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Artificial intelligence age prediction using electrocardiogram data: Exploring biological age differences

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ABSTRACT

BACKGROUND Biological age can be predicted using artificial intelligence (AI) trained on electrocardiograms (ECGs), which is prognostic for mortality and cardiovascular events.

OBJECTIVE We developed an AI model to predict age from an ECG and compared baseline characteristics to identify determinants of advanced biological age.

METHODS An AI model was trained on ECGs from cardiology inpatients aged 20–90 years. AI analysis used a convolutional neural network with data divided in an 80:20 ratio (development/internal validation), with external validation undertaken using data from the UK Biobank. Performance and subgroup comparison measures included correlation, difference, and mean absolute difference.

RESULTS A total of 63,246 patients with 353,704 total ECGs were included. In internal validation, the correlation coefficient was 0.72, with a mean absolute difference between chronological age and AI-predicted age of 9.1 years. The same model performed similarly in external validation. In patients aged 20–29 years, AI-ECG–predicted biological age was greater than chronological age by a mean of 14.3 ± 0.2 years. In patients aged 80–89 years, biological age was lower by a mean of 10.5 ± 0.1 years. Women were biologically younger than men by a mean of 10.7 months ($P = .023$), and patients with a single ECG were biologically 1.0 years younger than those with multiple ECGs ($P < .0001$).

CONCLUSION There are significant between-group differences in AI-ECG–predicted biological age for patient subgroups. Biological age was greater than chronological age in young hospitalized patients and lower than chronological age in older hospitalized patients. Women and patients with a single ECG recorded were biologically younger than men and patients with multiple recorded ECGs.

KEYWORDS deep learning; Machine learning; Convolutional neural network; Cardiology; Prognostication

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Introduction

Artificial intelligence (AI) has been shown to provide multiple useful insights using electrocardiograms (ECGs). One example has been the use of AI to estimate an individual's age from their ECG ("AI-ECG age").[1] AI-ECG age has produced consistent results when trained on large national databases. In a large (>1 million ECG) Brazilian cohort (Clinical Outcomes in Digital Electrocardiography), a deep neural network achieved a correlation coefficient (R) of 0.84.[1] Similar results have also been achieved in Korea by Baek et al (R = 0.84) and in Japan by Hirota et al (R = 0.86).[2,3] However, when Lima et al[1] tested their Clinical Outcomes in Digital Electrocardiography–derived model on the external populations, performance was lower.

These studies have also demonstrated a consistent signal that greater AI-ECG age is a negative prognostic marker

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and is a novel biomarker for biological age. When calculating the difference in AI-ECG age and chronological age, age gaps over 6 years were associated with an increased incidence of cardiovascular events and gaps over 7.4 and 8 years were associated with increased mortality.[1–4] Here we aimed to further explore the attributes for the differences between AI-ECG age (biological age) and chronological age in patients hospitalized to a cardiology service.

Methods

Study setting, design, and data collection

The development and internal validation cohorts included consecutive patients who had been admitted to a single institution cardiology service, attended the cardiology outpatient department, or presented to the emergency department with a chief complaint of chest pain, dyspnea, or palpitations. Electronic medical records were matched by patient identifiers to digital ECG storage (IntelliSpace ECG, Philips Healthcare, Andover, MA). Medical history was obtained from *International Classification of Diseases, Tenth Revision* coding data in the electronic medical record and was evaluated at the time of each ECG recording.

ECGs were collected between January 1, 2000, and October 10, 2023, for patients aged between 20 and 90 years at the time of ECG recording. Included individuals were matched to administrative electronic medical records by name, hospital record number, and date of birth.

For external validation, ECGs were obtained from the UK Biobank. The UK Biobank has more than 500,000 participants, with resting ECG data recorded in the subset of the cohort that attended an initial or follow-up imaging visit between 2014 and 2023.

The study was reviewed and approved by the Central Adelaide Local Health Network Human Research Ethics Committee. The study was granted exemption from individual patient consent.

Data preparation

To reduce ECG signal noise, median filtering (filter width 22 ms) and signal averaging were undertaken. R-wave detection was performed using the Python wfdb library, with each ECG lead signal averaged using 1.6 seconds centered on the QRS complex. The signal-averaged ECG was then resampled to 125 Hz and truncated to 0.8 seconds. An ECG was excluded if at least 2 R waves could not be detected to perform signal averaging, if they were not performed with a sample rate of 500 Hz, or if it did not record 12 channels simultaneously for 10 seconds.

