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ORIGINAL ARTICLE

Association Between Electrocardiographic Age and Cardiovascular Events in Community Settings: The Framingham Heart Study

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BACKGROUND: Deep neural networks have been used to estimate age from ECGs, the electrocardiographic age (ECG-age), which predicts adverse outcomes. However, this prediction ability has been restricted to clinical settings or relatively short periods. We hypothesized that ECG-age is associated with death and cardiovascular outcomes in the long-standing community-based FHS (Framingham Heart Study).

METHODS: We tested the association of ECG-age with chronological age in the FHS cohorts in ECGs from 1986 to 2021. We calculated the gap between chronological and ECG-age (Δage) and classified individuals as having normal, accelerated, or decelerated aging, if Δage was within, higher, or lower than the mean absolute error of the model, respectively. We assessed the associations of Δage, accelerated and decelerated aging with death or cardiovascular outcomes (atrial fibrillation, myocardial infarction, and heart failure) using Cox proportional hazards models adjusted for age, sex, and clinical factors.

RESULTS: The study population included 9877 FHS participants (mean age, 55±13 years; 54.9% women) with 34 948 ECGs. ECG-age was correlated to chronological age (r=0.81; mean absolute error, 9±7 years). After 17±8 years of follow-up, every 10-year increase of Δage was associated with 18% increase in all-cause mortality (hazard ratio [HR], 1.18 [95% CI, 1.12–1.23]), 23% increase in atrial fibrillation risk (HR, 1.23 [95% CI, 1.17–1.29]), 14% increase in myocardial infarction risk (HR, 1.14 [95% CI, 1.05–1.23]), and 40% increase in heart failure risk (HR, 1.40 [95% CI, 1.30–1.52]), in multivariable models. In addition, accelerated aging was associated with a 28% increase in all-cause mortality (HR, 1.28 [95% CI, 1.14–1.45]), whereas decelerated aging was associated with a 16% decrease (HR, 0.84 [95% CI, 0.74–0.95]).

CONCLUSIONS: ECG-age was highly correlated with chronological age in FHS. The difference between ECG-age and chronological age was associated with death, myocardial infarction, atrial fibrillation, and heart failure. Given the wide availability and low cost of ECG, ECG-age could be a scalable biomarker of cardiovascular risk.

Key Words: artificial intelligence ■ atrial fibrillation ■ cardiovascular diseases ■ electrocardiogram ■ heart failure ■ myocardial infarction ■ risk factors

See Editorial by Ebinger and Cheng

Worldwide, cardiovascular diseases (CVDs) were the leading cause of years of life lost and disability-adjusted life years in 2019.[1] With the global population aging, the health and economic impact of CVD are expected to increase.[2] The ECG is a simple non-invasive method widely used to diagnose and screen for

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WHAT IS KNOWN

- Electrocardiographic age (ECG-age) can be predicted by deep neural network models in health care–based data.
- A deep neural network estimated ECG-age higher than the chronological age of an individual, considering the model's mean absolute error, predicts mortality in the community setting with 9 years of follow-up and in health care settings using vital statistics after 12 years of follow-up. ECG-age also predicts cardiovascular outcomes in a single health care setting, ascertained in administrative data.

WHAT THE STUDY ADDS

- In the present study, we observed that deep neural network–estimated ECG-age was associated with adjudicated atrial fibrillation, myocardial infarction, heart failure, and mortality in the long-standing community-based FHS (Framingham Heart Study).
- Having accelerated ECG-age was related to a higher risk of atrial fibrillation, heart failure, and death, whereas having decelerated ECG-age was associated with decreased risk of heart failure and death.
- Considering that ECGs are low cost and widely available, even in areas with limited health access through telemedicine, ECG-age has the potential to be a scalable marker of cardiovascular risk.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CODE	Clinical Outcomes in Digital Electrocardiography
CVD	cardiovascular disease
ECG-age	electrocardiographic age
ELSA-Brasil	Brazilian Longitudinal Study of Adult Health
DNN	deep neural network
FHS	Framingham Heart Study
HDL	high-density lipoprotein
HR	hazard ratio
HF	heart failure
MI	myocardial infarction

CVD. Recently, artificial intelligence technology applied to the ECG has provided accurate models for CVD risk prediction, including the risk of left ventricular dysfunction, atrial fibrillation (AF), and death.[3–5] One of these models was a deep neural network (DNN)–based age prediction model developed on the CODE (Clinical Outcomes in Digital Electrocardiography) data set to predict an individual's age based on ECG waveform: the electrocardiographic age (ECG-age).

