npj | digital medicine

Article

Published in partnership with Seoul National University Bundang Hospital

https://doi.org/10.1038/s41746-025-01727-7

Determinants of artificial intelligence electrocardiogram-derived age and its association with cardiovascular events and mortality: a systematic review and meta-analysis

Shervin Mossavarali[1,6], Ali Vaezi[1,6], Zahra Gholami[2], Alireza Molaei[3], Mir Saeed Yekaninejad[3], Folkert W. Asselbergs[4] & Akbar Shafiee[5] ✉

Artificial intelligence (AI)-ECG-derived age (AI-ECG age) and Heart Delta Age (HDA)—the difference between AI-ECG and chronological age—are emerging tools for assessing cardiovascular health. We systematically searched PubMed, Embase, Web of Science, and Scopus from inception through September 2024. Seventeen original studies utilizing AI algorithms to measure HDA and cardiovascular risk factors, outcomes, or mortality were included. Data were pooled using random- and fixed-effects models for meta-analysis. Hypertension and diabetes mellitus emerged as the most prevalent factors contributing to higher HDA, while cardiac diseases including myocardial infarction and heart failure demonstrated the most significant impact. Pooled analysis revealed a significant association between elevated HDA and increased risks of all-cause mortality (hazard ratio [HR] 1.62, 95% confidence interval [CI] 1.49-1.77) and cardiovascular mortality (HR 2.12, 95% CI 1.71-2.63). HDA could enhance existing risk models and play a critical role in primary healthcare prevention.

Recently, biological age has been introduced as a surrogate indicator of aging-related diseases, conditions, and comorbidities[1]. Calculating biological age can be challenging due to the absence of a standardized method. However, various parameters, including demographic, physiological, biochemical markers, and multi-omics data, have been used for computing biological age. Imaging techniques, such as magnetic resonance imaging (MRI)[2] and chest X-ray (CXR)[3], have also been employed. Among them, the electrocardiogram (ECG) is a simple, widely available, and non-invasive tool that has proven to demonstrate aging patterns, making it a suitable choice for estimating biological age, also known as "heart age" or "cardiac age"[4].

Traditionally, electrophysiologists analyze and compare the morphological features of an ECG strip with established ECG standards and correlate them to specific age groups. However, this method is prone to inaccurate estimates, as different cardiovascular diseases may manifest with similar patterns on the ECG, and vice versa. As a result, cardiologists are forced to spend more time and effort on accurate evaluation, making the process more difficult and time-consuming[4]. Lately, artificial intelligence (AI) models, particularly deep learning and machine learning algorithms, are increasingly employed in healthcare due to their capacity to learn complex patterns and analyze large datasets, offering significant potential for addressing healthcare challenges[5].

The research community has calculated heart age through the analysis of 12-lead ECG strips by utilizing AI models such as deep and convolutional neural networks[4]. AI-ECG-derived age, commonly referred to as AI-ECG age, has demonstrated associations with cardiovascular diseases[6]. Heart Delta Age (HDA), the difference between AI-ECG age and chronological age, is a predictor of cardiovascular outcomes and mortality[7–9]. Most studies agree that having an AI-ECG age higher than chronological age, or a positive

[1]Tehran Heart Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Cardiology, Imam Khomeini Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. [3]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical, Tehran, Iran. [4]Department of Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, The Netherlands. [5]Cardiac Primary Prevention Research Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran. [6]These authors contributed equally: Shervin Mossavarali, Ali Vaezi. ✉e-mail: ashafiee@tums.ac.ir

HDA, elevates the risk of major adverse cardiovascular events (MACE) and mortality[10,11]. Currently, the focus is mainly on the relationship between HDA and cardiovascular outcomes. However, potential determinants and risk factors associated with biological heart age and HDA, such as lifestyle factors, comorbidities, and even genetic mutations, have been investigated[11–14]. This indicates the potential role of HDA in primary healthcare prevention and screening of high-risk individuals in the future[10].

Despite all the advances in AI models for calculating AI-ECG age, the associations and relationships of HDA with its determinants and cardiovascular-related outcomes have not yet been systematically investigated. Therefore, in this systematic review and meta-analysis, we provided an overview of the determinants of HDA and summarized the predictive role of HDA in cardiovascular events and mortality.

Results

Study selection

Our search strategy generated a total of 2473 studies through database searches. Following the removal of duplicates, a total of 1674 articles were identified and subsequently assessed. Articles that were excluded following the title/abstract screening stage (n = 1635) were mostly articles without an age estimation on ECG of human subjects. Among the 39 remaining articles, sixteen met the inclusion criteria. The primary causes of exclusion at this stage were being a preprint or conference abstract version of the study, application of traditional statistical methods, and investigating participants with cardiac intervention as the main study group (Supplementary Table 4). Citation searching identified another five articles, which after assessing the eligibility, only one met the inclusion criteria and was included in the study. Our PRISMA flow diagram is presented in Fig. 1.

