p < 0.05$).*

Figure 3. Comparing the effect size of vascular risk factors on brain aging in IHD vs non-IHD

Higher beta-value (in years) indicates faster brain aging. * *The association is statistically significant ($p < 0.05$).*

Central Illustration. IHD and vascular risk factors accelerate brain aging

Brain aging estimated from MRI data, reflects structural brain changes. Ischemic heart disease and coexisting vascular risk factors can accelerate biological brain aging and increase the risk of dementia.

Table 1. Demographic characteristics of the study groups used for brain age prediction

Demographic characteristics	Non-IHD (n= 35,237)	IHD (n= 1,341)
Age, at the imaging visit (years) *	54.6 (±7.44)	59.2(±6.3)
Male (n, %) *	16,338 (46.3%)	958 (71.4%)

Values are mean (±standard deviation) when continuous or number (percentage) when categorical. IHD = ischemic heart disease.

**Differences between the two groups are statistically significant (p <0.05).*

Table 2. Baseline characteristics of the IHD vs non-IHD groups

Baseline characteristics	Non-IHD (test-set)	IHD
Clinical characteristics		
Deprivation (Townsend score)	-2.5 (-3.9, -0.7)	-2.6 (-3.9, -0.5)
Current smoker (%, n)*	251 (6.1%)	86 (8%)
Diabetes (%, n)*	128 (3.1 %)	88 (8.2 %)
Hypertension (%, n)*	193 (4.7 %)	125 (11.6 %)
High cholesterol (%, n)*	566 (13.9 %)	204 (19%)
Biomedical measurements		
Waist-hip ratio*	0.9 (±0.1)	0.90 (±0.08)
BMI (kg/m^2), median (IQR)*	26 (23.6, 28.6)	27.1 (25, 29.7)
Indices of arterial compliance		
Aortic distensibility (10^{-3}/mmHg), median (IQR)*	2.2 (1.59, 2.9)	2.0 (1.5, 2.7)
TAC (ml/m2 x mmHg), median (IQR)*	0.7 (0.6, 0.8)	0.6 (0.5, 0.8)
CMR indices of cardiac structure and function		
LVEDVI (ml/m^2)*	79.2 (±13.6)	81.5 (±16.3)
LVESVI (ml/m2), median (IQR)*	31.4 (26.5, 36.9)	32.8 (27.4, 39.3)
LVSVI (ml/m2)	46.9 (±8.2)	46.5(±8.2)
LVMI (g/m2)*	45.8 (±8.6)	49.0 (±9.6)
RVEDVI (ml/m2)	84.2 (±15.4)	83.4 (±14.3)
RVESVI (ml/m2)	36.4 (±9.5)	36.4 (±8.9)
RVSVI (ml/m2)*	47.7 (±8.7)	46.9 (±8.5)
LVEF (%)*	59.5 (±6)	57.7 (±7.4)
M/V ratio (g/ml), median (IQR)*	0.56 (0.5, 0.62)	0.59 (0.54, 0.66)
LVGFI (%)*	47.7 (±6.7)	45.1 (±7.4)

Values are mean (±standard deviation) when continuous or number (percentage) when categorical. Data are presented as median (interquartile range) where absolute skew is ≥ 0.9. The data shown here are from the subjects with values that were available. IHD = ischemic heart disease, BMI = body mass index, TAC = total arterial compliance, LVEDVI = left ventricular end-diastolic volume index, LVESVI = left ventricular end-systolic volume index, LVSVI = left ventricular stroke volume index, LVMI = left ventricular mass index, RVEDVI = right ventricular end-diastolic volume index, RVESVI = right ventricular end-systolic volume index, RVSVI = right ventricular stroke volume index, LVEF = left ventricular ejection fraction, M/V = LV mass-to-volume ratio, LVGFI = left ventricle global function index.

* *Differences between the two groups are statistically significant ($p < 0.05$).*

Table 3. Model performance for brain age prediction

Model performance	Non-IHD (Train)	Non-IHD (Test)	IHD
MAE (years)	4.72	4.69	6.96
R^2 (variance in age explained)	0.38	0.39	-0.76

MAE indicates the mean difference between the chronological age and the predicted brain age expressed in years, with higher values indicating older-appearing brain. R2 represents the proportion of variance in the predicted brain age explained by the used features in the model. In IHD group, a greater deviation of predicted brain age from chronological age was observed compared to non-IHD (test-set) (MAE = 6.96 years for IHD vs MAE =4.69 years for non-IHD). IHD = ischemic heart disease, MAE = Mean Absolute Error, R2 = Coefficient of determination.

Table 4. Association of brain-age delta with incident dementia

Model 1				
Sample (n)	***Dementia (n, %)***	***Beta value***	***Odds ratio (95% CI)***	***P value***
8,389	27 (0.32%)	0.124	1.13 (0.04 – 1.22)	0.002
Model 2				
Sample (n)	***Dementia (n, %)***	***Beta value***	***Odds ratio (95% CI)***	***P value***
54	27 (50%)	0.146	1.15 (1.01 – 1.33)	0.04

Model 1 was performed using all non-IHD (test-set) and IHD subjects. Model 2 was performed after selecting the sample using propensity score matching based on age and sex. CI = confidence interval.