The DNN-estimated ECG-age is correlated to, but often remains distinct from chronological age, with the gap between ECG-age and chronological age being a predictor of overall mortality in adjusted models. In a prior study, accelerated ECG-age compared with chronological age was strongly correlated with overall mortality after 9 years of follow-up.[6] Moreover, in 2 other studies with different ECG-age algorithms, accelerated ECG-age was related to 12- to 15-year cardiovascular outcomes in health care settings, using either vital statistics or electronic medical records for ascertainment.[7,8] However, information is lacking on whether ECG-age can predict cardiovascular outcomes in the community, and for longer follow-up periods. Thus, we aimed to evaluate, whether the DNN-estimated ECG-age algorithm developed by the CODE study is associated with clinical outcomes in the large and long-standing community-based FHS (Framingham Heart Study), accounting for potential confounders.

METHODS

Data Availability

The data that support the findings of this study are available through FHS for Researchers Portal https://www.framinghamheartstudy.org/fhs-for-researchers/ upon reasonable request. The DNN-based ECG-age model developed by the CODE study is publicly available (doi.org/10.5281/zenodo.4892365).

Study Design

FHS is a longitudinal study that originally recruited adults residing in the city of Framingham, MA in 1948, and subsequently their next 2 generations—in 1971 the Offspring (along with spouses of the Offspring) and in 2002 the Third Generation (along with some additional spouses of the Offspring cohort and parent of Third Generation participant) cohorts. To add representativeness to the study, 2 cohorts of residents from underrepresented racial and ethnic groups were added in 1994 (Omni 1) and in 2003 (Omni 2). In 2003, the New Offspring Spouse cohort was added, which included new spouses of participants in the Offspring cohort. The design of the study and detailed information about these cohorts is published elsewhere.[9] Of the eligible participants, for the CVD outcome analysis, we excluded participants who had a prevalent case of the respective outcome (n=219 for AF, n=316 for myocardial infarction [MI], and n=70 for heart failure [HF]), as shown in the flowchart of study participants (Figure S1)

Clinical Variables

We accounted for traditional CVD risk factors to evaluate the relationship between ECG-age and outcomes. Participants underwent interviews, physical examinations, and laboratory measurements, as detailed previously.[9,10] Current cigarette smoking (within the year before examination) and medications for blood pressure, diabetes, and lipid-lowering were assessed by self-report. Body mass index was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic

blood pressures were measured according to the FHS protocol. Diabetes was defined as treatment with a hypoglycemic agent, fasting blood glucose ≥126 mg/dL, or nonfasting plasma glucose of ≥200 mg/dL. The ratio of total cholesterol to HDL (high-density lipoprotein) cholesterol, HDL cholesterol, and triglyceride levels were used to assess lipid levels. CVD and cancer were adjudicated. MI was defined when the participant had ≥2 of 3 findings: (1) symptoms indicative of ischemia, (2) changes in blood biomarkers of myocardial necrosis, and (3) serial changes in the ECG. HF was defined by FHS uniform criteria,[11] and AF was adjudicated by an FHS cardiologist reviewing ECGs from the FHS research center and outside medical records.

Electrocardiographic Age

DNN-Estimated ECG-Age

The ECG-age was predicted by a DNN that uses the raw ECG waveform in an end-to-end approach.[12] The model was trained to predict an individual's age learning to detect and extract features directly from the data, not relying on traditional ECG interpretation.[12,13] The goal of the learning was to capture how aging affects ECG waveform.

The raw ECG signals used to derive the ECG-age model herein were from the CODE study.[14] The CODE study is part of the Telehealth Network of Minas Gerais, Brazil, and its database comprises ECGs obtained from 2010 to 2017 in Brazilian primary care settings.[14] The CODE data set has been recognized as the largest ECG database in the world used to develop deep learning artificial intelligence–ECG applications with 1 558 415 patients.[15] The development of the ECG-age model in the CODE study has been previously described.[6] The ECG-age model uses a convolutional neural network to make the predictions, similar to the residual network proposed for image classification but adapted to unidimensional signals. This architecture was also used for other ECG analysis tasks.[12] The code for the DNN-estimated ECG-age model training, evaluation, and statistical analysis are available at https://github.com/antonior92/ecg-age-prediction.