AI analysis

Data were randomly split into sets with a 64:16:20 ratio (train/test/holdout), with all ECGs belonging to a single patient grouped together to avoid data contamination. In the training data set, random oversampling of minority age groups was used to balance age distribution and eliminate model bias against underrepresented age groups. Time-shifting transformations were used to augment AI training data and to reduce sensitivity of the model to alignment of the QRS complex in the sample window. The model was trained on the train set, with periodic evaluation on the test set to adjust model parameters and prevent overfitting. The holdout set was used on the final trained model for internal validation. The best-performing model architecture—a convolutional neural network—used 7 convolutional layers, a global average pooling layer, dense layer, dropout layer (0.1), another dense layer and dropout layer (0.1), and output layer (Figure 1). The model was compiled with an Adam optimizer and a mean squared error loss function. This analysis was performed with Python libraries including SciKit-learn and TensorFlow.[5,6] Internal and external validation was measured using correlation coefficients and mean absolute error.

Abbreviations

AI: artificial intelligence

ECG: electrocardiogram

Subgroup analysis

In the holdout data set, we compared AI-ECG–estimated ages between chronological age and sex groups as well as between patients with a single recorded ECG and those with multiple recorded ECGs. Kolmogorov-Smirnov testing was performed to identify underlying differences in age distribution between groups. Where this was identified, subgroup comparisons were adjusted by bootstrapping age-stratified random samples and compared to mixed linear modeling for consistency. If nonparametric adjustment was not possible (eg, highly collinear variables), mixed linear modeling was adjusted with inverse probability weighting to improve balance in covariate distributions.

Results

Study characteristics

We included 63,246 patients in this study, with 353,704 total ECGs (mean 5.6 ± 8.4 per patient) (Figure 2). The mean age at ECG recording was 62.4 ± 16.9 years, and 29,060 (46%) of participants were female. Other baseline demographic characteristics are presented in Table 1. The AI model was trained to predict chronological age using the training and test set data. In the internal validation (holdout) data set of 70,657 ECGs, the model achieved a correlation coefficient (*R*) between predicted age and chronological age of 0.721. The mean absolute difference between chronological age and AI-predicted age was 9.13 years (Figure 3).

External validation

In the UK Biobank external validation set, there were 51,056 participants with 54,979 ECGs recorded. Of these, 54,190 ECGs (50,345 participants) met the inclusion/exclusion criteria. The mean age of participants was 64.7 ± 7.8 years (range 44–85 years), and 52% were female. The same AI model was tested using an identical ECG denoising/signal averaging algorithm. The correlation coefficient between

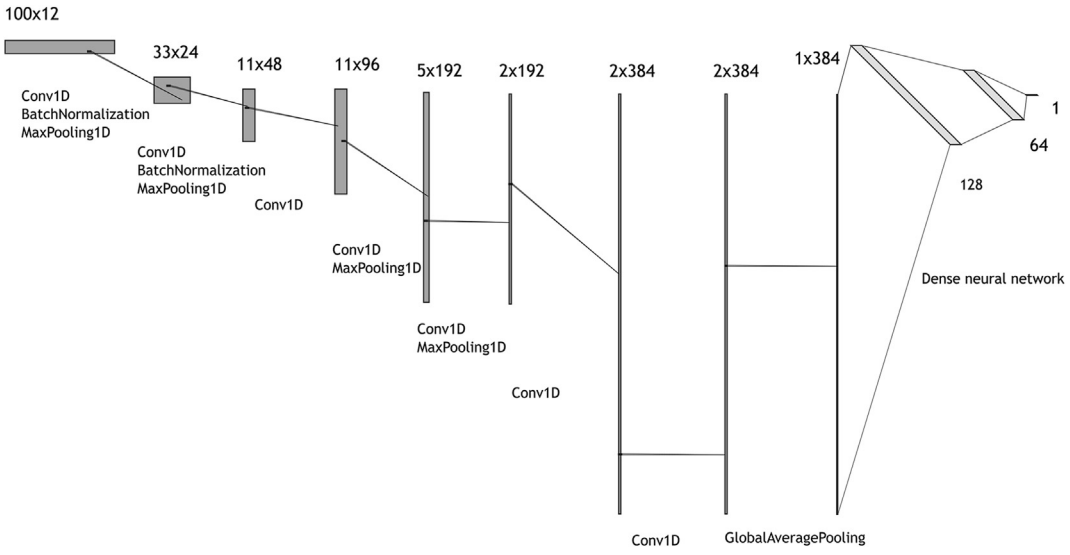

Figure 1
Convolutional neural network architecture.

predicted age and chronological age was 0.457, and the mean absolute difference in predicted age vs chronological age was 7.65 years (Table 2 and Figure 3). To compare the internal validation set and the UK Biobank despite large differences in baseline age distribution, we recalculated a correlation coefficient and mean absolute difference for the internal validation set patients in the common age range of the 2 populations (the *comparison group*): $R = 0.557$ and mean absolute error 8.24 years.