Table 5. Associations between brain-age delta and vascular risk factors

Exposures	Non-IHD		IHD	
	Beta value	***P value***	***Beta value***	***P value***
Smoking [a]	0.58	0.26	0.56	1
Deprivation	0.05	0.33	0.05	1
BMI, kg/m^2	0.03	1	0.1	0.003*
Diabetes [a]	1.3	0.001*	2.06	<0.001*
Hypertension [a]	0.45	1	0.84	1
Hypercholesterolemia [a]	0.21	1	0.25	1
Waist-hip-ratio	1.72	0.81	8.02	<0.001*

The beta value is interpreted as the difference in the dependent variable (brain-age delta) for changing one unit in the independent variable (exposure). Specifically, changing one unit in the exposure leads to increasing (positive beta value) or decreasing (negative beta value) in brain-age delta. For instance, in non-IHD, diabetes is associated with an increased brain-age delta = 1.3 years, whilst in IHD such increase is near 2.1 years. IHD = ischemic heart disease, BMI = body mass index.

[*] *Statistically significant after Bonferroni correction ($p < 0.05$).*

[a] *Indicate categorical variables. The other variables are continuous.*

Table 6. Associations between brain-age delta and cardiovascular imaging parameters

Exposures	Non-IHD		IHD	
	Beta value	***P value***	***Beta value***	***P value***
LVEDVI, ml/m2	-0.03	<0.001 *	-0.01	0.65
LVEF, %	-0.03	0.05	0.01	1
LVESVI, ml/m2	-0.03	0.001*	-0.02	0.82
LVMI, g/m2	-0.03	<0.001 *	-0.004	1
LVSVI, ml/m2	-0.05	<0.001 *	-0.01	1
RVEDVI, ml/m2	-0.03	<0.001 *	-0.02	0.27
RVESVI, ml/m2	-0.03	<0.001 *	-0.03	0.95
RVSVI, ml/m2	-0.05	<0.001 *	-0.03	0.86
LVGFI, %	-0.04	<0.001 *	0.001	1
M/V ratio, g/ml	1.41	0.75	2.19	1
Aortic distensibility, 10^{-3}/mmHg	-0.37	<0.001 *	-0.07	1
TAC, ml/m2 x mmHg	-1.65	<0.001 *	-1.29	0.66

The beta value is interpreted as the difference in the dependent variable (brain-age delta) for changing one unit in the independent variable (exposure). Specifically, changing one unit in the exposure leads to increasing (positive beta value) or decreasing (negative beta value) in brain-age delta. IHD = ischemic heart disease, LVEDVI = left ventricular end-diastolic volume index, LVEF = left ventricular ejection fraction, LVESVI = left ventricular end-systolic volume index, LVMI = left ventricular mass index, LVSVI = left ventricular stroke volume index, RVEDVI = right ventricular end-diastolic volume index, RVESVI = right ventricular end-systolic volume index, RVSVI = right ventricular stroke volume index, LVGFI = left ventricle global function index, M/V = LV mass-to-volume ratio, TAC = total arterial compliance.

[*] *Statistically significant after Bonferroni correction ($p < 0.05$).*

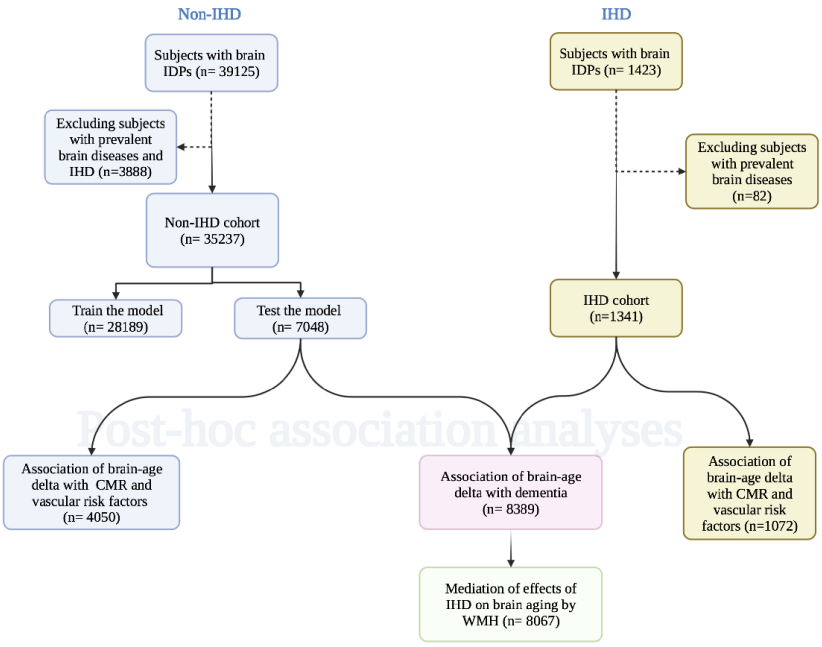


Figure 1: Study population selection IDPs = imaging-derived phenotypes, IHD = ischemic heart disease, WMH = white matter hyperintensity.