Accelerated and Decelerated ECG-Age Definitions

To use the DNN-estimated ECG-age information as a variable for CVD risk prediction, which, therefore, captures the excess risk caused by a greater decline in functional status than expected by chronological aging, we divided the participants into 3 categories, as described previously.[6] Those with a DNN-estimated ECG-age in the range of ±9 years, which was the mean absolute error of the studied sample (considered as reference), those with an ECG-age older than the chronological age by ≥9 years (named accelerated ECG-age), and those with an ECG-age younger than the chronological age by ≥9 years (named decelerated ECG-age).

Application to the FHS

The ECG was performed as standard practice in all FHS participants. In 1986, the FHS adopted machines that allowed digital ECG storage (Marquette MAC/PC followed by the Marquette MAC 5000; General Electric). Currently, the system being used is the MUSE 8 ECG Management System (General Electric), which allows contemporary analysis of all ECG data since the digital ECG adoption.[16] We opted to use all ECGs available collected from 1986 to 2021 to validate the algorithm in relation to the chronological age. To study the correlation between the DNN-estimated ECG-age with clinical outcomes, we included only the first available ECG after 40 years of age for each participant.

Study Outcomes

We evaluated all-cause death and specific cardiovascular outcomes for our analysis. Cardiovascular outcomes were incident AF, MI, and HF. The outcomes were confirmed after adjudication by the Framingham End Point Review Committee (a panel of 2–3 clinicians) with information from the study's research examinations and outside medical records (hospital and clinic) as previously stated for the respective condition.[17]

Statistical Analyses

Descriptive statistics were calculated using means and SDs for continuous variables, or frequency counts and percentages for categorical variables. We defined the difference between DNN-estimated ECG-age and chronological age as delta age (Δage). The association of Δage with all-cause mortality or cardiovascular outcomes was assessed using Cox proportional hazards models, with follow-up times censored at the last follow-up time or death. The proportional hazards assumption was assessed using Schoenfeld residuals.[18,19] Participants who developed the cardiovascular outcomes of interest before ECG exams were excluded from the Cox models. All models were adjusted for age and sex. In addition, the models were also adjusted for specific clinical factors related to each cardiovascular outcome using information from previously published risk prediction models that have been validated in diverse populations. For death, the models were additionally adjusted for body mass index, smoking, diabetes, systolic blood pressure, hypertension treatment, HDL cholesterol, triglycerides, lipid treatment, prevalent CVD, and prevalent cancer.[20] For AF, additional covariates were from the Cohorts for Heart and Aging Research in Genomic Epidemiology for Atrial Fibrillation (CHARGE-AF) score, namely, height, weight, smoking, diabetes, systolic blood pressure, diastolic blood pressure, hypertension treatment, prevalent MI, and prevalent HF.[21–23] Additional covariates for MI were smoking, diabetes, systolic blood pressure, diastolic blood pressure, hypertension medication, and the ratio of total cholesterol to HDL cholesterol.[24] For HF, additional covariates were body mass index, smoking, diabetes, systolic blood pressure, hypertension treatment, the ratio of total cholesterol to HDL cholesterol, and prevalent MI.[25]

In the secondary analyses, to account for the competing risk of mortality, we used Fine-Gray models to calculate subdistribution hazard ratios (HRs).[26] In a sensitivity analysis, we excluded ECGs with prevalent MI and AF and tested the association with mortality. We also examined the association of Δage with each clinical outcome stratified by sex. We tested for effect modification by sex in relation to each clinical outcome by including interaction terms in the Cox models. To examine the association of accelerated/decelerated aging with different clinical risk factors, we used logistic regression models adjusted for age and sex. Lastly, we included Δage in the multivariable prediction models for all-cause mortality and the different CVD outcomes to evaluate its incremental discriminatory value and net reclassification improvement. All the statistical analyses were performed using R software, version 4.0.3 (https://www.r-project.org/).

Ethical Considerations

This study complies with all relevant ethical regulations. The Boston University Medical Center Institutional Review Board approved the FHS, and all participants provided written informed consent. The CODE study was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais, protocol 49368496317.7.0000.5149. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting our study.