Exploring differences in biological age

For ECGs recorded in patients between the age of 20 and 29 years, AI-ECG biological age exceeded chronological age by a mean of 14.3 ± 0.2 years. In comparison, chronological age for patients aged 80–89 years exceeded AI-ECG age by 10.5 ± 0.1 years. Mean differences by decade are provided in Table 3.

AI-ECG biological age was greater than chronological age in male patients by a mean of 0.24 ± 0.06 years. In female patients, chronological age was greater by 0.61 ± 0.07 years (Table 4). This resulted in an unadjusted mean difference of +0.85 ± 0.09 years (male patients older). The Kolmogorov-Smirnov test statistic was 0.06 for chronological age distribution by gender ($P < .001$), indicating an underlying significant difference. Using balanced, age-stratified samples, the adjusted difference between male and female AI-ECG age

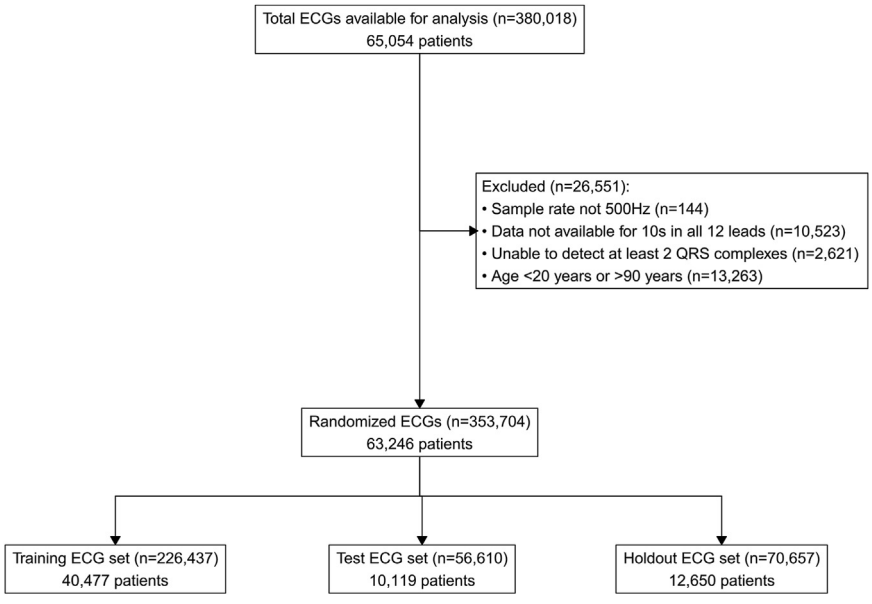

Figure 2
Study cohort data sets. ECG = electrocardiogram.

Table 1 Baseline demographic characteristics

Characteristic	Per ECG	Per patient
Number	353,704	63,246
Age (y)	62.4 ± 16.9	
Female	150,753 (42.6)	29,060 (45.9)
Mean number of ECGs		5.9 ± 8.4
1 ECG		15,637 (24.7%)
2 ECG		11,266 (17.8%)
3 ECG		7,595 (12.0%)
4 ECGs		5,216 (8.2%)
5+ ECGs		23,532 (37.2%)
Medical history*		
Atrial fibrillation	50,521 (14.3)	7,550 (11.9)
Ischemic heart disease	66,977 (18.9)	10,873 (17.2)
Diabetes mellitus	63,220 (17.8)	10,143 (16.0)
Hypertension	43,647 (12.3)	6,943 (11.0)
Heart failure	44,410 (12.6)	6,095 (9.6)

Values are presented as mean ± SD or n (%).
ECG = electrocardiogram.
*On a per-ECG basis, medical history was taken at the time of the hospital encounter. On a per-patient basis, it was taken at the time of the last ECG recorded.

