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ORIGINAL ARTICLE

# Machine-learning-derived heart and brain age are independently associated with cognition

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## Abstract

**Background and purpose:** A heart age biomarker has been developed using deep neural networks applied to electrocardiograms. Whether this biomarker is associated with cognitive function was investigated.

**Methods:** Using 12-lead electrocardiograms, heart age was estimated for a population-based sample ($N = 7779$, age 40–85 years, 45.3% men). Associations between heart delta age (HDA) and cognitive test scores were studied adjusted for cardiovascular risk factors. In addition, the relationship between HDA, brain delta age (BDA) and cognitive test scores was investigated in mediation analysis.

**Results:** Significant associations between HDA and the Word test, Digit Symbol Coding Test and tapping test scores were found. HDA was correlated with BDA (Pearson's $r = 0.12$, $p = 0.0001$). Moreover, 13% (95% confidence interval 3–36) of the HDA effect on the tapping test score was mediated through BDA.

**Discussion:** Heart delta age, representing the cumulative effects of life-long exposures, was associated with brain age. HDA was associated with cognitive function that was minimally explained through BDA.

KEYWORDS
cognitive tests, deep neural networks, dementia, ECG, MRI

## INTRODUCTION

Alzheimer's disease and related dementia (ADRD) represents one of the leading public health problems in aging populations due to its increasing prevalence and high management costs [1]. Affected individuals may experience a long period of illness, for example more than 10 years, and display varying clinical symptoms, from subjective memory complaints and mild cognitive impairment to complete loss of daily functioning. Currently, there is no effective treatment to slow down or cure ADRD development [2].

Recently, the Lancet 2020 Commission evaluated the impact of 12 risk factors on ADRD and estimated that up to 40% of cases could be prevented by properly managing these factors over the life course [3]. Amongst these, five are vascular risk factors, that is, hypertension, diabetes mellitus, smoking, high alcohol consumption and obesity. Cerebrovascular pathology has long been recognized as a key contribution to ADRD [4]. It has been estimated that as many as 50% of ADRD patients have cerebrovascular pathology, in addition to AD pathology [5]. Therefore, advancement in our understanding of the connections between the heart or vascular health and brain and cognitive health may facilitate the prognosis, prevention, diagnosis and management of ADRD.

An electrocardiogram (ECG), which records the electrical activity of the heart, has been used to monitor heart functioning for more than a century [6]. The standard 12-lead ECG is routinely used to detect abnormal rhythms, structural abnormalities and acute cardiac events. Combined with other clinical measures, it assists clinicians with making diagnoses of arrhythmia, ventricular hypertrophy and other heart conditions. In the past decade, advances in machine learning (ML) algorithms and computational power have made it possible to predict chronological age using raw digitized ECG recordings [7]. Heart delta age (HDA), defined as the difference between ECG-predicted age and chronological age, has emerged as a novel marker for cardiovascular health. For example, larger HDA has been shown to be associated with an adverse cardiovascular disease (CVD) risk factor profile and higher mortality [8, 9]. In addition, it has been shown that HDA is an independent predictor of CVD after controlling for traditional vascular risk factors such as blood pressure, dyslipidaemia, smoking and diabetes [8, 10]. However, the association of HDA with cognitive functioning or dementia has not yet been examined.

Previously, ML models have been applied to magnetic resonance imaging (MRI) of the brain to estimate the brain delta age (BDA), defined as the difference between MRI-predicted brain age and chronological age [11, 12]. Because of its association with cognitive performance and neurological disorders [13–16], BDA has been used as an indicator of general brain and cognitive health.

Here, the aim was to study the effect of HDA on cognitive performance in a well-characterized Norwegian population cohort—the Tromsø Study [17]. In addition, the BDA was estimated for a subset of participants to study the relationship between the two ML-based age estimators and its possible role as a mediator of the relationship between HDA and cognitive function.

## METHODS

### Study population

The Tromsø Study began in 1974 and has had repeated waves of measurements for a range of CVD risk factors plus cognitive function for a population-based sample in Tromsø (Norway) [17]. The most recent wave (Tromsø7) was completed in 2016 and included digital 12-lead ECGs for 7779 participants (40–85 years old; 45.3% men), amongst whom 1694 had T1-weighted structural MRI available [17]. This analysis is based on data collected in Tromsø7 and thus is a cross-sectional study. The detailed characteristics of the study population, sampling procedure, recruitment procedure, collected questionnaires and measurements, and participation rates are described in the cohort profile [17]. None of the participants had a diagnosis of dementia at the time of data collection.