RESULTS

We included 9877 participants from the FHS cohorts with 34 948 valid digital ECGs. The clinical characteristics of the study participants are shown in Table 1, including the prevalence of traditional cardiovascular risk factors. The mean age was 55±13 years, and 54.9% were women. The detailed age distribution of the sample is depicted in Figure S2. There was a strong correlation between chronological age and DNN-estimated ECG-age among the study participants, with a correlation coefficient of 0.81 (Figure 1). The mean absolute error of DNN-estimated ECG-age was 9±7 years (Figure S3). No significant correlation between chronological age and the age gap was found in this study, revealing that the difference between chronological age and ECG-age occurs along the whole age spectrum (Figure S4).

Table 1. Clinical Characteristics of Study Participants When First ECG Was Done After the Age of 40 y

Characteristics	n=9877
Age, y	55±13
Women, n (%)	5424 (54.9)
Current smoker, n (%)	1747 (17.7)
BMI, kg/m^2	27.2±5.3
Diabetes, n (%)	376 (3.8)
SBP, mm Hg	127±20
DBP, mm Hg	77±10
Hypertension treatment, n (%)	2209 (22.4)
Total cholesterol, mg/dL	202±40
HDL, mg/dL	52±16
Ratio of total cholesterol to HDL cholesterol	3.9 (3.1–5.1)
Triglycerides, mg/dL	100 (68–150)
Lipid treatment, n (%)	655 (6.6)
Height, cm	169±39
Weight, kg	66±4
Prevalent AF, n (%)	219 (2.2)
Prevalent MI, n (%)	316 (3.2)
Prevalent HF, n (%)	70 (0.7)
Prevalent CVD, n (%)	663 (6.7)
Prevalent cancer, n (%)	752 (7.6)

Values are n (%) for dichotomous variables and mean±SD (or median [25%–75%] if skewed distribution) for continuous variables. AF indicates atrial fibrillation; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HF, heart failure; MI, myocardial infarction; and SBP, systolic blood pressure.

Association of ΔAge With All-Cause Mortality

Table 2 shows the association of Δage with all-cause mortality in the age- and sex-adjusted model, and the multivariable-adjusted model. After 17±8 years of follow-up, every 10-year increase in Δage was associated with 18% of all-cause mortality (HR, 1.18 [95% CI, 1.12–1.23]) even after adjusting for known risk factors. The result remained largely the same after excluding participants with prevalent AF or MI (HR, 1.17 [95% CI, 1.11–1.24]). Moreover, accelerated aging (Δage, ≥9 years) was associated with a 28% increase in all-cause mortality (HR, 1.28 [95% CI, 1.14–1.45]), while decelerated aging (Δage, ≤9 years) was associated with 16% decrease of all-cause mortality (HR, 0.84 [95% CI, 0.74–0.95]). Figure 2 shows survival curves computed from the multivariable-adjusted Cox proportional hazards models. During a mean follow-up of 17±8 years, individuals with accelerated aging showed a higher mortality rate than those with normal aging. In contrast, individuals with decelerated aging showed a lower mortality rate than those with normal aging (P<0.001). It should also be noted that the number of patients at risk decreased over time, which contributed to a relatively wider CI at the later stage of follow-up, especially after 20 years of follow-up.

Association of ECG-Age With Cardiovascular Outcomes

Table 3 shows the association of DNN-estimated ECG-age with different cardiovascular outcomes. Every 10-year increase in Δage was associated with a 23% increase in AF risk (HR, 1.23 [95% CI, 1.17–1.29]), a 14% increase in MI risk (HR, 1.14 [95% CI, 1.05–1.23]), and 40% increase of HF risk (HR, 1.40 [95% CI, 1.30–1.52]). When competing risk of death was taken into account in secondary analysis, most of the associations were attenuated but remained significant (HR, 1.18 [95% CI, 1.12–1.24] for AF, 1.10 [95% CI, 1.01–1.20] for MI, and 1.31 [95% CI, 1.21–1.43] for HF; Table S1). The survival curves for AF/MI/HF were shown in Figures S5 through S7, respectively. Similar to the association with all-cause mortality, different aging groups had different risks to develop cardiovascular outcomes. The difference becomes more obvious when participants got older, and more events were observed.