Table 2 Comparison of internal and external validation results

Population	Mean absolute error (y)	Correlation coefficient *R*
Internal validation (N = 70,657)	9.13	0.721
Internal comparison group (N = 55,503)	8.24	0.557
UK Biobank (N = 54,190)	7.65	0.457

To compare with the UK Biobank cohort, the comparison group was restricted to the common age range (44–85 years) of the internal validation data set.

was +0.51 years (male patients older), which remained statistically significant. When the adjusted analysis incorporated both age distribution and cardiovascular comorbidities, the difference increased to +0.89 years ($P = .023$).

Differences were also observed between participants with a single ECG recorded and those with multiple ECGs recorded. The unadjusted mean difference was 1.75 years. The Kolmogorov-Smirnov test statistic of 0.10 ($P < .0001$) confirmed that the age distributions between groups were significantly different. In the adjusted analysis for age distribution, patients with multiple ECGs were estimated to be biologically older by a mean of 2.43 years (Table 5). Nonparametric adjustment could not be performed to include cardiovascular comorbidities because of high collinearity (variance inflation factor 11.8), so a mixed linear model was fit using inverse probability weighting. With this adjustment, the magnitude of difference was reduced to 0.99 years ($P < .0001$). The nonparametric findings for sex were consistent with the results of mixed linear modeling (see Online Supplemental Tables A1 and A2).

Discussion

In this study using a cohort of patients hospitalized for cardiovascular causes, we found that biological age as determined by AI from an ECG is relatively lower than that in older patients, women, and patients with a single ECG recording in the hospital. We observed a divergence between cardiovascular biological age and chronological age at both ends of the age spectrum. It is a concerning finding that younger patients hospitalized for cardiovascular conditions are functionally older than expected, with a mean difference of over a decade (14.3 years) in the youngest group. The direction of this relationship is reasonably expected on the basis of the cohort, but the magnitude is striking. Conversely, we demonstrated biological resilience in older populations. Again, the difference in the oldest group was over a decade (−10.5

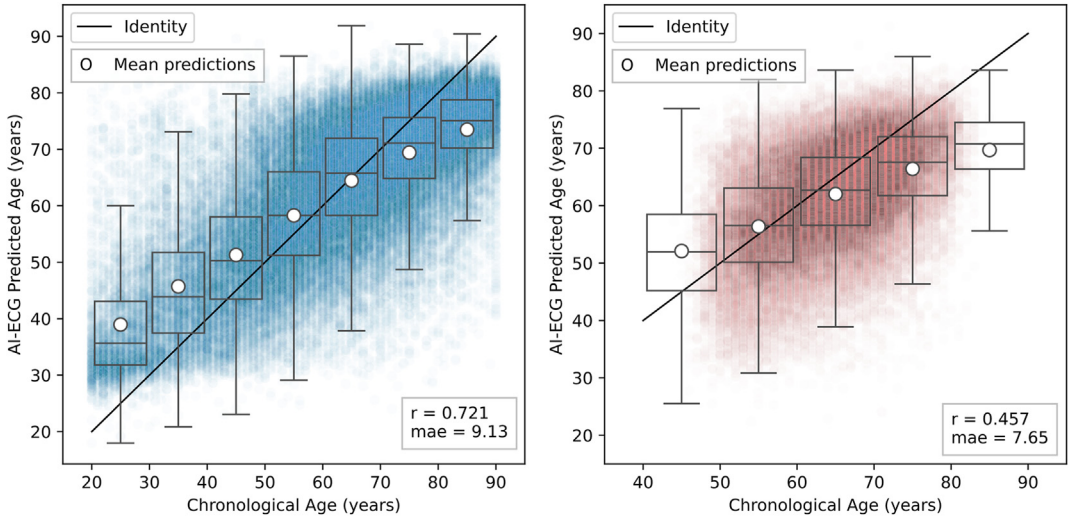

Figure 3
Prediction of age from an electrocardiogram (ECG) with the convolutional neural network and external validation on the UK Biobank. AI = artificial intelligence; mae = mean absolute error.