### Data collection

#### Demographic and CVD risk factors

The following characteristics were collected for the study participants during the health examination: mean of second and third systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI) (weight/height$^2$) and low-density lipoprotein (LDL) cholesterol (mmol/L). Information about smoking (current/past), diabetes, education, self-reported previous CVD (myocardial infarction, stroke, atrial fibrillation) and use of blood pressure medication or lipid lowering drugs was collected from the questionnaires.

#### Estimating ECG-predicted age and brain age using deep neural networks (DNNs)

Resting 10-s digital 12-lead ECGs were obtained from 7779 participants using the Schiller device AT104 PC, and the raw ECG signal was stored digitally. A novel DNN model developed by our group in collaboration with the Mayo Clinic (Rochester, MN, USA) was used to estimate age based on ECG [7]. Briefly, the regression model was trained on standard 10-s 12-lead ECGs, sampled at 500 or 250 Hz and resampled to 500 Hz, acquired in the supine position from 774,783 adult patients (18 years or older) from the Mayo Clinic. The data were split into training/validation (499,727 persons) and testing data (275,056 persons) [7]. A convolutional neural network architecture, adjusted to have spatial and temporal feature extraction layers, was implemented using the Keras Framework in Tensorflow (Google) [18]. The only data used for training were the raw digital 12-lead ECG signal and age of each individual. This model has also been extensively validated in other populations and has been shown to predict total and cardiovascular mortality [8].

Heart delta age was computed for 7779 adults in the Tromsø7 as the difference between the ECG-predicted age and the

chronological age (Table S1). Amongst these participants, 1694 also had T1-weighted structural MRI scans performed. Participants were scanned at the University Hospital North Norway in a 3T Siemens Skyra MR scanner (Siemens Healthcare). A 64-channel head coil was used in most examinations, but in 39 examinations a slightly larger 20-channel head coil had to be used. The MRI-predicted brain age was estimated using a previously published DNN algorithm [11]. Briefly, this DNN model was built on a large multisite collection of T1-weighted brain MRI scans from healthy participants ($n = 11{,}729$) covering individuals of ages 3–95 for training the DeepBrainNet model and for calculating cross-validated brain age predictions, the testing sample consisted of 2739 participants. Raw T1-weighted scans were input to the DeepBrainNet model after minimally and fully automated pre-processing [11]. The BDA was computed for 1693 Tromsø7 study participants as the MRI-predicted brain age minus chronological age at MRI scanning.

### Cognitive function tests

Cognitive function was assessed with four standardized tests, chosen because of their ability to detect early cognitive decline and their feasibility in screenings. The cognitive tests included the Digit Symbol Coding Test (DSCT), the finger tapping test, the Word test 1 and 2 (WT1 and WT2) and the Mini-Mental State Examination (MMSE). The MMSE shows high sensitivity for detecting moderate-to-severe cognitive impairments but has lower sensitivity at detecting mild degrees of impairment [19]. Performance on the DSCT, WT1, WT2 and the finger tapping test is sensitive to early cognitive changes [20, 21]. Further details on cognitive tests are given in the footnote of Table S2.

## Statistical analysis

### Descriptive and bivariate analysis

Descriptive analyses for all study variables were performed to obtain the mean and standard deviation (SD) for continuous variables and proportions for categorical variables. The correlation between HDA and BDA in 1694 participants with both measures available was calculated using the Pearson correlation coefficient. The bivariate analysis for association of each of the CVD risk factors with HDA and cognitive test scores was done using linear regression analysis adjusting for chronological age and sex. For further regression analysis the complete case analysis was conducted including participants who had non-missing values for cognitive testing and covariates. Regression towards the mean is a well-known problem when studying estimators for biological age [22]. Therefore, to obtain unbiased results, all analyses were done adjusting for chronological age in the regression models [22]. SAS version 9.4 was used for statistical analysis, and R software with the medflex package [23] was used for mediation analysis.

### Associations between HDA and cognitive scores, BDA and cognitive scores

Scores for DSCT, the finger tapping test and the WT1 were used as continuous dependent variables and continuous HDA was the independent variable in the ordinary least squares regression models. A median regression analysis was used for MMSE and the WT2 due to non-normal residuals from the ordinary least squares regression models. The linearity of the relationship between exposure variables (HDA and BDA) and cognitive tests was assessed with restricted cubic splines (four knots). No substantial nonlinear associations were observed when using the Akaike information criterion as the test criterion between the nested models. Two nested models were used to adjust for variables associated both with cognitive test scores and HDA. Model 1 was adjusted for chronological age and sex. Model 2 was adjusted for the variables in model 1 + CVD risk factors (SBP, DBP, LDL cholesterol, BMI, diabetes, smoking) and education. Final sample size for these analyses was 6764–6967 participants depending on the cognitive test investigated. In the additional analysis model 2 was adjusted for previous self-reported CVD (stroke, myocardial infarction, atrial fibrillation), blood pressure medication use and lipid lowering drug use. To examine interactions with age and sex, interaction terms were added in separate models. Age groups were defined as <65 and ≥65 years to obtain approximately equally sized groups. Interactions were considered statistically significant at $p < 0.1$.