Aligned with the results for mortality, accelerated aging also was associated with incident AF, MI, and HF in the age- and sex-adjusted models, but only for AF and HF in the multivariable-adjusted multivariable models. Similarly, decelerated aging was associated with reduced risk of incident MI, AF, and HF in the age- and

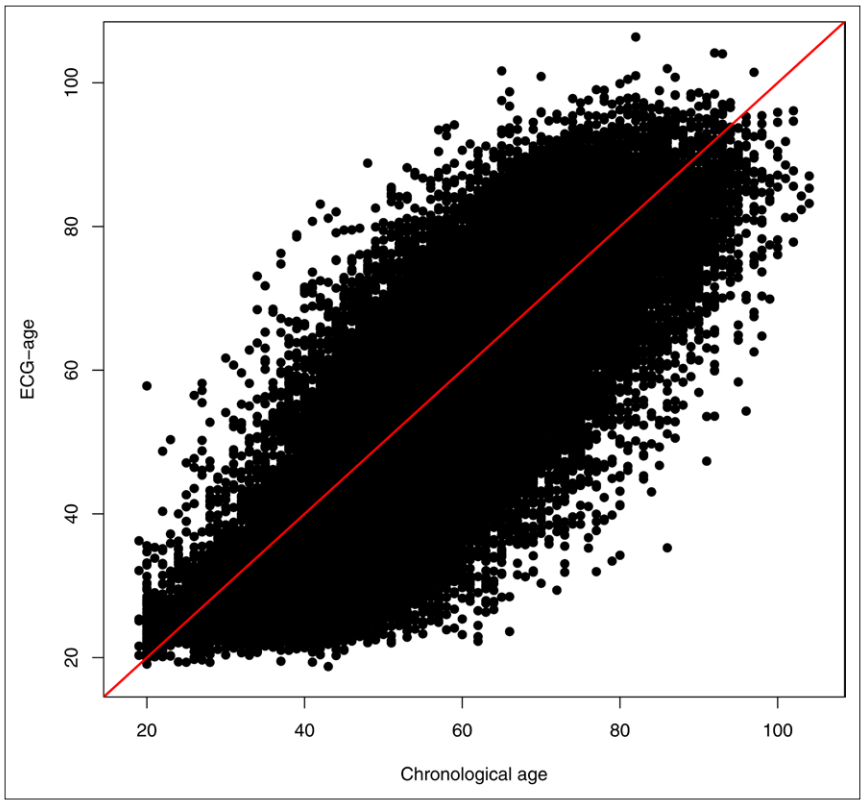

Figure 1. Correlation between chronological age and deep neural network estimated electrocardiographic age (ECG-age; Pearson correlation coefficient, 0.81; $P<2.2\times10^{-16}$).

sex-adjusted models, but only for HF in the multivariable model (HR, 0.70 [95% CI, 0.56–0.88]; Table 3).

We also examined the effect modification by sex for the association between Δage and clinical outcomes. As shown in Table S2, the association of Δage with incident AF was more significant for women than men (*P* interaction, 0.004). For women, a 10-year increase of Δage was associated with 33% higher AF risk (HR, 1.33 [95% CI, 1.24–1.44]), compared with 13% for men (HR, 1.13 [95% CI, 1.06–1.21]). However, we did not observe significant sex-related differences in the association with all-cause mortality, MI, or HF.

Table 2. Association of the Difference Between Deep Neural Network ECG-Age and Chronological Age (ΔAge), Accelerated and Decelerated ECG-Aging With All-Cause Mortality in Age- and Sex-Adjusted Models and in the Multivariable-Adjusted Models

	Adjusted for age and sex			Multivariable model*		
	All-cause deaths; number of events, 3332					
	HR	95% CI	*P* value	HR	95% CI	*P* value
10-y Δage	1.20	1.16–1.24	<0.001	1.18	1.12–1.23	<0.001
Accelerated vs normal aging	1.37	1.25–1.50	<0.001	1.28	1.14–1.45	<0.001
Decelerated vs normal aging	0.79	0.73–0.86	<0.001	0.84	0.74–0.95	0.006

Accelerated aging: participants with predicted ECG-age older than the chronological age by 9 y (1 mean absolute error); decelerated aging: participants with predicted ECG-age younger than the chronological age by 9 y. HR after adjusting for covariates. BMI indicates body mass index; CVD, cardiovascular disease; ECG-age, electrocardiographic age; HDL, high-density lipoprotein; HR, hazard ratio; and SBP, systolic blood pressure.