Table 3 Comparison of chronological age and AI-ECG age by chronological age decades with 95% confidence intervals

Decade of chronological age (y)	Difference in AI-ECG age and chronological age (y)	*P*
20–29 (n = 3743)	14.3 (14.0 to 14.6)	<.0001
30–39 (n = 4973)	11.0 (10.7 to 11.3)	<.0001
40–49 (n = 8159)	6.30 (6.06 to 6.54)	<.0001
50–59 (n = 12,623)	3.61 (3.43 to 3.79)	<.0001
60–69 (n = 15,046)	−0.11 (−0.26 to −0.05)	.176
70–79 (n = 15,357)	−4.91 (−5.05 to −4.78)	<.0001
80–89 (n = 10,422)	−10.5 (−10.6 to −10.3)	<.0001

AI = artificial intelligence; ECG = electrocardiogram.

years), which may reflect a survival bias as well as bias toward less frail patients who were considered functionally appropriate for inpatient cardiovascular team care.

Although smaller in magnitude, we also found that there appears to be a significant sex difference in cardiovascular biological age, with women an adjusted mean of 10.6 months younger than men with the same chronological age. This fits with the observation that women have a greater mean life expectancy than do men.[7] The underlying reasons for our finding in this selected, hospitalized population are likely to be multifactorial. We postulate that this is the result of a predisposition to earlier development of atherosclerotic disease in men and higher rates of smoking, poorer diet, and alcohol consumption behavior in men.[8–11] This could result in a greater burden of background or subclinical atherosclerotic disease in this study cohort. Biological aging reflected in AI-ECG may also be simply more sensitive to aging in men than women.

Patients with a single ECG were biologically 1.0 years younger than those who had multiple ECGs on average. The need for repeated ECGs is therefore an indicator of advanced biological age. We hypothesize that the number of ECGs recorded is a proxy for contact with the hospital services, and this difference in biological age reflects the better average health of patients who require less frequent medical attention and may be in a more stable phase of clinical management. A substantial portion of the unadjusted effect was attenuated after incorporating common cardiovascular comorbidities, yet a portion of the residual effect may also be attributable to other or noncardiovascular diagnoses.

In the development of the AI model, measures of accuracy and correlation were comparable to other large studies that used similar techniques. The performance of this model on an external validation data set using the UK Biobank yielded similar metrics. This shows a robust model that performs well on an international population of healthy volunteers despite being derived from hospitalized patients. Given that the correlation between AI estimates of age from an ECG and mortality/cardiovascular outcomes have been demonstrated by other researchers, the AI-predicted age can be considered a measure of biological age.[1–3] This has been explored further in a genome-wide association study on the UK Biobank, where several genes linked to cardiovascular disease and cardiac myocyte development were found to be strongly associated with AI-ECG–predicted biological age.[12]

Our study has several limitations, most importantly that medical diagnoses were obtained from coding data and not adjudicated, which would enable a better understanding of the comorbidity profile of the cohort. It has been shown that comorbidities affect AI-ECG age and the adjusted analysis would be sensitive to any systematic bias in coding data.[13] There were disproportionately more ECGs belonging to patients older than 50 years, and this has the potential to introduce bias to biological age predictions. Similarly, while the model was tested for external validation on the UK Biobank, the ages of these participants were predominantly 50–80 years at the time of ECG recording, so the external validity of the model is limited to this age range. Given the divergence seen in estimated biological ages of the younger hospitalized patients, it would be instructive to see the results on young healthy controls who had ECGs recorded for study purposes (similar to the UK Biobank). It is regrettable that no cardiologist or coded diagnosis was available for this ECG data set to assess the AI performance across the spectrum of heart rhythm disorders. However, by using a signal-averaging algorithm, we suspect that R-R irregularity in the ECG will have a minor effect on predicted biological ages.

AI-based biological age measurement has the potential to advance precision medicine with cardiovascular risk assessment. It may help identify younger patients at higher-than-average risk to guide selective testing and early aggressive risk factor management. If individual changes in AI estimates progress or regress with time, this may reflect response to lifestyle/treatment and provide individualized feedback to patients. Incorporating ECG into multimodality risk prediction

Table 4 Comparison of chronological age and AI-ECG age by sex with 95% confidence intervals

Gender	Unadjusted difference in AI-ECG age and chronological age (y)	Age-adjusted difference (y)	Age- and comorbidity-adjusted difference (y)
Male (n = 40,329)	0.242 (0.128 to 0.355)	3.029 (2.829 to 3.233)	1.054 (0.628 to 1.479)
Female (n = 30,304)	−0.613 (−0.748 to −0.477)	2.523 (2.322 to 2.730)	0.165 (−0.273 to 0.596)
Difference (male – female)	0.854 (0.677 to 1.031)	0.506 (0.219 to 0.797)	0.889 (0.287 to 1.498)
P (difference)	<.0001	.0004	.023

AI = artificial intelligence; ECG = electrocardiogram.