Next, the analysis was restricted to 1694 participants who had both HDA and BDA available and the analytical steps outlined above were repeated. The final sample size of these analyses was in the range from 1450 to 1481 participants for regression models controlling for cardiovascular risk factors. The association between HDA, BDA and declined cognitive performance (MMSE < 24) was estimated using logistic regression.

### Mediation analysis

A formal mediation analysis was applied to test whether BDA mediates the effects of HDA on cognitive function by estimating total, direct and indirect effects using the natural effects model [23]. The HDA and BDA were standardized to $z$ scores to allow between-biomarker comparability. Chronological age and sex were controlled for in the mediation analysis. Here, it is noted that our use of the term 'effect' is purely statistical and does not imply causality.

## RESULTS

The mean age of the total sample of 7779 participants was 63.8 years; 45.3% were men. A subsample of 1694 participants had MRI available in addition to ECG. Table 1 shows the demographic characteristics, CVD risk factors and cognitive test results separately for total sample and subsample. Amongst these demographic and CVD risk

**TABLE 1** Descriptive characteristics of the study sample: the Tromsø Study 2015–2016.

| | Total sample (*N* = 7779), mean (SD) or percentage (*N*) | Subsample (*N* = 1694)[a], mean (SD) or percentage (*N*) |
|---|---|---|
| Demographic characteristics[b] | | |
| Male sex, % (*N*) | 45.3 (3522) | 46.3 (785) |
| Chronological age, mean (SD) | 63.78 (10.41) | 64.32 (10.59) |
| Heart delta age (HDA), mean (SD) | −4.63 (7.30) | −4.92 (7.31) |
| Brain delta age (BDA), mean (SD) | −4.85 (5.12) | −4.85 (5.12) |
| Education, % (*N*) | | |
| Primary/partly secondary | 22.3 (2220) | 29.6 (490) |
| Upper secondary | 28.0 (2126) | 27.6 (946) |
| College/university <4 years | 18.4 (1399) | 20.2 (1281) |
| College/university >4 years | 24.3 (1846) | 22.6 (1655) |
| CVD risk factors[b] | | |
| Systolic blood pressure, mean (SD) | 134.0 (20.2) | 134 0.0 (20.8) |
| Diastolic blood pressure, mean (SD) | 75.5 (9.9) | 75.2 (9.9) |
| Smoking, % (*N*) | | |
| Current | 12.3 (941) | 13.0 (218) |
| Past | 47.4 (3639) | 48.0 (805) |
| Never | 40.3 (3095) | 39.0 (654) |
| Diabetes, % (*N*) | 8.6 (670) | 7.7 (131) |
| BMI, mean (SD) | 27.3 (4.4) | 27.2 (4.2) |
| LDL cholesterol, mean (SD) | 3.58 (1.0) | 3.57 (1.0) |
| Previous self-reported CVD (MI, stroke, atrial fibrillation), % (*N*) | 14.2 (1103) | 23.9 (405) |
| Blood pressure medication, % (*N*) | 33.9 (2639) | 33.8 (573) |
| Lipid lowering drugs, % (*N*) | 22.3 (1736) | 23.9 (405) |
| Cognitive tests[b] | | |
| Mini-Mental State Examination, median (IQR) | 28.0 (27–29) | 28.0 (27–29) |
| Word test 1 (immediate recall), mean (SD) | 7.23 (2.04) | 7.30 (2.0) |
| Word test 2 (cued recall), median (IQR) | 23.0 (21–24) | 23.0 (21–24) |
| Digit Symbol Coding Test, mean (SD) | 42.8 (13.2) | 43.0 (12.4) |
| Tapping test (dominant hand), mean (SD) | 59.9 (8.9) | 60.5 (8.4) |
| Tapping test (non-dominant hand), mean (SD) | 53.9 (9.3) | 54.1 (8.9) |

Abbreviations: BDA, brain delta age (MRI-predicted brain age − chronological age); BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; HDA, heart delta age (ECG-predicted age − chronological age); IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; SBP, systolic blood pressure; SD, standard deviation.