Characteristics of included studies

All of the included studies were published in the years following 2019 and utilized patients' electrocardiograms and information derived from both retrospective[15] and prospective[16] cohorts. Most of the studies were conducted in the USA[10,11,14–20]. The included studies involved a variable number of participants, ranging from 37[17] up to 226,476[21] individuals. Primarily, participants were adults ranging from 16[9] to 85[22] years.

In the studies analyzed, standard 12-lead ECGs were collected from participants and converted into digital formats. These digital ECGs underwent preprocessing steps to ensure consistency across the dataset. The preprocessed ECG data were then input into advanced AI techniques, such as deep learning or convolutional neural networks to perform age estimation. For this purpose, the AI models were trained using a diverse dataset, and their performance was evaluated on multiple validation sets. Once the training and validation processes were completed, the holdout set was utilized to obtain a conclusive evaluation of the AI model's effectiveness[10,18,23]. A majority of studies employed the model trained on the patients of the Mayo Clinic[19] and CODE study[9]. The difference between the AI-ECG age and the individual's chronological age, referred to as HDA, was calculated. A positive HDA indicates accelerated cardiovascular aging, while a negative HDA suggests a younger heart age relative to chronological age (see Supplementary Note 1 and Supplementary Fig. 1 for further explanation).

The risk of bias assessments consisted of 34 criteria based on the STROBE checklist. Within this assessment, the mean score was approximately 20 out of 34. Two studies met fewer than half of the criteria[17,19], and the highest reported score was 27 out of 34[16]. Detailed results of the risk of bias are shown in Fig. 2.

High HDA determinants

Sixteen of the included studies identified various factors associated with elevated HDA. The genetic basis of cardiovascular aging was shown to be mainly determined by genes directly involved in the cardiovascular system, such as those related to cardiac muscle development and those associated with cardiovascular diseases. This influence surpasses that of genes connected to more general aging mechanisms[24]. The occurrence of mutations in these genes, including the Lamin A/C (LMNA) gene[14] and changes in the activity of the telomerase enzyme[17] was also associated with a higher HDA.

In investigating imaging modalities, ECG abnormal findings, such as left bundle branch block, atrial fibrillation (AF), atrioventricular block, left ventricular hypertrophy, left atrial enlargement, ventricular premature