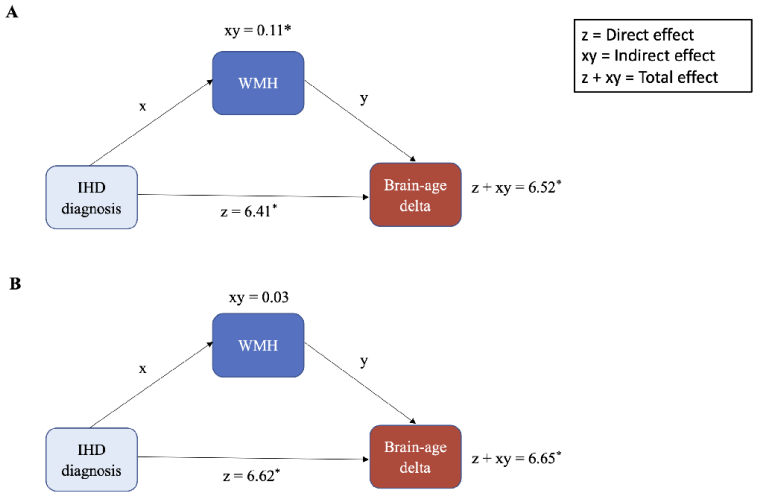


Figure 2: Mediation of effects of IHD on brain-age delta Unadjusted (A) and adjusted models (B). The (beta) values indicate the effect size. IHD = ischemic heart disease, WMH = white matter hyperintensity. * The association is statistically significant ($p < 0.05$).

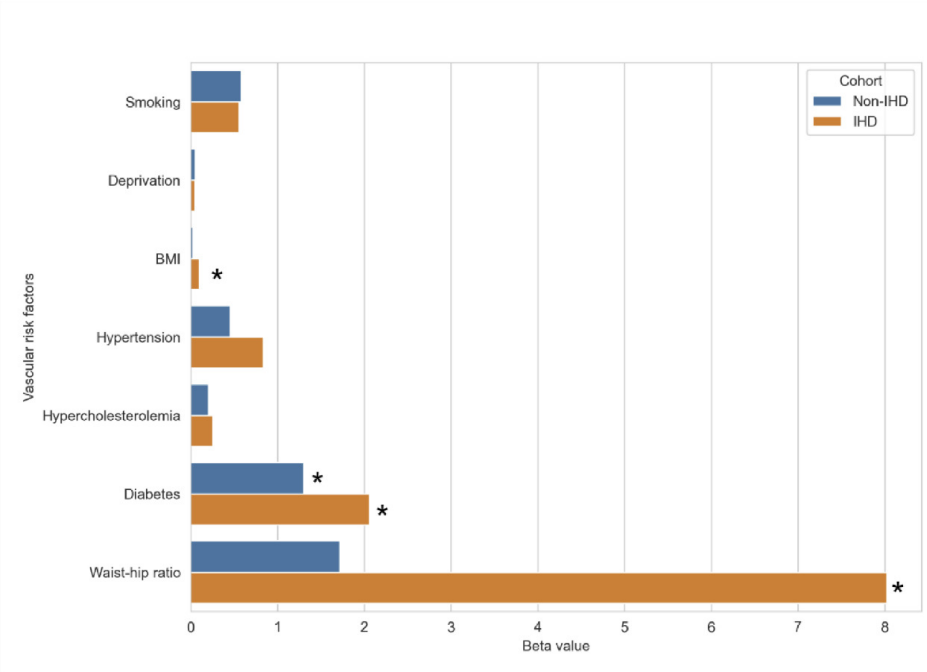
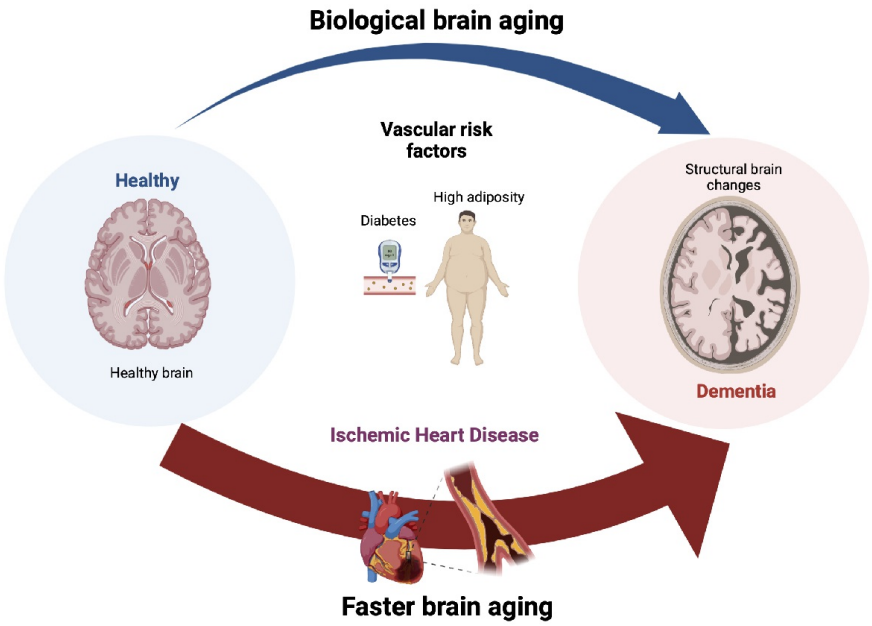


Figure 3: Comparing the effect size of vascular risk factors on brain aging in IHD vs non-IHD Higher beta-value (in years) indicates faster brain aging. * The association is statistically significant ($p < 0.05$).



Central Illustration: IHD and vascular risk factors accelerate brain aging Brain aging estimated from MRI data, reflects structural brain changes. Ischemic heart disease and coexisting vascular risk factors can accelerate biological brain aging and increase the risk of dementia.