[a]Subsample with MRI available.

[b]Missing: education 188, smoking 104, LDL 37, SBP/DBP 21, BMI 6, MMSE 517, Digit Symbol Coding Test 634, Word test 1 and 2 489, tapping test (dominant) 695, tapping test (non-dominant) 695.

factors, education, SBP, BMI, smoking, previous CVD, and taking blood pressure and lipid lowering medication were associated with cognitive test scores (Table S3).

The ECG-predicted age for the study sample was estimated by the DNN model [7]; then HDA was computed as the difference between the ECG-predicted age and the chronological age. The estimated ECG-predicted age was significantly correlated with chronological age ($r = 0.72$, $p < 0.0001$; Figure 1a). The mean HDA for these participants was −4.63 (SD 7.30) years. The HDA was significantly associated with education, SBP, DBP, BMI, smoking, previous CVD, and taking blood pressure and lipid lowering drugs (Table S4). There was a negative association between HDA and WT1, WT2, DSCT, tapping test (dominant hand) and tapping test (non-dominant hand) (Table 2). Controlling for CVD risk factors partially attenuated

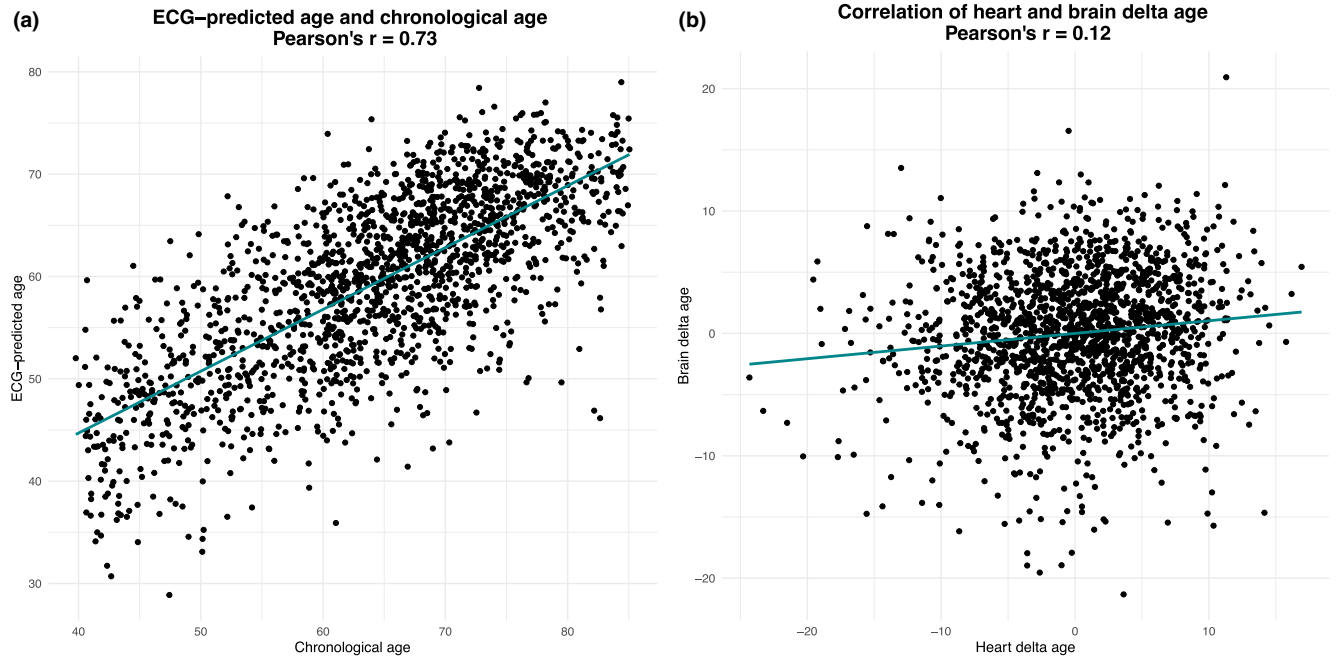


**FIGURE 1** (a) Scatter plot of ECG-predicted age versus chronological age. (b) Scatter plot of HDA versus BDA.

**TABLE 2** Regression coefficients for the association between HDA (per 1 SD = −7.3 years) and cognitive test scores: the Tromsø Study 2015–2016.