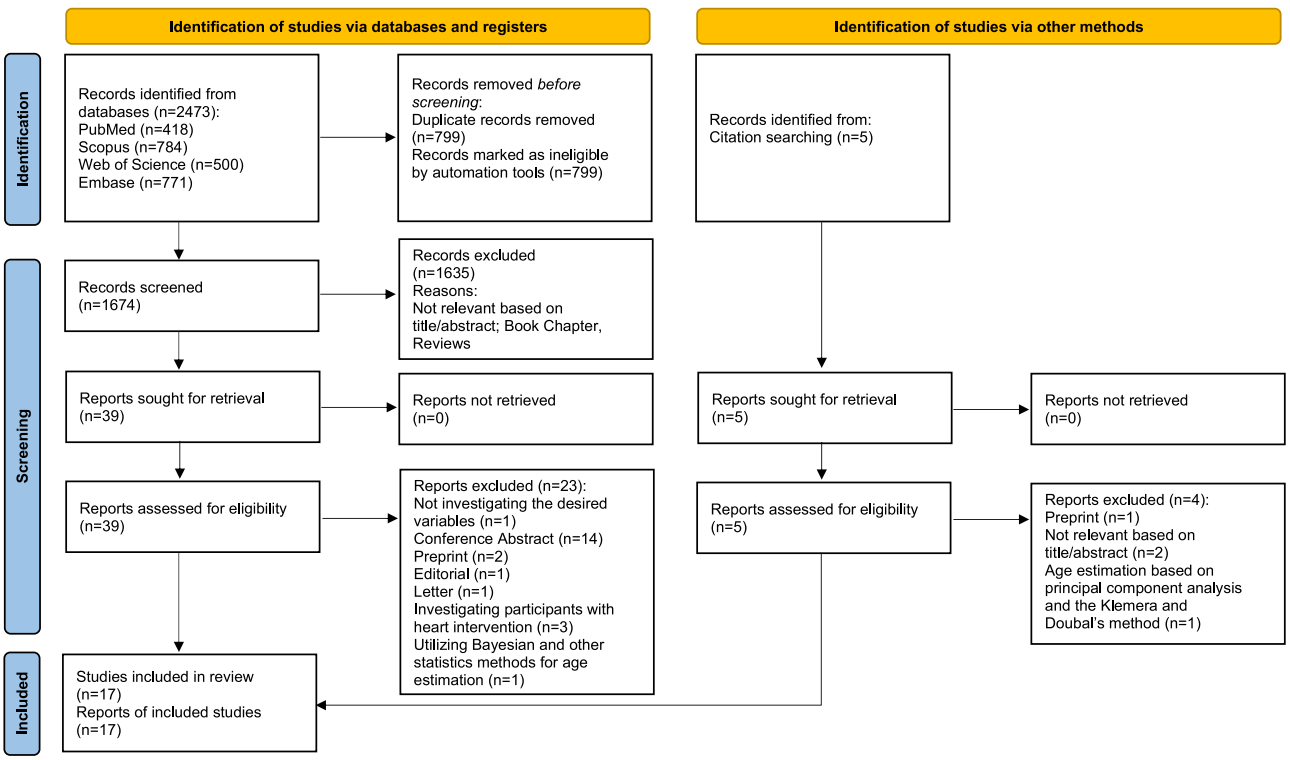

Fig. 1 | The PRISMA flow diagram. Illustration of the identification, screening, eligibility assessment, and inclusion of studies in the systematic review.

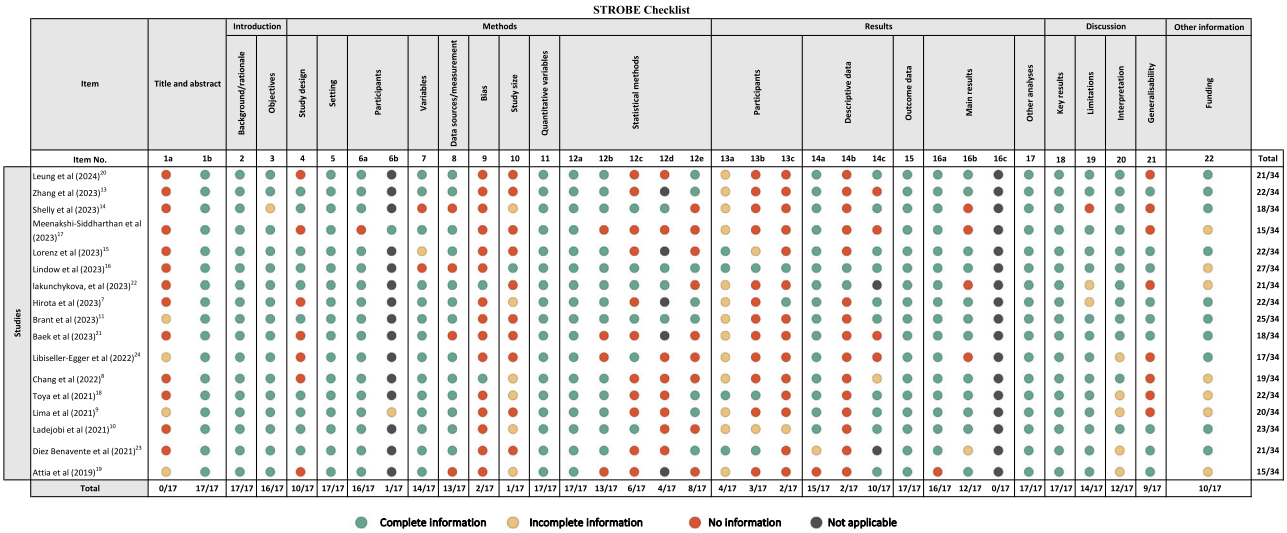

Fig. 2 | Quality assessment of the included studies. Evaluations of each of the included studies with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist, with criteria categorized as "Complete", "Incomplete", "No Information", or "Not Applicable" to evaluate methodological rigor.

complex, and prolonged QT interval, were all associated with higher HDA[8]. Moreover, cardiac MRI abnormalities like dilation of the left ventricle, presence of late gadolinium enhancement, decrease in the ejection fraction of the left ventricle, and increase of the left ventricular mass were associated with an increment of 5 years in the HDA[16].

As demonstrated in Table 1, adopting a healthy lifestyle was reported to be associated with a reduced AI-ECG age[13]. Conversely, making unhealthy lifestyle choices, particularly leading a sedentary life, engaging in alcohol consumption[13,24], having a high body mass index, and dyslipidemia[8,10,22–24] was associated with a higher HDA. Several studies have investigated smoking as a risk factor for cardiovascular diseases, with the majority indicating that it is associated with an elevated AI-ECG, and consequently, a higher HDA[9–11,13,22,24].

HTN and DM have been identified in various studies as contributing factors to the acceleration of HDA[7,9–11,13,15,16,19]. It has been reported that, apart from the DM itself, increased fasting blood sugar and hemoglobin A1C levels were associated with a higher HDA[8]. Furthermore, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were all associated with an increase in HDA[22–24]. Besides these conditions, the use of medications such as antihypertensive and lipid-lowering drugs significantly contributes to an elevated HDA[22].

Cardiac diseases, including ischemic heart diseases and HF, were also reported to be associated with elevated levels of HDA[7,10,13,15,16,19]. Among the various conditions, ischemic heart diseases and HF were reported to have the greatest impact on increasing HDA (Supplementary Table 5). Additionally, previous cardiac surgery and prevalent stroke have also been reported to be associated with increased HDA[19,20]. More details on HDA determinants are presented in Supplementary Table 5.