*Adjusted for age, sex, BMI, current smoking, diabetes, SBP, hypertension treatment, HDL, triglyceride, lipid treatment, prevalent CVD, and prevalent cancer.

To better understand the potential mechanism of accelerated and decelerated aging, we also examined their association with different clinical risk factors, including smoking, hypertension, diabetes, obesity, and dyslipidemia. As shown in Table S3, smoking, hypertension, and diabetes were associated with a higher risk of accelerated aging. On the contrary, smokers with hypertension and obesity were also less likely to have decelerated aging.

Lastly, when we included Δage in the multivariable prediction models for the different outcomes, the increase in C statistics ranged from 0.0% for all-cause mortality to 0.7% for HF (all with $P>0.05$), suggesting that ECG-age only provided limited incremental discriminatory value to existing multivariable models. No significant net reclassification improvement was observed.

DISCUSSION

In the large and long-standing FHS, we observed that the DNN-estimated ECG-age was highly correlated to chronological age. The difference between DNN-estimated ECG-age and chronological age (referred to as Δage)

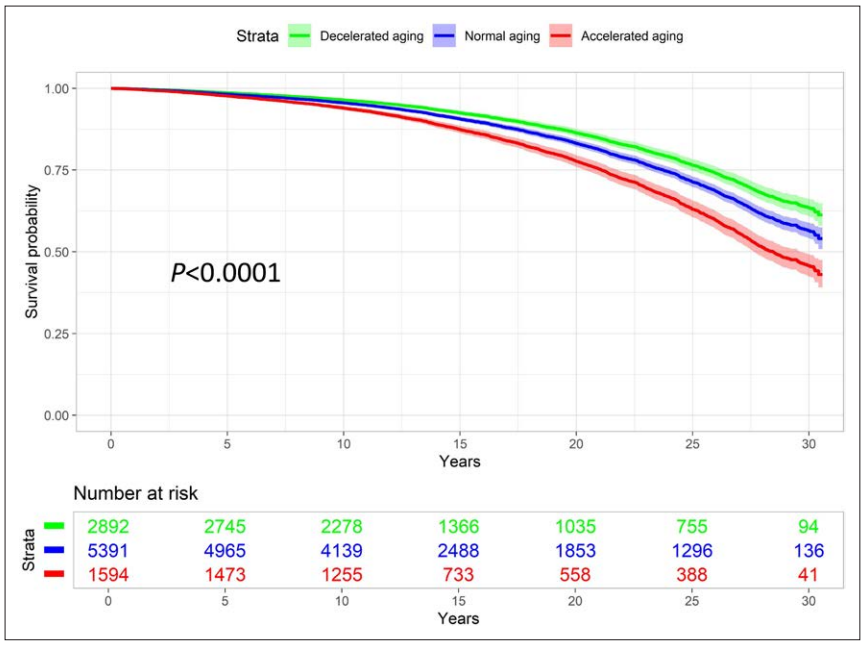

Figure 2. Survival curves computed from the multivariable-adjusted Cox proportional model for all-cause mortality, stratified into 3 groups of participants: those with deep neural network estimated electrocardiographic age (ECG-age) ≥9 years less than the chronological age (decelerated aging); those with deep neural network estimated ECG-age within a range of ±9 years from their chronological age (normal aging); and those with deep neural network estimated ECG-age ≥9 years greater than the chronological age (accelerated aging).

was associated with all-cause mortality and adjudicated cardiovascular outcomes—AF, MI, and HF—in the FHS. Our study suggests that ECG-age may reflect an accelerated compromise in cardiac electrical function, possibly captured from the ECG waveform through artificial intelligence. On the other hand, decelerated aging was a protective factor for mortality, corroborating our findings. For specific cardiovascular outcomes, accelerated and decelerated aging were able to predict AF and HF in multivariable models, but not MI. Taken together, our results suggest that ECG-age is related to adverse events in the community, with the potential to be scalable considering the broad availability, low cost, and simplicity of the ECG.