Table 5 Comparison of chronological age and AI-ECG age by number of ECGs performed with 95% confidence intervals

ECG number	Unadjusted difference in AI-ECG age and chronological age (y)	Age-adjusted difference (y)	Age- and comorbidity-adjusted difference (y)
One ECG (n = 3327)	1.541 (1.166 to 1.916)	0.573 (0.037 to 1.115)	11.00 (10.55 to 11.46)
Multiple ECG (n = 67,420)	−0.207 (−0.296 to −0.117)	3.001 (2.395 to 3.596)	12.00 (11.56 to 12.43)
Difference (one – multiple)	1.748 (1.362 to 2.134)	−2.427 (−3.231 to −1.620)	−0.992 (−1.314 to −0.670)
P (difference)	<.0001	<.0001	<.0001

AI = artificial intelligence; ECG = electrocardiogram.

may also be valuable to hospitals and broader health care systems if it is able to improve modeling accuracy. Understanding the baseline differences in biological age will be critical to ensuring an unbiased and reliable tool.

Conclusion

Underlying differences in biological age exist between patient groups linked to hospital-based cardiology services. As measured with AI-ECG predictions, mean biological age was greater than chronological age in younger individuals, male patients, and those with numerous ECG recordings. Further work in AI-ECG is required to examine the potential clinical utility in patient care and risk stratification.

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References

1. Lima EM, Ribeiro AH, Paixao GMM, et al. Deep neural network-estimated electrocardiographic age as a mortality predictor. Nat Commun 2021;12:5117.
2. Hirota N, Suzuki S, Motogi J, et al. Cardiovascular events and artificial intelligence-predicted age using 12-lead electrocardiograms. Int J Cardiol Heart Vasc 2023;44:101172.
3. Baek YS, Lee DH, Jo Y, Lee SC, Choi W, Kim DH. Artificial intelligence-estimated biological heart age using a 12-lead electrocardiogram predicts mortality and cardiovascular outcomes. Front Cardiovasc Med 2023;10:1137892.
4. Ladejobi AO, Medina-Inojosa JR, Shelly Cohen M, et al. The 12-lead electrocardiogram as a biomarker of biological age. Eur Heart J Digit Health 2021; 2:379–389.
5. Pedregosa F, Varoquaux G, Gramfort A, et al. Scikit-learn: machine learning in Python. J Mach Learn Res 2011;12:2825–2830.
6. Abadi M, Barham P, Chen J, et al. TensorFlow: a system for large-scale machine learning. November 2–4, 2016. Paper presented at: Proceedings of OSDI '16: 12th USENIX Symposium on Operating Systems Design and Implementation; November 2–4, 2016. Savannah, GA.
7. Australian Bureau of Statistics. Life expectancy: statistics about life tables and life expectancy at birth estimates for Australia, states and territories and sub-state regions, https://www.abs.gov.au/statistics/people/population/life-expectancy/latest-release. Accessed February 16, 2024.
8. Australian Bureau of Statistics. Insights into Australian smokers, 2021-22: snapshot of smoking in Australia, https://www.abs.gov.au/articles/insights-australian-smokers-2021-22. Accessed February 16, 2024.
9. Australian Bureau of Statistics. Dietary behaviour: key statistics and data about child and adult consumption of fruit and vegetables, https://www.abs.gov.au/statistics/health/health-conditions-and-risks/dietary-behaviour/latest-release#cite-window1. Accessed February 16, 2024.
10. Australian Bureau of Statistics. Alcohol consumption: contains key statistics and information from survey data about alcohol consumption and its prevalence within Australia, https://www.abs.gov.au/statistics/health/health-conditions-and-risks/alcohol-consumption/latest-release#cite-window1. Accessed February 16, 2024.
11. George J, Rapsomaniki E, Pujades-Rodriguez M, et al. How does cardiovascular disease first present in women and men? Circulation 2015; 132:1320–1328.
12. Libiseller-Egger J, Phelan JE, Attia ZI, et al. Deep learning-derived cardiovascular age shares a genetic basis with other cardiac phenotypes. Sci Rep 2022; 12:22625.
13. Attia ZI, Friedman PA, Noseworthy PA, et al. Age and sex estimation using artificial intelligence from standard 12-lead ECGs. Circ Arrhythm Electrophysiol 2019; 12:e007284.