| Dependent variable | *N* | Model 1[a] *β* (95% CI) | *p* value | Model 2[a] *β* (95% CI) | *p* value |
|---|---|---|---|---|---|
| Mini-Mental State Examination[b] | 6940 | −0.02 (−0.07 to 0.04) | 0.521 | 0.03 (−0.02 to 0.08) | 0.291 |
| Word test 1 (immediate recall) | 6967 | −0.08 (−0.13 to −0.02) | 0.004 | −0.04 (−0.09 to 0.01) | 0.124 |
| Word test 2 (cued recall)[b] | 6967 | −0.06 (−0.13 to 0) | 0.038 | −0.05 (−0.1 to 0) | 0.070 |
| Digit Symbol Coding Test | 6836 | −0.59 (−0.89 to −0.32) | <0.001 | −0.31 (−0.57 to −0.06) | 0.017 |
| Tapping test (dominant hand) | 6775 | −0.31 (−0.52 to −0.09) | 0.005 | −0.18 (−0.39 to 0.03) | 0.097 |
| Tapping test (non-dominant hand) | 6764 | −0.38 (−0.6 to −0.16) | <0.001 | −0.25 (−0.46 to −0.03) | 0.029 |

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDA, heart delta age; LDL, low-density lipoprotein; SBP, systolic blood pressure.

[a]Model 1, adjusted for chronological age, sex; model 2, adjusted for chronological age, sex, SBP, DBP, smoking (current/past), diabetes, BMI, LDL cholesterol, education.

[b]Median regression was used for the Mini-Mental State Examination and Word test 2 (cued recall); linear regression was used for the other cognitive scores.

these associations (Table 2), but the DSCT and tapping test (non-dominant hand) were still statistically significantly associated with HDA.

There were 1694 participants with both HDA and BDA available for analyses. In this subsample, the estimated ECG ages were also correlated with chronological age ($r = 0.73$, $p < 0.0001$) and the HDA was within the range of our full sample (mean −4.92, SD = 7.31), both values very similar to the values in the total sample. Furthermore, HDA was associated with education, SBP, DBP, BMI, smoking, previous CVD (Table S4). HDA was significantly correlated with BDA ($r = 0.12$, $p < 0.0001$) (Figure 1b). In line with previous reports [15, 24–26], BDA (per SD) was negatively associated with cognitive abilities: WT2, DSCT, tapping test (dominant hand) and tapping test (non-dominant hand) (Table 3). After controlling for CVD risk factors, these associations were attenuated, but DSCT, tapping test (dominant hand) and tapping test (non-dominant hand) remained significantly associated with BDA. No significant associations were found between BDA and WT1 or MMSE (Table 3).

Adjustment for history of cardiovascular events or taking blood pressure or lipid lowering medications did not noticeably attenuate the relationship between HDA and cognitive scores, BDA and cognitive scores; however, for HDA it became not statistically significant (Tables S5 and S6). The associations of HDA and BDA with cognitive scores did not differ by sex (*p* values for interaction term >0.1). However, they differed by age group (<65 and ≥65 years), and age group specific results are presented in Tables S7 and S8. Briefly, for participants <65 years old the associations of HDA with cognitive scores were stronger than for those ≥65 years old. The opposite was true for BDA: associations with cognitive scores were stronger for participants ≥65 years old than for those <65 years old.

**TABLE 3** Regression coefficients for the association between BDA (per 1 SD = −5.1 years) and cognitive function scores: the Tromsø Study 2015–2016.

| | *N* | Model 1[a] *β* (95% CI) | *p* value | Model 2[a] *β* (95% CI) | *p* value |
|---|---|---|---|---|---|
| Mini-Mental State Examination[b] | 1483 | −0.8 (−0.17 to 0.02) | 0.107 | −0.02 (−0.11 to 0.06) | 0.603 |
| Word test 1 (immediate recall) | 1481 | −0.04 (−0.13 to 0.05) | 0.365 | 0.01 (−0.08 to 0.11) | 0.748 |
| Word test 2 (cued recall)[b] | 1481 | −0.1 (−0.2 to −0.01) | 0.038 | −0.07 (−0.15 to 0.02) | 0.133 |
| Digit Symbol Coding Test | 1456 | −1.36 (−1.84 to −0.88) | <0.001 | −1.10 (−1.57 to −0.63) | <0.001 |
| Tapping test (dominant hand) | 1450 | −0.78 (−1.14 to −0.42) | <0.001 | −0.52 (−0.89 to −0.16) | 0.005 |
| Tapping test (non-dominant hand) | 1453 | −0.75 (−1.13 to −0.38) | <0.001 | −0.49 (−0.87 to −0.10) | 0.013 |

Abbreviations: BDA, brain delta age; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDA, heart delta age; LDL, low-density lipoprotein; SBP, systolic blood pressure.