High HDA outcomes

Study characteristics with outcomes associated with high HDA are presented in Table 2. Detailed hazard ratios can be found in Supplementary Table 6. Nine of the included studies investigated cardiovascular outcomes of high HDA. In a study exploring new-onset cardiovascular diseases, it was reported that an elevation in HDA exceeding seven years is associated with an elevated risk of HF (HR = 2.79 [95% CI; 2.25, 3.45]), AF (HR = 2.38 [95% CI; 1.86, 3.04]), DM (HR = 1.70 [95% CI; 1.53, 1.89]), HTN (HR = 1.67 [95% CI; 1.51, 1.85]), chronic kidney disease (HR = 1.67 [95% CI; 1.41, 1.97]), acute myocardial infarction (MI) (HR = 1.76 [95% CI; 1.20, 2.57]), and stroke (HR = 1.65 [95% CI; 1.42, 1.92]) in the future[8]. In a separate investigation, HDA exceeding 9 years was found to be associated with an elevated onset of HF (HR = 1.75 [95% CI; 1.45, 2.12]) and AF (HR = 1.44 [95% CI; 1.23, 1.69])[11]. In the same study, each 10-year increment in HDA was associated with an increased risk of MI (HR = 1.10 [95% CI; 1.01, 1.20]), AF (HR = 1.18 [95% CI; 1.12, 1.24]), and HF (HR = 1.31 [95% CI; 1.21, 1.43])[11] when the competing risk of death was taken into account. Moreover, HF hospitalization or death probability escalated with each 5-year increment in HDA (HR = 1.11 [95% CI; 0.01, 1.21])[16]. A 10-year increase in HDA was associated with a 22% increased risk of stroke (HR = 1.22 [95% CI; 1.00, 1.49])[20]. All outcomes extracted from the studies, along with reported HRs are shown in Table 2 and Supplementary Table 6.

All-cause mortality

Five studies reported the HR of high HDA on all-cause mortality[8–11,21], two of which also calculated this estimate using external cohorts for validation[8,9]. Ultimately, nine HRs from these studies were included in the meta-analysis. The pooled estimate for all-cause mortality was HR = 1.62 [95% CI; 1.49, 1.77] indicating a significantly increased risk associated with high HDA. Heterogeneity among the included studies was substantial, with $I^2 = 68.38\%$ and a significant Cochran's Q test ($p < 0.001$) (Fig. 3). To evaluate publication bias, a funnel plot was generated (Supplementary Fig. 2). Furthermore, Begg's test didn't demonstrate a statistically significant result ($p = 0.18$). A subsequent trim-and-fill analysis showed that no studies were missing, confirming that all eligible studies were included in the meta-analysis, which supports the robustness of the pooled estimate (Supplementary Fig. 3).

Cardiovascular mortality

Similarly, three studies reported the HRs of high HDA on cardiovascular mortality[8,10,21]. The pooled estimate for cardiovascular mortality was HR = 2.12 [95% CI; 1.71, 2.63], demonstrating a significantly higher risk associated with high HDA. Heterogeneity among the included studies was low, with $I^2 = 20.25\%$ and a Cochran's Q test result of $p = 0.29$, suggesting no substantial variability across the studies (Fig. 4). The Begg's test showed no statistically significant results ($p = 0.30$). Two studies were imputed using the trim-and-fill method to address potential publication bias in the funnel plot (Supplementary Fig. 4). After adding these studies, the pooled effect size decreased from 2.12 [1.71, 2.63] to 1.94 [1.61, 2.33] (Supplementary Fig. 5). This adjustment does not substantially alter the overall results, suggesting that the results are still robust.

Discussion

This systematic review and meta-analysis outlined HDA determinants and related outcomes, such as mortality and cardiovascular events. Among the

https://doi.org/10.1038/s41746-025-01727-7

Table 1 | Characteristics of the studies exploring determinants associated with heart delta age