Previous studies have linked traditional electrocardiographic data, not including DNN-estimated ECG-age, to cardiovascular risk. In a post hoc analysis of a randomized controlled trial of the Women's Health Initiative, Denes et al[27] observed that ECG abnormalities were related to cardiovascular mortality after 3 years of follow-up in 14 749 asymptomatic women. In the Multi-Ethnic Study of Atherosclerosis, ECG abnormalities were also associated with a higher incidence of cardiovascular outcomes, in 6765 asymptomatic individuals (mean age, 60±9 years; follow-up, 12 years).[28] In the ELSA-Brasil cohort study (Brazilian Longitudinal Study of Adult Health; n=13 428; mean age, 51±8 years; 45% men; follow-up, 8±1 years), having a major ECG abnormality was an independent predictor of all-cause death in the community with an HR of 2.3 (95% CI, 1.7–2.9), and cardiovascular death with an HR of 4.6 (95% CI, 3.0–7.0).[29] Additionally, in the FHS, nonspecific ECG abnormalities and left ventricular hypertrophy have been identified as predictors of coronary artery disease, while longer electrocardiographic QRS was associated with increased HF risk.[30–32]

Regarding ECG-age, Raghunath et al[3] developed a DNN model based on ECG waveforms, which predicted 1-year all-cause mortality with an area under the curve of 0.86. The ECG-age model developed by the CODE study itself has also been tested for all-cause mortality in the derivation and 2 validation cohorts from Brazil.[6] One of these validation cohorts is the community-based ELSA-Brasil cohort study (n=15 105; mean age, 52±9 years; women, 54%), for which accelerated aging was able to predict 1-year overall mortality in age- and sex-adjusted Cox models, with an area under the curve of 0.77 (95% CI, 0.66–0.87).[6] Ladejobi et al and Chang et al have also explored the relation of an age gap between the ECG and chronological ages using different artificial intelligence algorithms. In both studies, DNN-estimated ECG-age was a predictor of cardiovascular mortality in health care settings, with an HR of 1.94 (95% CI, 1.48–2.54) and 3.49 (95% CI, 1.74–7.01).[7,8] Our study adds to these findings, revealing that ECG-age is also able to predict adjudicated cardiovascular outcomes in the community setting in a longer follow-up compared with previous validation cohorts both from Brazil, a racially-admixed middle-income country.

The mechanisms by which DNN-estimated ECG-age can explain cardiovascular risk may be complicated since the DNN model remains partially unclear in terms of interpretation. In a previous analysis of more than 88 000 participants, no significant differences were observed between regular ECG features (heart rate, P duration, QRS axis and duration, RR intervals, and QTc interval) among individuals with accelerating, normal, or decelerating aging.[6] To better comprehend the phenomenon, an analysis restricted to normal ECGs classified by traditional analysis reported that even for normal ECGs, the DNN-estimated ECG-age association with death

Table 3. Association of the Difference Between Deep Neural Network ECG-Age and Chronological Age (ΔAge), Accelerated, and Decelerated ECG-Aging With Cardiovascular Outcomes (Incident Atrial Fibrillation, MI, and Heart Failure) in Age- and Sex-Adjusted Models and in the Multivariable-Adjusted Models

	Adjusted for age and sex			Multivariable model*		
	HR	95% CI	*P* value	HR	95% CI	*P* value
AF; number of events, 1443						
10-y Δage	1.26	1.20–1.32	<0.001	1.23	1.17–1.29	<0.001
Accelerated vs normal aging	1.49	1.31–1.70	<0.001	1.44	1.23–1.69	<0.001
Decelerated vs normal aging	0.74	0.65–0.84	<0.001	0.89	0.75–1.05	0.16
MI; number of events, 732						
10-y Δage	1. 23	1.15–1.32	<0.001	1.14	1.05–1.23	0.002
Accelerated vs normal aging	1.30	1.07–1.57	0.008	1.17	0.94–1.47	0.16
Decelerated vs normal aging	0.76	0.63–0.91	0.003	0.89	0.72–1.11	0.32
HF; number of events, 965						
10-y Δage	1.40	1.32–1.49	<0.001	1.40	1.30–1.52	<0.001
Accelerated vs normal aging	1.71	1.46–2.00	<0.001	1.75	1.45–2.12	<0.001
Decelerated vs normal aging	0.65	0.55–0.76	<0.001	0.70	0.56–0.88	0.002

Accelerated aging: participants with predicted ECG-age older than the chronological age by 9 y (1 mean absolute error); decelerated aging: participants with predicted ECG-age younger than the chronological age by 9 y. HR after adjusting for covariates. AF indicates atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; ECG-age, electrocardiographic age; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; and SBP, systolic blood pressure.