[a]Model 1, adjusted for chronological age, sex; model 2, adjusted for chronological age, sex, SBP, DBP, smoking (current/past), diabetes, BMI, LDL cholesterol, education.

[b]Median regression was used for the Mini-Mental State Examination and the Word test 2 (cued recall); linear regression was used for the other cognitive scores.

**TABLE 4** Total, direct and indirect effects of HDA[a] on cognitive score with BDA[a] included as a mediator of indirect effect: the Tromsø Study 2015–2016.

| | *N* | Total | Direct | Indirect | Proportion mediated |
|---|---|---|---|---|---|
| Word test 1 (immediate recall) | 1540 | −0.01 (−0.03 to 0) | −0.01 (−0.03 to 0) | 0 (0 to 0) | –[b] |
| Digit Symbol Coding Test | 1510 | −0.54 (−1.15 to 0.07) | −0.34 (−0.95 to 0.28) | −0.2 (−0.32 to −0.08) | –[b] |
| Tapping test (dominant hand) | 1507 | −0.79 (−1.19 to −0.39) | −0.67 (−1.08 to −0.27) | −0.12 (−0.19 to −0.04) | 15 (5 to 35) |
| Tapping test (non-dominant hand) | 1503 | −0.81 (−1.27 to −0.35) | −0.71 (−1.18 to −0.24) | −0.11 (−0.18 to −0.03) | 13 (3 to 36) |

Abbreviations: BDA, brain delta age; HDA, heart delta age.

[a]HDA and BDA were standardized to *z* scores; chronological age and sex are controlled for in the mediation model.

[b]Not enough power in the subsample to assess the mediated proportion in the mediation analysis.

No significant associations were found between HDA and MMSE below threshold (<24) (odds ratio 1.01, 95% confidence interval [CI] 0.99–1.03; $p = 0.31$) but BDA increased the odds of MMSE <24 (odds ratio 1.08, 95% CI 1.00–1.15; $p = 0.04$).

To test whether BDA mediates the effect of HDA on cognitive ability, mediation analyses were performed for tapping test scores which were significantly associated with both. Only 15% (95% CI 5–35; dominant hand) and 13% (95% CI 3–36; non-dominant hand) of the total effects of HDA on these scores were mediated by BDA (Table 4; Figure 2). These mediation effects were in the same direction as the direct effect, that is, high BDA and HDA additively impact cognitive performance.

## DISCUSSION

The relationship of the new indicator of cardiovascular age—HDA—and cognitive performance was examined in detail in a population-based sample. Here a novel finding of association between HDA and cognitive scores is presented capturing verbal memory, psychomotor speed, attention and mental flexibility. For the subsample of participants with both HDA and BDA measured a mediation analysis was conducted and it was found that only 13% of the association between HDA and cognitive scores was mediated by BDA (indirect effect). Most of the HDA effect on the cognitive scores occurs through a direct effect. Based on this finding and the weak association between HDA and BDA, it can be suggested that both biomarkers have value as independent predictors of cognitive performance.

Heart delta age apparently represents the accumulated effect to the cardiovascular system from life-long exposure to the range of risk factors (blood pressure, low-density cholesterol, adiposity, smoking, high blood glucose) in addition to factors yet to be identified [8]. Adjustment for common CVD risk factors partially attenuated the association between HDA and cognitive scores, suggesting that HDA is on the path between these factors and cognitive function. The fact that HDA was independently associated with cognitive function after controlling for traditional risk factors supports the idea that HDA may better reflect the accumulated exposure to measured and unmeasured risk factors. HDA values probably change following improvement or worsening of cardiovascular risk factors or incident comorbidities [7]; however, more studies are needed to determine what factors predict the longitudinal change in HDA and what effect this change can have on overall and cognitive health. Because the history of acute cardiovascular events may be reflected in HDA [7, 8], analysis adjusting for previous CVD and blood pressure or lipid lowering medications was also conducted. In this model the relationship between HDA and cognitive scores was not noticeably attenuated; however, it became not