Author-year	Country	Study design	Data collection period	Artificial intelligence model	Sample size	Population	Male (%)	HDA (years)	Cut-off	Determinants associated with HDA
Leung et al.[20]	USA	Retrospective cohort	2006–2023	Deep neural network (developed by CODE study[12])	68,565	Volunteers aged 40–69 years who enrolled in the UK Biobank	48.3%	−0.01 ± 5.88	–	Prevalent stroke
Zhang et al.[13]	UK	Prospective cohort	2006–2010	Deep neural network (developed by CODE study[12])	44,094	Participants aged 40–69 years	48.6%	9.1 ± 6.6[b]	>20 years >0 years	• Lifestyle factors (diet, alcohol consumption, physically active, and smoking) • AF • Type 2 DM • HF • Hypercholesterolemia • HTN • MI • Stroke
Shelly et al.[14]	USA	Retrospective cohort	2003–2019	Convolutional neural network (developed by Attia et al.[24])	186 (31 LMNA; 155 controls)	Participants with LMNA gene mutations who underwent at least a 12-lead ECG[a]	54.8%	20 [−5 to 39] in LMNA vs 8 [−19 to 39] in controls	>10 years	LMNA mutation
Meenakshi-Siddharthan et al.[17]	USA	Prospective cohort	2016–2020	Convolutional neural network (developed by Attia et al.[24])	37 (10 healthy controls; 10 ambulatory HF; 17 advanced HF)	Patients with chronic stable HFrEF and advanced HFrEF (being evaluated as candidates for left ventricular assist device implantation) and with healthy controls[a]	56.7%	NR	–	• HF • Telomerase activity • CRP
Lorenz et al.[15]	USA	Retrospective cohort	2014–2019	Convolutional neural network (developed by Attia et al.[24])	2183	Adult patients who underwent evaluation for kidney transplant alone or simultaneous pancreas/kidney transplant[a]	59.1%	0 ± 7.9	–	• Male sex • Black • Current or previous smoker • Dialysis dependence • Dyslipidemia • CAD • DM • History of MI • BMI (per 1 kg/m2 increase) • Charlson comorbidity Index • Duration dialysis (per year) • Left ventricular EF (%)
Lindow et al.[16]	USA	Prospective cohort	2010–2018	Deep neural network (developed by CODE study[12])	731	Patients undergoing clinical cardiovascular MRI	56.4%	7.9 ± 11.9	–	• Cardiovascular risk factors (HTN, CAD, DM, HF) • Cardiac MRI findings
Hirota et al.[7]	Japan	Retrospective cohort	2010–2018	Convolutional neural network (developed by Attia et al.[24])	17,042	Patients visiting the cardiovascular institute (20–90 years old) without pacing beats, atrial or ventricular tachyarrhythmia	58.6%	6.14 ± 0.07	>6 years	• Cardiovascular events (cardiovascular-related death, HF, acute coronary syndrome, ischemic stroke, aortic disease, and intracranial hemorrhage) • Cardiovascular related comorbidities (HTN, DM, HF, ischemic heart disease, valvular heart disease, cardiomyopathy, and AF)

https://doi.org/10.1038/s41746-025-01727-7

Table 1 (continued) | Characteristics of the studies exploring determinants associated with heart delta age

Author-year	Country	Study design	Data collection period	Artificial intelligence model	Sample size	Population	Male (%)	HDA (years)	Cut-off	Determinants associated with HDA
Iakunchykova et al.[22]	Norway	Cross-sectional study	1974–2016	Deep neural network (developed by Attia et al.[24])	7779	All inhabitants (aged 40–85 years) in Tromsø municipality,	45.3%	−4.63 ± 7.30	–	• Smoking • DM • Education • Previous self-reported CVD (MI, stroke, AF) • Use of blood pressure medication • Lipid lowering drugs • LDL-cholesterol • SBP and DBP • BMI
Brant et al.[11]	USA	Prospective cohort	1986–2021	Deep neural network (developed by CODE study[12])	9877	Adults enrolled in Framingham cohort	45.1%	9 ± 7[b]	>9 years	• Smoking • HTN • DM • Obesity • Dyslipidemia
Libiseller-Egger et al.[24]	UK	Prospective cohort	2006–2014	Convolutional neural network (developed by Attia et al.[24])	36,349 (age estimation); 34,432 (genome-wide association)	Participants aged 40–69 years	48.4%	0.27 (−4.81, 5.15)	–	• Age • Sex • Education • DM • HTN • Angina • Stroke • Heart attack • BMI • MAP • LDL • Smoking status • Genes (SIPA1L1, VGLL2, CAMK2D, DEFB136, TTN, SCN5A, SCN10A, PKD2L2, EXT1, AGAP5, CTNNA3, TBX3, SPTBN1, SOX5, CHD9)
Chang et al.[8]	Taiwan	Retrospective cohort	2012–2019	Deep neural network (developed by CODE study[12])	71,741	Patients (20–80 years old) with ECGs from the health examination center	54.8%	1.03 ± 8.69	>7 years	• Abnormal ECG features • Preexisting comorbidities (DM, HTN, CKD, AMI, CAD, and HF) • BMI • Laboratory examination (blood urea nitrogen, fasting glucose, hemoglobin A1C, white blood cell counts, triglyceride, eGFR)
Toya et al.[18]	USA	Cross-sectional and observational cohort	2006–2019	Convolutional neural network (developed by Attia et al.[24])	531	Patients who underwent ECG and peripheral microvascular endothelial function testing	38%	1.3 ± 7.8	Quartiles	• Chronological age • Male sex • HTN • Dyslipidemia • DM • Smoking history • RH-PAT index

https://doi.org/10.1038/s41746-025-01727-7 Article

Table 1 (continued) | Characteristics of the studies exploring determinants associated with heart delta age