*Adjustments: for AF, height, weight, smoking, diabetes, SBP, DBP, hypertension treatment, prevalent MI, and prevalent HF; for MI, SBP, DBP, hypertension medication, diabetes, ratio of total cholesterol to HDL cholesterol, and smoking status; for HF, additionally adjusted for BMI, SBP, hypertension treatment, diabetes, ratio of total cholesterol to HDL cholesterol, smoking status, and prevalent MI. These results were not adjusted for the competing risk of death, which is presented in Table S2.

remained significant.[6] It seems that, at least in part, ECG-age prediction was not related to traditional ECG abnormalities.[6] The hypothesis is further confirmed by studies merging traditional and deep learning features, suggesting that the traditional ECG features alone do not account for the good performance in age prediction from ECGs.[13] In the present analysis, the association of DNN-estimated ECG-age with all-cause death did not change when excluding ECGs from individuals with previous MI and AF. Previous studies have found that known ECG features that better capture the excess risk are related to low-frequency components of the ECG, usually related to P and T waves, but are not restricted to them.[6]

Prior data suggest that DNN-estimated ECG-age is able to capture changes that are not completely determined by known cardiovascular risk factors.[6,7] In fact, the presence of cardiovascular risk factors has been correlated to accelerated aging in previous studies and in the present analysis.[6,7] However, in our analysis and others, these risk factors did not fully explain the association of accelerated and decelerated ECG-age with adverse outcomes, particularly for AF and HF.

Comprehending the risk associated with accelerated aging or the benefit of decelerated aging is more intuitive since the concept of biological aging (decline in functional status) versus chronological aging (time from birth) has already been examined using different types of biomarkers, including those from inflammatory and epigenetic pathways[33–36] However, these were not compared with DNN-estimated ECG-age. Clinical, inflammatory, and genomic markers of biological aging were complementary in predicting mortality in an FHS 30-year follow-up study.[34] The interesting aspect of DNN-estimated ECG-age is that it appears to be a proxy for biological aging from a single input, perhaps capturing the residual risk from traditional and unknown factors.

However, the drawbacks to the applicability of DNN-estimated ECG-age must be acknowledged. The obscurity about what ECG-age indeed measures leads to uncertainty about interpreting the results. Future research should focus on understanding the determinants associated with DNN-estimated ECG-age, investigating if ECG-age measures modifiable excess risk, and how to translate the knowledge to clinical practice. For this reason, we did not aim to evaluate the incremental discriminatory value provided by Δage on traditional cardiovascular risk scores in the present analysis. Moreover, the prediction models for DNN-estimated ECG-age may be specific to certain populations, based on sociodemographic characteristics or the prevalence of cardiovascular risk factors. As such, using large and representative derivation data sets to develop the algorithms are fundamental to improving ECG-age prediction, along with evaluating the ECG-age prediction ability in the community setting and for different cardiovascular outcomes.

Our study addresses some of these barriers. First, we replicated the DNN-estimated ECG-age algorithm derived from the largest digital ECG data set currently available (CODE study),[6,15] which is from a population with diverse backgrounds from FHS participants. Moreover, we evaluated DNN-estimated ECG-age prediction ability for different cardiovascular outcomes in the community setting in the long-standing FHS, which has a comprehensive assessment of risk factors, comorbidities, and adjudicated outcomes. Previous studies have only assessed mortality,[6–8] or specific cardiovascular outcomes ascertained in administrative data.[8] However, our limitations must also be acknowledged. We were not able to include all ECGs from FHS participants because some were not digitalized, and others did not pass quality control. We did not find significant improvement by adding DNN-estimated ECG-age to multivariable clinical risk models in terms of C statistics or net reclassification improvement. In addition, we cannot implicate the causality of ECG-age to cardiovascular outcomes or death

due to the observational nature of our study and potential residual confounding. In addition, the FHS was a single-site cohort, largely of European ancestry, and the generalizability of the findings to more diverse populations is unknown.

In conclusion, DNN-estimated ECG-age correlates with chronological age and was associated with all-cause death, MI, AF, and HF in the community setting. Due to the wide availability and low cost of the ECG, DNN-estimated ECG-age has the potential to be a scalable marker of cardiovascular risk, as a strategy to promote cardiovascular health.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S7

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