Supplemental Methods

Brain MRI feature extraction

We used imaging-derived phenotypes (IDP)s resulted from an image pre-processing pipeline developed by the UK Biobank (UKB) working group described in details elsewhere (1). Further protocols details are available online at: https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf.

In brief, pre-processing structural MRI included face removal, brain extraction, linear alignment to standard MNI152 brain template. Brain MRIs were segmented into three categories that are: white matter, grey matter, and cerebrospinal fluid using a Functional MRI of the Brain (FMRIB)'s Automated Segmentation Tool (FAST). Then, the segmented data were used to perform a SIENAX-style analysis (Structural Image Evaluation, using Normalization, of Atrophy: Cross-sectional) (2). Volumes of different regions were calculated both normalized and not normalized to head size to generate the IDPs accessible through the UKB showcase. The subcortical structural volumes for each hemisphere were calculated using, an FMRIB's Integrated Registration and Segmentation tool (FIRST). The total volume of white matter hyperintensities (WMH), used in the mediation analysis, was calculated using T2-weighted brain MRI data and the lesion is segmented using the Brain Intensity Abnormality Classification Algorithm (BIANCA) tool.

Statistical analysis

To assess whether IHD was associated with faster brain aging, whether it, in turn, was related to the risk of dementia, and to investigate potential mechanistic links between IHD and brain aging, including the role of some risk factors, we used a four-staged approach, which can be summarized as follow (Figure 1): A) estimating brain age in IHD; B) assessing the relationship between brain age and risk of dementia; C) evaluating the role of WMH as a

potential mediator in the association between IHD and brain aging; D) evaluating the association of brain aging with vascular risk factors and imaging parameters. A detailed description of each stage of our analysis is provided below.

Differences between groups were assessed using proportions t-tests for categorical variables and Student's t-tests with unequal variances for continuous variables, with $p < 0.05$ considered statistically significant for all tests (corrected for multiple comparisons).

Brain age estimation

Brain age was estimated using Python 3.8.10 and Scikit-learn version 0.23.2. Bayesian Ridge regression was used as a regression model to estimate brain age as it was shown to provide competitive performance (3). In the model, the 25 brain MRI features (described in Supplemental Table 2) were the independent variables while the chronological age was the dependent variable. The features were normalized to zero mean and unit variance to account for different measurement scales. The actual age was demeaned (shifted to have zero mean) before fitting it into the model to have a centered version of the outcome (4). Sex, education level, height, and volumetric scaling from T1 head image to standard space were used as confounds as they can significantly affect the outcome. The confounds were regressed from the features using a linear regression model prior to modeling brain age.

The brain aging model was built based on participants with non-IHD by splitting the data into two subsets (training set, 80%; testing set, 20%). The model performance for both training and test datasets was assessed using the Mean Absolute Error (MAE) and the coefficient of determination (R2). MAE in brain age studies is interpreted as the deviation between predicted brain age and the chronological age expressed in years, with higher values indicating older appearing brains. R2 represents the proportion of variance in the predicted brain age explained by the used features in the model.

Brain age estimation may involve an observed bias, with age underestimation in older participants, overestimation in younger subjects and more accurate estimation for those with ages close to the mean age (5). We removed the age-dependency bias using the statistical method described previously (6)(3). In brief, we calculated the slope (α) and the intercept (β) from the training data as follow: $D = \alpha^{*}\Omega+\beta$, where D is the brain age delta and Ω is the actual age. Then we used the slope and the intercept to correct the estimated brain age in the test dataset as follows: corrected predicted brain age = predicted brain age – $(\alpha^{*}\Omega+\beta)$. After bias-correction, we calculated brain-age delta by subtracting the chronological age from the predicted brain age in the test datasets, with positive values (expressed in years) indicating accelerated brain aging. Pearson correlation was also calculated between actual age and brain-age delta, before and after bias correction.

Next, brain age was estimated on IHD subjects using the previously trained model to assess the deviation of the brain-age delta from the reference (non-IHD) population. The same steps of features preparation and bias correction using the parameters calculated on the training data were applied. IHD and non-IHD groups were compared in terms of model performance and difference in mean brain-age delta, the latter considered as a measure of apparent brain aging (4).

Relationship between brain age and risk of dementia

To evaluate whether brain age was related with risk of dementia, we studied the association between brain-age delta and incident dementia using logistic regression on a sample comprising both IHD and non-IHD (test set) subjects (n = 8,389). Among them, 27 developed dementia after the imaging visit (incident event). Criteria used to define dementia based on selected UKB fields are reported in Supplemental Table 6.

Logistic regression model was fitted using brain-age delta as the predictor variable and incident dementia (0 = non-dementia, 1= dementia) as the response variable. The model was adjusted for age, sex, and education level.

Since there were fewer subjects with incident dementia than those without (27 vs 8,362, respectively), to account for imbalance between the two groups, we used propensity score matching based on age and sex to identify an equal number of non-dementia subjects. We then repeated the association analysis using logistic regression on the 54 subjects (dementia, n=27 vs non-dementia, n=27) adjusted for education level. The association between brain-age delta and risk of dementia are presented in terms of beta value, odds ratio (OR) and 95% confidence interval (CI).