Author-year	Country	Study design	Data collection period	Artificial intelligence model	Sample size	Population	Male (%)	HDA (years)	Cut-off	Determinants associated with HDA
Lima et al.[9]	Brazil	Prospective cohort	2010–2017	Deep neural network (self-developed)	218,169	Participants aged between 35 and 74 years	46%	8.38 ± 7[b]	>8 years	• HTN • DM • Smoking • Obesity • Dyslipidemia • Exercise status
Ladejobi et al.[10]	USA	Historical cohort	1997–2016	Convolutional neural network (developed by Attia et al.[24])	25,144	Patients ≥30 years who had primary care outpatient visits	46%	0.88 ± 7.41	+2 SD above 1–2 SD above	• Female sex • Current smoker • DM history • HTN history • Dyslipidemia history • BMI, per 5 kg/m2 increase • COPD history • CKD history • HF history
Diez Benavente et al.[23]	Russia	Cross-sectional	2015–2018	Convolutional neural network (developed by Attia et al.[24])	4542	Patients aged 35–69 years recruited from the general population	41.3%	5.32 ± 7.6	–	• SBP • DBP • MAP • Mean pulse wave velocity • BMI • LDL/HDL ratio • Smoking status • Cardiac pathologies (NT-proBNP and hs-cTnT)
Attia et al.[19]	USA	Retrospective cohort	1994–2017	Convolutional neural network (self-developed)	100	Patients (≥18 years) with at least one digital, standard 10 s 12-lead ECG acquired in the supine position	52%	NR	>7 years	• No comorbidities • Prior diagnoses of MI • Low EF (< 50%) • CAD • DM • HTN • Any cardiac surgery • AF

Data are reported with mean ± SD, median (IQR), and median [range], unless specified.

AF atrial fibrillation, *AMI* acute myocardial infarction, *BMI* body mass index, *CAD* coronary artery disease, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *CVD* cardiovascular disease, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *ECG* electrocardiogram, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *HDA* heart delta age, *HDL* high density lipoprotein, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HTN* hypertension, *IQR* interquartile range, *LDL* low density lipoprotein, *LMNA* lamin A/C, *MAP* mean arterial pressure, *MI* myocardial infarction, *MRI* magnetic resonance imaging, *NR* not reported, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *Hs-cTnT* high-sensitivity cardiac troponin T, *RH-PAT* reactive hyperemia peripheral arterial tonometry, *SD* standard deviation, *SBP* systolic blood pressure.

[a]Special population.

[b]Mean absolute error ± SD used for reporting.

https://doi.org/10.1038/s41746-025-01727-7

Table 2 | Characteristics of the studies exploring cardiovascular outcomes associated with heart delta age

Author-year	Country	Study design	Data collection period	Follow-up (years)	Artificial intelligence model	Sample size	Population	Male %	HDA	Cut-off	Outcomes associated with HDA
Leung et al.[20]	USA	Retrospective cohort	2006–2023	2014–2023	Deep neural network (developed by CODE study![12])	67,757	Volunteers aged 40–69 years who enrolled in the UK Biobank	48.3%	−0.01 ± 5.88	–	Stroke
Lorenz et al.[15]	USA	Retrospective cohort	2014–2019	NR	Convolutional neural network (developed by Attia et al.[24])	2183	Adult patients who underwent evaluation for kidney transplant alone or simultaneous pancreas/kidney transplant[a]	59.1%	0 ± 7.9	–	Mortality
Lindow et al.[16]	USA	Prospective cohort	2010–2018	5.7 (4.7, 6.7)	Deep neural network (developed by CODE study![12])	731	Patients undergoing clinical cardiovascular MRI	56.4%	7.9 ± 11.9	–	• Death • HF hospitalization
Brant et al.[11]	USA	Prospective cohort	1986–2021	17 ± 8	Deep neural network (developed by CODE study![12])	9877	Adults enrolled in Framingham cohort	45.1%	9 ± 7[b]	>9 years	• All-cause mortality • Cardiovascular events (incidence of AF, MI, and HF)
Baek et al.[21]	South Korea	Retrospective cohort	2006–2021	NR	Deep neural network (self-developed)	226,476	Adults ≥18 years old who underwent standard 12-lead ECG	52.3%	5.8 ± 3.9[b]	>6 years	• All-cause mortality • Cardiovascular-related mortality • Cardiovascular hospitalization • MACE
Chang et al.[8]	Taiwan	Retrospective cohort	2012–2019	NR	Deep neural network (developed by CODE study![12])	71,741	Patients (20–80 years old) with ECGs from the health examination center	54.8%	1.03 ± 8.69	>7 years	• All-cause mortality • Cardiovascular-related mortality • HF • DM • CKD • AMI • Stroke • CAD • AF • HTN
Toya et al.[18]	USA	Cross-sectional and observational cohort	2006–2019	NR	Convolutional neural network (developed by Attia et al.[24])	531	Patients who underwent ECG and peripheral microvascular endothelial function testing	38%	1.3 ± 7.8	Quartiles	MACEs (all-cause death; MI; clinically driven coronary revascularization; cerebrovascular disease, such as transient ischemic attack, ischemic stroke, and hemorrhagic stroke; and peripheral artery disease causing claudication)
Lima et al.[9]	Brazil	Prospective cohort	2010–2017	3.4 (2.1, 5.0)	Deep neural network (self-developed)	218,169	Patients over 16 years old with a valid ECG	41%	8.38 ± 7[b]	>8 years	All-cause mortality