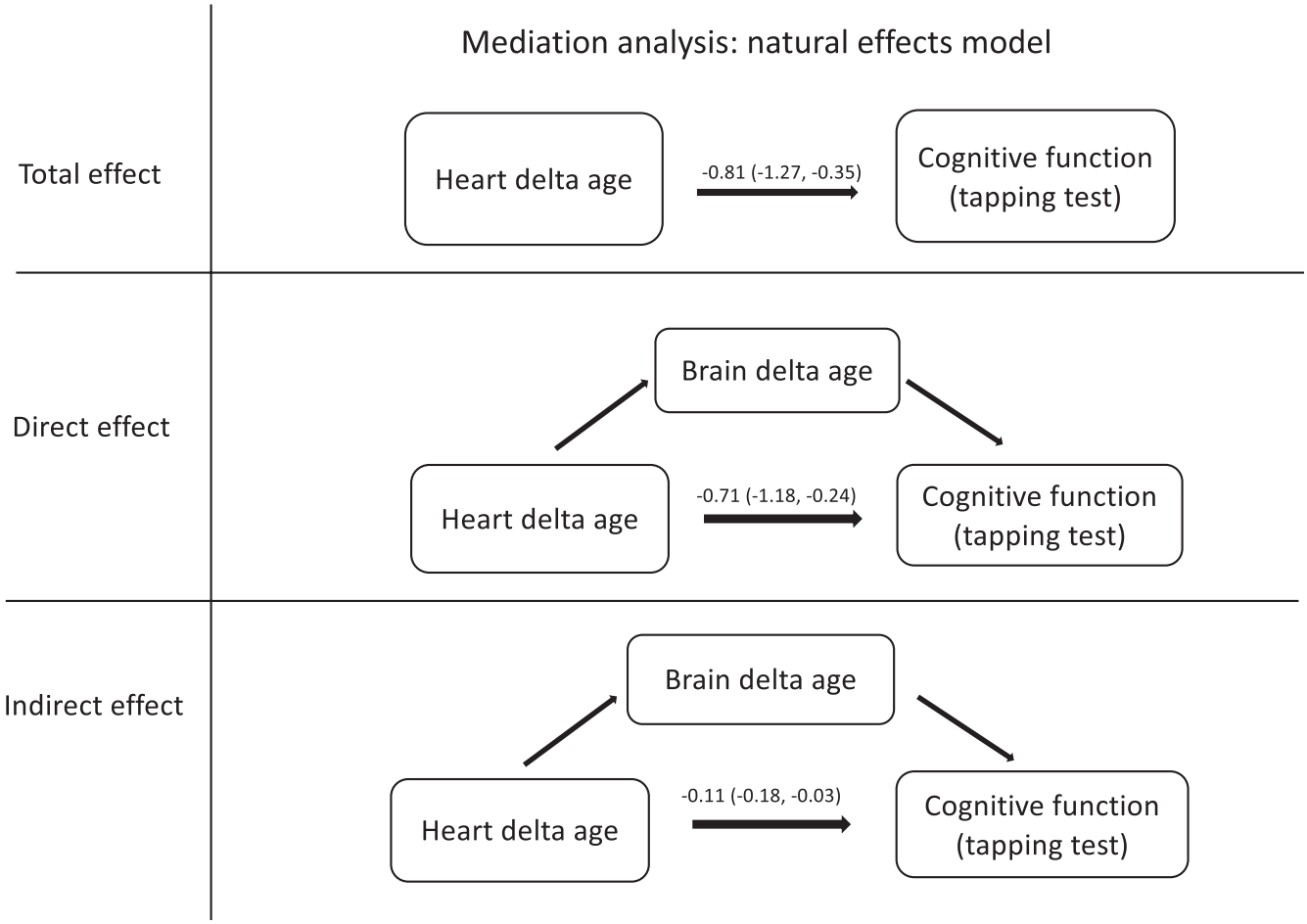


**FIGURE 2** Mediation analysis.

statistically significant. In this paper the direction of effect from cardiovascular system to brain is assumed; however, there is evidence of effects in the opposite direction. For example, the stroke–heart syndrome has been described to cause acute damage to the heart, increasing risk of immediate death after stroke [27]. However, evidence of long-term complications to the cardiovascular system given that the patient survived the stroke is scarce [27]. In our study, 249 (3%) participants have reported that they had stroke previously, which suggests that some of them may experience long-term complications affecting the cardiovascular system due to the stroke–heart syndrome.