Mediation effects of WMH on IHD and brain age

We performed a mediation analysis to test to what extent the effects of IHD on brain aging (as expressed by brain-age delta) were mediated by WMH, a proxy of cerebrovascular injury. The analysis was conducted using ordinary least squares regression, as described in a previous publication (7). In the model, the input was whether the subject had IHD or not (0, 1), the output was the brain-age delta, and the mediator was WMH. For this analysis, the associations between variables were described using the term effect as per statistical convention. Specifically, we evaluated the following associations' pathways: 1) IHD with brain-age delta (direct effect), indicating that IHD directly affects brain aging without any mediator; 2) IHD with brain-age delta through WMH (indirect effect), indicating that the effects of IHD on brain aging are indirect as WMH mediates them. The total effect indicates the combination of both direct and indirect effects of IHD on brain aging.

We conducted both unadjusted and adjusted analyses using sex, education level, age, height, and volumetric scaling from the T1 head image to standard space as covariates. We used the tool PROCESS (R & SPSS) as an implementation of the mediation analysis.

Association of brain age with vascular risk factors and imaging parameters

To assess the role of vascular risk factors and imaging parameters to model brain age, the association between brain-age delta values and such exposures was evaluated using a linear regression model in both IHD and non-IHD (test-set) groups. In the model, the brain-age delta was the dependent variable while the exposure was the independent variable adjusted for the same confounds as before plus age. The p-values were corrected for multiple comparisons using the Bonferroni method (alpha= 0.05; number of tests = 19). In the regression model we used unstandardized measures to reveal the effect (beta value) of changing one unit in the exposure on the brain-age delta. Specifically, changing the exposures may lead to increasing or decreasing in brain-age delta (estimated in years) based on the direction of the association (positive vs negative beta value).

Finally, to evaluate whether the imaging parameters were actually linked with the risk of dementia, we studied the association between the CMR metrics and incident dementia using logistic regression. This test was conducted only on the non-IHD group (test-set) (n= 8,389) as this was the only subset where we observed significant associations between brain-age delta and some imaging parameters. The number of non-IHD (test-set) subjects with available CMR metrics who developed dementia (incident event) was 8. Logistic regression model was fitted using the CMR measures as the predictor variable and incident dementia (0 = non-dementia, 1= dementia) as the response variable. The model was adjusted for age and sex.

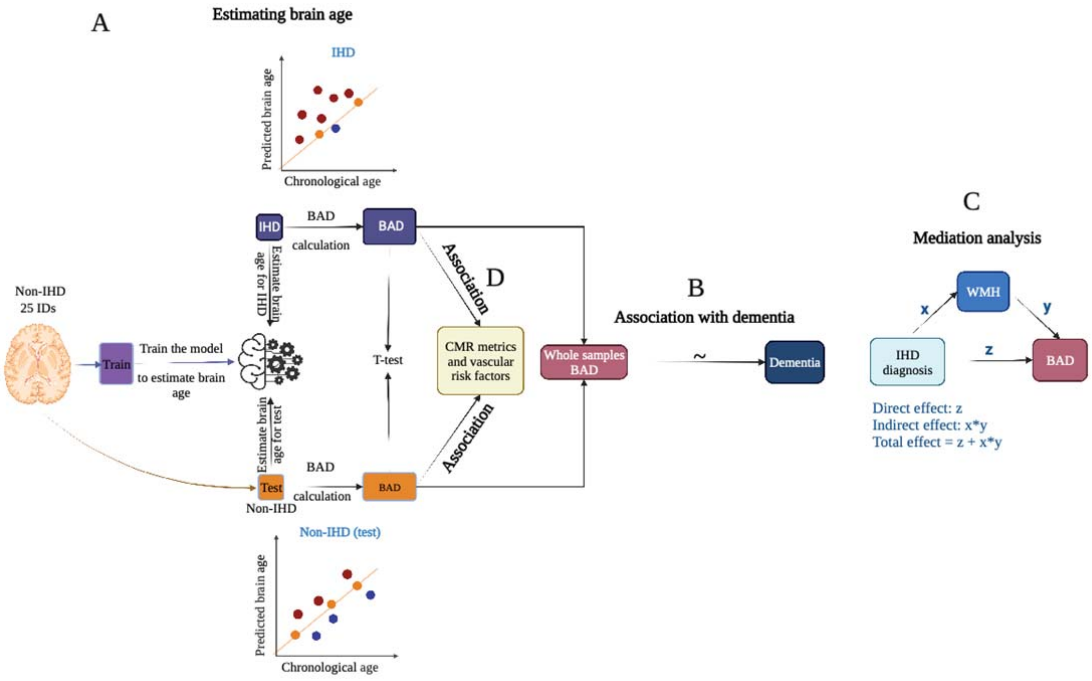
REFERENCES

1. Miller KL., Alfaro-Almagro F., Bangerter NK., et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci 2016;19(11):1523–36. Doi: 10.1038/nn.4393.
2. Smith SM., Zhang Y., Jenkinson M., et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17(1):479–

89. Doi: 10.1006/nimg.2002.1040.

3. Salih A., Galazzo IB., Jaggi A., et al. Multi-modal Brain Age Estimation: A Comparative Study Confirms the Importance of Microstructure. Math Vis 2021:239–50. Doi: 10.1007/978-3-030-73018-5_19.
4. Smith SM., Vidaurre D., Alfaro-Almagro F., Nichols TE., Miller KL. Estimation of brain age delta from brain imaging. Neuroimage 2019;200(February):528–39. Doi: 10.1016/j.neuroimage.2019.06.017.
5. de Lange AMG., Cole JH. Commentary: Correction procedures in brain-age prediction. NeuroImage Clin 2020;26. Doi: 10.1016/j.nicl.2020.102229.
6. Beheshti I., Nugent S., Potvin O., Duchesne S. Bias-adjustment in neuroimaging-based brain age frameworks: A robust scheme. NeuroImage Clin 2019;24:102063. Doi: 10.1016/j.nicl.2019.102063.
7. Hayes Andrew F. Introduction to Mediation, Moderation, and Conditional Process Analysis - Model Numbers. vol. 46. 2013.