Table 2 (continued) | Characteristics of the studies exploring cardiovascular outcomes associated with heart delta age

Author-year	Country	Study design	Data collection period	Follow-up (years)	Artificial intelligence model	Sample size	Population	Male %	HDA	Cut-off	Outcomes associated with HDA
Ladejobi et al.[10]	USA	Historical cohort	1997–2016	12.4 ± 5.3	Convolutional neural network (developed by Attia et al.[24])	25,144	Patients ≥30 years old who had primary care outpatient visits	46%	0.88 ± 7.41	+2 SD above 1-2 SD above	All-cause and cardiovascular mortality

Data are reported with mean ± SD, median (IQR), unless specified.
AF atrial fibrillation, *AMI* acute myocardial infarction, *CAD* coronary artery disease, *CKD* chronic kidney disease, *DM* diabetes mellitus, *ECG* electrocardiogram, *HDA* heart delta age, *HF* heart failure, *HTN* hypertension, *IQR* interquartile range, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *MRI* magnetic resonance imaging, *NR* not reported, *SD* standard deviation.
[a]Special population.
[b]Mean absolute error ± SD used for reporting.

potential determinants of HDA, HF, AF, and MI demonstrated the most impact on HDA. In addition, higher HDA increases the risk of all-cause mortality and cardiovascular events.

Aging extends beyond the mere passage of time and is closely associated with changes in cellular function. The stability of DNA and genetic profiling have been proven to play an important role in determining lifespan[25]. Several genetic and epigenetic factors, including DNA methylation, repair mechanisms, histone modification, and protein translation modifications, regulate aging[26]. Furthermore, chronic diseases (e.g., cancer and diabetes) and lifestyle factors (e.g., diet and physical activity) have also been associated with accelerated aging through several different mechanisms[27,28]. Biological age, which takes these factors into account, has been introduced as a surrogate biomarker that provides a deeper understanding of the aging process than chronological age.

Recently, several methods such as principal component analysis, multiple linear regression, and Klemera and Doubal's method have been introduced for estimating biological age[29]. However, these approaches have significant limitations, making them less suitable for widespread use[29]. Recently, advancements in deep learning models and convolutional neural networks have led to the development of new approaches. Among them is AI-ECG age, introduced by Attia et al., which provides a more comprehensive assessment of overall cardiac health and aging processes than traditional scoring methods[19]. As individuals age, several changes in the ECG, such as changes in rate, ST-T wave alterations, and axis deviation, are expected to occur[30]. The AI-ECG model identifies age-related patterns and alterations caused by various conditions and diseases to estimate biological age. The discrepancy between this biological age (AI-ECG age) and chronological age, known as HDA, has been extensively studied and proven to effectively and transparently indicate cardiovascular risk, establishing it as a promising and reliable biomarker for overall health.

In addition to AI-ECG age, efforts have been made to estimate biological age using chest X-rays (CXR) and cardiac MRI. While both AI-ECG age and CXR-derived age provide valuable prognostic insights, AI-ECG age offers a deeper understanding of latent cardiovascular factors due to its direct reflection of heart physiology. Furthermore, cardiac MRI-derived age is based on ventricular shape and myocardial characteristics, highlighting sex-specific aging patterns and linking biological heart age to cardiovascular risk factors. However, its use in routine clinical practice is limited by accessibility. Integrating these modalities could enable a more comprehensive assessment of cardiovascular health[2,3].

Cardiovascular risk factors and diseases have been extensively studied as potential predictors of HDA. For example, individuals who maintain a healthy lifestyle tend to have a lower HDA, making them biologically younger than those with unfavorable habits[13]. Thus, we encourage researchers to focus on identifying protective factors for HDA to slow aging and enhance life expectancy.

Although the exact mechanisms underlying these predictors remain unclear, biological age—and consequently, HDA—is believed to be closely linked to vascular endothelial function. Disruptions in endothelial function, particularly in the coronary vasculature, may contribute to increased HDA[18]. Current literature primarily associates HDA with mortality and cardiovascular events, with preliminary findings on ECG-derived heart age supporting its relevance to cardiovascular health[6]. In addition, studies have indicated that an elevated brain delta age may be linked to a higher risk of future mortality[31,32].

Genome-wide association studies (GWAS) serve as a comprehensive catalog of genome-wide associations with various diseases and have identified numerous genes related to cardiovascular health. GWAS have demonstrated connections between genetic variants and traits such as left ventricular mass and other cardiac structures, potentially influencing ECG readings and biological age[33].