The ECG-derived HDA is increasingly being considered as a marker of cardiovascular system aging. This aging marker is related to endothelial function [28] and predicts cardiovascular outcomes [8]. As expected, a modest association between HDA and cognitive scores was found. This association can be explained by the importance of the vascular component in age-related cognitive decline and dementia, although the mechanisms are not fully understood. The subtype of dementia which is primarily driven by vascular factors (vascular dementia) constitutes 10%–15% of all dementia cases with arteriosclerotic microangiopathy being a predominating pathology [29]. In about 50% of dementia cases that are diagnosed as pure AD the incidence of vascular pathology is low and neurodegenerative pathology dominates, whilst the rest of dementia cases are diagnosed as mixed [30]. There is strong evidence that vascular factors contribute not only to vascular dementia subtype but also to AD and mixed dementia [31]. Hypertension, diabetes, dyslipidaemia, tobacco smoking and obesity have been found as AD risk factors [32]. Vascular-derived pathophysiology in AD includes blood–brain barrier leakage, hypoperfusion/hypoxia and endothelial metabolic dysfunction [31]. As a consequence of the cascade of these molecular mechanisms, β-amyloid production and tau-protein synthesis are induced. Moreover, imbalance in cerebrovascular metabolic functions leads to the release of a set of neurotoxic and inflammatory factors (nitric oxide, cytokines, chemokines, prostaglandins etc.) that can trigger neuronal damage directly or indirectly by activating astrocytes and microglia [33]. Apparently, there is an interplay between vascular disease and neurodegeneration which either interact or are in a potentially bidirectional cause–effect relationship, despite the lack of conclusive evidence for a causal link [31].

The MRI-based BDA is a well-known marker of brain age that has been explored intensively [11, 12, 34]. Higher individual BDA is linked to poor brain health, schizophrenia, depression, mild cognitive impairment, dementia and AD [13–16]. The results of the previous studies that BDA is related to lower scores on cognitive tests are confirmed. The magnitude of the association reported in other studies was

dependent on the model used to estimate the BDA and the sample studied (population-based vs. clinical, old vs. young age) [15, 24–26]. There are two dominant views in the literature regarding the explanation of this association, although they should not be regarded as mutually exclusive [25]. One view is that a higher BDA is an indicator of accelerated brain aging that has accumulated over an individual's lifetime [35]; another postulates that individuals vary in their brain and body health from the beginning of life [36, 37]. Both perspectives are supported by the results of empirical studies; perinatal variables (birth weight) and genetic variability are associated with BDA [36, 38], as well as unfavourable lifestyle factors: obesity, diabetes, alcohol consumption, traumatic brain injury, smoking, blood pressure [15, 26, 38–41].

The damaging effects of cardiovascular factors on the brain and cognitive capacity of an individual presumably occur via several mechanisms and only some of them are reflected in the BDA biomarker. A causal mediation framework was used to estimate what proportion of the HDA effect on cognitive function is mediated by the BDA. It is important to state that this causal mediation model does not claim a causal effect of HDA or BDA on cognitive function but rather implies the causal effect of factors of vascular or neurodegenerative origin that lead to elevated values of these aging biomarkers. It was found that only about 13% of the total effect of HDA on cognitive scores is mediated by BDA. This indicates that vascular dysfunction is not necessarily reflected in morphological structures of the brain, at least not at the time point when the measurements of HDA and BDA were conducted in our population-based sample. Vascular risk factors may be reflected in features seen on brain MRI, for example global white matter hyperintensities [42, 43], which may not be fully captured by the DNN algorithm of BDA.

The HDA was associated with the tapping test, WT1, WT2 and DSCT that are sensitive to early cognitive changes [20, 21]. It is believed that lack of association with MMSE is explained by lack of variation in values in our sample of individuals without dementia. Given the age (40–85 years, mean 64 years) of the Tromsø Study participants and a population-based sampling, it is perhaps not surprising that the observed cross-sectional associations with cognitive status were only of moderate strength. Besides, the selective participation in the study may also weaken the association between HDA and cognitive scores in our study. Another limitation of our study is the relatively small number of participants that might have led it to be underpowered for some of the analyses presented.

The advantage of the novel ECG-derived biomarker of cardiovascular age—HDA—is that it is directly obtained from the raw data at low cost in a standardized manner. Whilst its associations with intermediate phenotypes, like cognitive test scores, are important to investigate, the end-point of interest must be dementia. Based on our findings, an attempt to predict, diagnose or manage dementia using brain images should consider vascular factors not captured through the images. Further investigation of novel ECG-derived biomarkers of cardiovascular age in relation to cognitive decline and dementia is warranted as these may hold promise for improved understanding of mechanisms and clinical prediction.

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## CONFLICT OF INTEREST STATEMENT

None.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the Tromsø Study (contact email tromsous@uit.no). The data are not publicly available due to privacy or ethical restrictions.

## ETHICS STATEMENT

The Tromsø Study complies with the Declaration of Helsinki and has been approved by the Regional Committee for Medical and Health Research Ethics (REK), the Data Inspectorate and the Norwegian Directorate of Health. All participants provided written informed consent. The current study was approved by REK North (application number 68185, approved 06.05.2021).

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