Figure 1. Illustration of the staged approach



A – Brain age and its deviation from chronological age (brain-age delta, a marker of brain aging), was estimated in subjects with prevalent IHD using a Bayesian ridge regression model with 25 structural (volumetric) brain MRI features (IDPs) and built using UK Biobank participants with non-IHD. **B** – Validation of brain aging model by studying its association with dementia risk using logistic regression analysis. **C** – Evaluating potential mechanistic links between IHD and brain aging using mediation analysis: to what extent WMH, marker of microvascular injury, mediated the effects of IHD on brain aging. **D** – Evaluating the association of vascular risk factors and CMR metrics with brain aging in IHD vs non-IHD using linear regression analysis. *IHD, ischemic heart disease; BAD, brain-age delta; IDPs, imaging-derived phenotypes; WMH, white matter hyperintensity.*

Supplemental Tables

Supplemental Table 1. List of ICD-10 codes used to define ischemic heart disease from the UK Biobank showcase

Source	UKB Field	ICD-10 value	Description
ICD10 Summary diagnoses	41270, 41280	I20	Angina pectoris
		I21	Acute myocardial infarction
		I22	Subsequent myocardial infarction
		I23	Certain current complications following acute myocardial infarction
		I24	Other acute ischaemic heart diseases
		I25	Chronic ischaemic heart disease

Supplemental Table 2. UK Biobank data sources for ascertainment of brain imaging-derived phenotypes (IDP)s

UKB Field	Description
25 brain IDPs used in the brain age model	
T1 structural brain MRI	
25001	Volume of peripheral cortical grey matter (normalised for head size)
25002	Volume of peripheral cortical grey matter
25003	Volume of ventricular cerebrospinal fluid (normalised for head size)
25004	Volume of ventricular cerebrospinal fluid
25005	Volume of grey matter (normalised for head size)
25006	Volume of grey matter
25007	Volume of white matter (normalised for head size)
25008	Volume of white matter
25009	Volume of brain, grey + white matter (normalised for head size)
25010	Volume of brain, grey + white matter
25025	Volume of brain stem + 4th ventricle
Subcortical volumes (FIRST)	
25011	Volume of thalamus (left)
25012	Volume of thalamus (right)
25013	Volume of caudate (left)
25014	Volume of caudate (right)
25015	Volume of putamen (left)
25016	Volume of putamen (right)
25017	Volume of pallidum (left)
25018	Volume of pallidum (right)
25019	Volume of hippocampus (left)
25020	Volume of hippocampus (right)
25021	Volume of amygdala (left)
25022	Volume of amygdala (right)
25023	Volume of accumbens (left)
25024	Volume of accumbens (right)
Brain IDP used in the mediation analysis	
T2-weighted brain MRI	
25781	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)

Supplemental Table 3. UK Biobank data sources for ascertainment of clinical exposures

Source	UKB Field	Description
Body Mass Index (BMI)		
Body size measures: Standing height, weight	50, 21002	BMI (Kg/m^2) = weight (kg)/ $height^2$ (m)
Diabetes		
Diagnosed by doctor	2443	Diabetes
Self-reported medication	6177, 6153	Insulin
Blood biochemistry	30750	Glycated haemoglobin (HbA1c) > 48 mmol/mol
Hypercholesterolemia		
Self-reported medication	6177, 6153	Cholesterol lowering medication
Blood biochemistry	30690	Serum total cholesterol >7 mmol/L
Hypertension		
Self-reported medication	6177, 6153	Blood pressure medication
Smoking (current smoker)		
Self-report	1239	Yes, on most or all days Only occasionally
Townsend index		
Baseline characteristics	189	Townsend deprivation index at recruitment
Waist-hip-ratio		
Body size measures: Waist circumference, hip circumference	48,49	Waist-hip-ratio = Waist circumference/ Hip circumference

Supplemental Table 4. UK Biobank data sources for ascertainment of incident dementia

Data source	Data-Field	Code
Non-cancer illness code, self-reported	20002	1263
ICD10	41270	A810, F106, G300, G301, G308 F000, F001, F002, F009, G310 G311, G318, F010, F011, F012 F013, F018, F019, F020, F021 F022, F023, F024, F028, F03, F051
ICD9	41271	2900, 2904, 2941, 3310, 3312, 3315
First occurrence	130836	Date F00 first reported (dementia in Alzheimer's disease)
	130838	Date F01 first reported (vascular dementia)
	130840	Date F02 first reported (dementia in other diseases classified elsewhere)
	130842	Date F03 first reported (unspecified dementia)
	131036	Date G30 first reported (Alzheimer's disease)

Supplemental Table 5. Volumes of brain structures (IDPs) in non-IHD vs IHD cohorts

Brain IDPs	Non-IHD cohort		IHD cohort		P-value
	mean	std	mean	std	
Volume of peripheral cortical grey matter (normalised for head size)	618959.8	40626.84	599087.3	40014.86	< 0.001
Volume of peripheral cortical grey matter	480148	46281.87	473869.2	44952.75	< 0.001
Volume of ventricular cerebrospinal fluid (normalised for head size)	46237.34	19787.14	53153.54	21182.61	< 0.001
Volume of ventricular cerebrospinal fluid	36319.79	17036.72	42494.42	18274.66	< 0.001
Volume of grey matter (normalised for head size)	794023.4	47572.36	768429.7	47479.02	< 0.001
Volume of grey matter	615842.1	55827.31	607745.1	54850.85	< 0.001
Volume of white matter (normalised for head size)	702272.1	40667.01	698004	41216.11	< 0.001
Volume of white matter	545987.3	61865.18	553256.1	60999.43	< 0.001
Volume of brain, grey + white matter (normalised for head size)	1496296	72794.98	1466434	70042.4	< 0.001
Volume of brain, grey + white matter	1161829	111840	1161001	108259.5	0.790
Volume of thalamus (left)	7763.514	770.7964	7652.83	760.4853	< 0.001
Volume of thalamus (right)	7570.728	746.9204	7467.788	742.5225	< 0.001
Volume of caudate (left)	3381.543	425.1762	3392.709	426.7801	0.350
Volume of caudate (right)	3564.397	448.1929	3579.341	451.284	0.244
Volume of putamen (left)	4771.879	605.4202	4738.842	601.0369	0.057
Volume of putamen (right)	4828.078	595.7929	4800.423	598.7282	0.105
Volume of pallidum (left)	1757.298	246.4241	1756.316	257.1644	0.889
Volume of pallidum (right)	1802.18	246.7956	1784.172	257.2562	0.011
Volume of hippocampus (left)	3785.05	482.4387	3723.634	499.445	< 0.001
Volume of hippocampus (right)	3898.62	494.3978	3833.532	527.2664	< 0.001
Volume of amygdala (left)	1263.909	247.5637	1287.664	257.5384	0.001
Volume of amygdala (right)	1226.507	273.073	1249.522	279.9848	0.003
Volume of accumbens (left)	494.9743	120.8047	477.5845	126.1691	< 0.001
Volume of accumbens (right)	389.2074	111.4514	365.6991	112.4412	< 0.001
Volume of brain stem + 4th ventricle	22885.63	2889.264	22917.28	2888.373	0.702
Total volume of white matter hyperintensities (from T1 and	4858.15	6323.31	6724	7612.60	< 0.001

T2_FLAIR images)					

Values (expressed in mm^3) are presented as mean ± standard deviation with the p-value for the difference (assessed with the t-test) between the two cohorts. IHD = ischemic heart disease.

Supplemental Table 6. Correlation between brain-age delta and actual age before and after age-bias adjustment

Correlations	Non-IHD Train	Non-IHD Test	IHD
Correlation between predicted age and chronological age before correction	0.62	0.62	0.55
Correlation between brain age-delta and chronological age before correction	-0.001	-0.001	-0.70
Correlation between predicted age and chronological age after correction		089	0.85
Correlation between brain age-delta delta and chronological age after correction		0.004	0.02

The correlation value between brain-age delta and chronological age in both cohorts decreased to close to zero after the predicted brain age was corrected from bias, indicating that the derived brain-age delta was free from age dependency.

Supplemental Table 7: Association of CMR indices with incident dementia in non-IHD

Feature	Beta value	P value
LVEF, %	-0.0002	0.07
LVEDVI, ml/m2	0.0000	1
LVESVI, ml/m2	0.0000	1
LVSVI, ml/m2	-0.0001	1
LVMI, g/m2	0.0000	1
RVEDVI, ml/m2	-0.0001	1
RVESVI, ml/m2	0.0000	1
RVSVI, ml/m2	-0.0001	0.45
TAC, ml/m2 x mmHg	-0.002	1
M/V ratio, g/ml	-0.003	1
Aortic distensibility, 10^{-3}/mmHg	-0.001	1
LVGFI, %	-0.0002	0.05

LVEDVI = left ventricular end-diastolic volume index, LVEF = left ventricular ejection fraction, LVESVI = left ventricular end-systolic volume index, LVMI = left ventricular mass index, LVSVI = left ventricular stroke volume index, RVEDVI = right ventricular end-diastolic volume index, RVESVI = right ventricular end-systolic volume index, RVSVI = right ventricular stroke volume index, LVGFI = left ventricle global function index, M/V = LV mass-to-volume ratio, TAC = total arterial compliance.

Supplemental Figures

Figure legends (titles and captions)

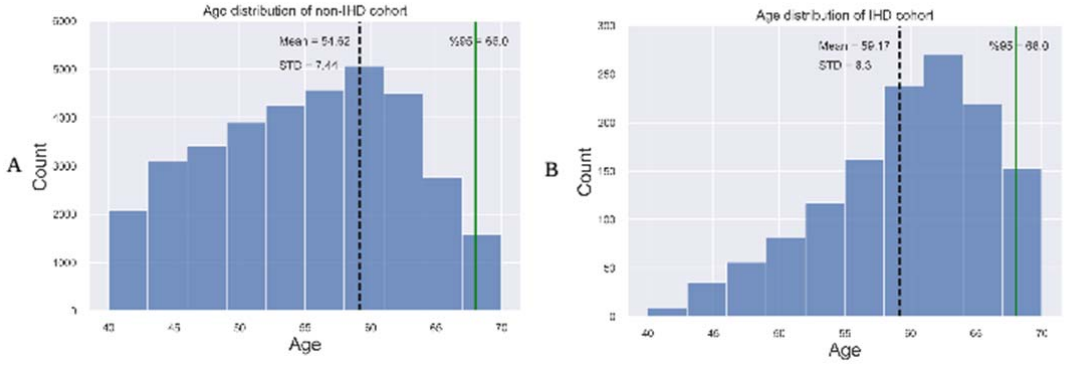
Supplemental Figure 1. Distribution of actual age range in IHD vs non-IHD groups

The two cohorts showed a similar age range (40-70), albeit the distribution was slightly skewed to the left in the IHD cohort. The black dashed line indicates the mean value; the solid green line indicates the 95% percentile. The mean age for non-IHD (A) was 54.6 ± 7.4 years, and for IHD (B) was 59.2 ± 6.3 years. Very few participants had an age range above the 95% percentile in both groups.

Supplemental Figure 2. Predicted brain age in both groups

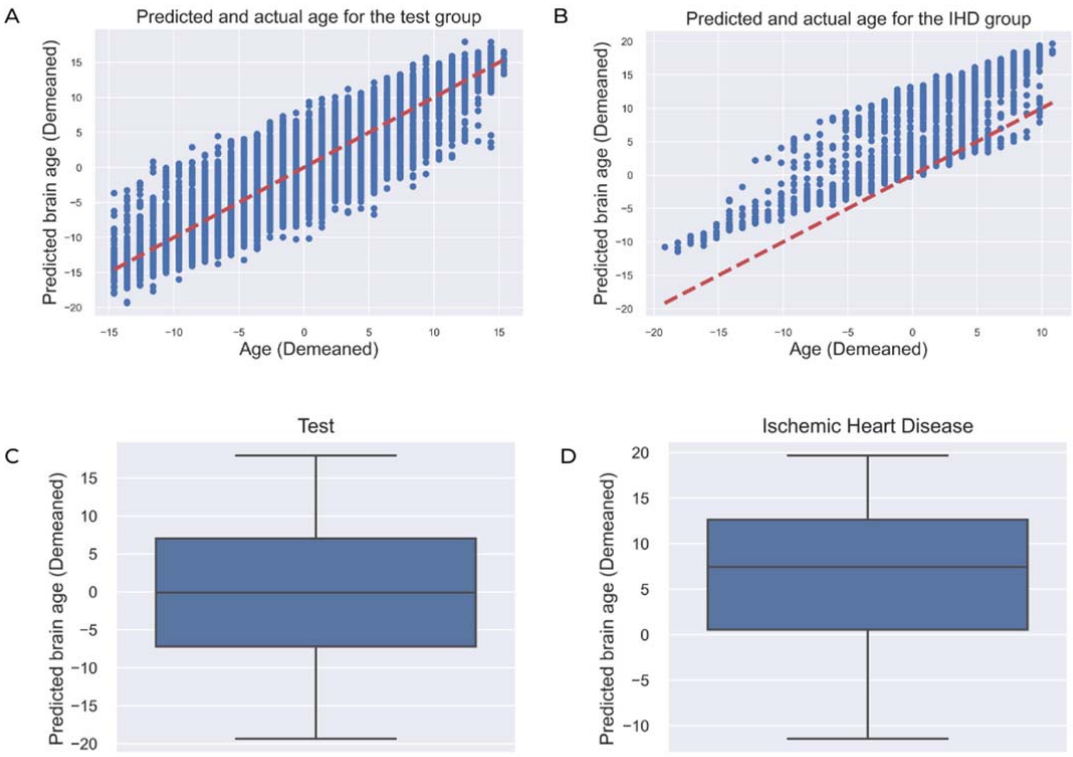
The regression line (red dashed) from the trained model fits well with the test (non-IHD) (A) but not with the IHD data (B), explaining the higher MAE value in the IHD group. The age ranges in both cohorts appear different from the actual ones (40-70) because age was demeaned before fitting into the model. The boxplots (C, D) describe the distribution of predicted brain age (demeaned) in both cohorts, with the mean (median) value, and the first and third quartiles. The mean predicted brain age for IHD (D) is higher than for the test group (C). Furthermore, both cohorts have no predicted brain age as an outlier.

Supplemental Figure 1. Distribution of actual age range in IHD vs non-IHD group



The two cohorts showed a similar age range (40-70), albeit the distribution was slightly skewed to the left in the IHD cohort. The black dashed line indicates the mean value; the solid green line indicates the 95% percentile. The mean age for non-IHD (A) was 54.6 ± 7.4 years, and for IHD (B) was 59.2 ± 6.3 years. Very few participants had an age range above the 95% percentile in both groups.

Supplemental Figure 2. Predicted brain age in both groups



The regression line (red dashed) from the trained model fits well with the test (non-IHD) (A) but not with the IHD data (B), explaining the higher MAE value in the IHD group. The age ranges in both cohorts appear different from the actual ones (40-70) because age was demeaned before fitting into the model. The boxplots (C, D) describe the distribution of predicted brain age (demeaned) in both cohorts, with the mean (median) value, and the first and third quartiles. The mean predicted brain age for IHD (D) is higher than for the test group (C). Furthermore, both cohorts have no predicted brain age as an outlier.