For instance, variants of the SIPA1L1, VGLL2, and DEFB136 genes have been associated with specific ECG morphologies, AF, and blood pressure[34]. LMNA is a crucial gene involved in the processing of Lamin A, an essential protein in the nuclear scaffold, and is associated with physiological

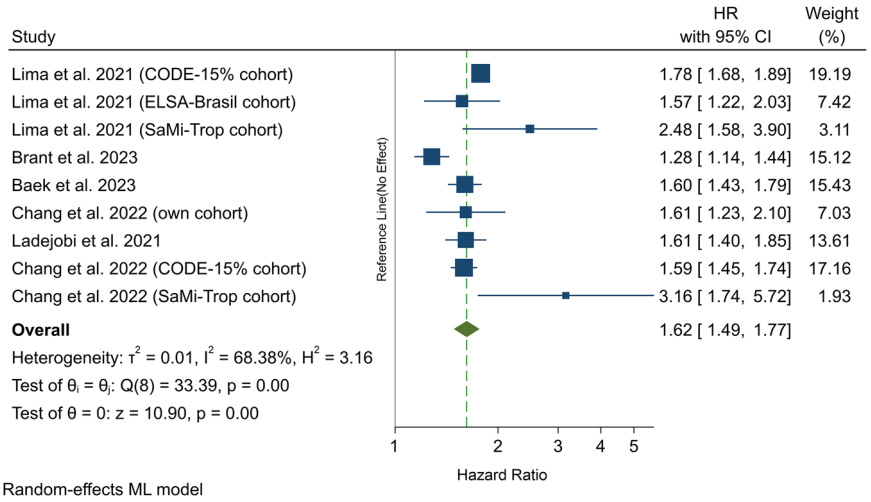

Fig. 3 | Forest plot for all-cause mortality meta-analysis. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of for all-cause mortality in higher heart delta age group.

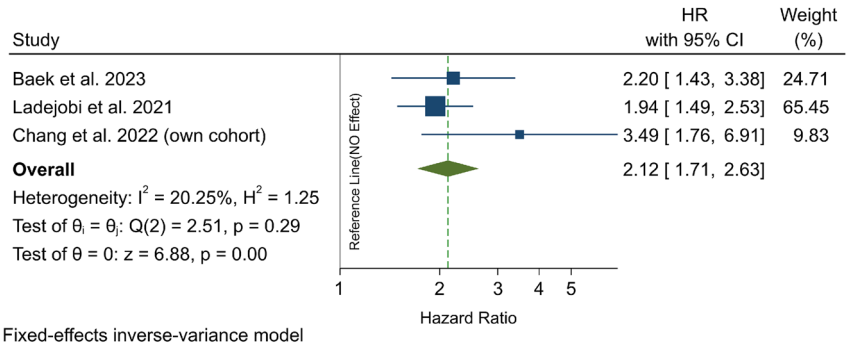

Fig. 4 | Forest plot for cardiovascular mortality meta-analysis. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of for cardiovascular mortality in higher heart delta age group.

aging[35]. Lamin A deterioration with age can potentially be mitigated through genetic therapies (e.g., FTIs, CRISPR)[35], lifestyle interventions (caloric restriction, antioxidants)[26,28], and telomere maintenance[36] strategies. Emerging approaches like senolytics[27] and mTOR[37] inhibition also show promise in preserving Lamin A function, delaying aging-related decline. Further research is needed to validate these strategies in humans.

Mutations in LMNA are linked to premature aging disorders and have been found to correlate with ECG abnormalities, including atrioventricular block, flat P waves, and both ventricular and supraventricular arrhythmias[38]. Both LMNA[14] and GWAS-obtained genes[24] have shown statistically significant associations with HDA, even in asymptomatic patients. However, when comparing results across diverse genetic models, not all associations could be explained by the currently known loci, highlighting the need for validation in larger studies. Another genetic factor is telomerase activity[37], which can potentially shorten the lifespan via altering the telomere length and has an established role in aging-related diseases[36] and HDA[17].

While GWAS have identified cardiovascular-specific genes as key drivers of HDA multi-omics studies reveal how these genetic variants manifest in protein-level dysfunction. As highlighted by Belfiori et al.[39], atrial fibrillation exhibits proteomic signatures (e.g., dysregulated collagen turnover, impaired energy metabolism proteins) that mirror aging pathways implicated in HDA.

The mark of various cardiovascular diseases could be captured by the ECG (e.g. axis deviations, conduction blocks, and QRS widening)[40]. In fact, studies have used ECG abnormalities as predictors of MACE[41]. Traditional methods (e.g. Bayesian approach[6] or Linear regression[42]) have been utilized to estimate age from ECG strips and have identified correlations between certain ECG features, such as widened QRS-T angle, and ECG age[43]. Similarly, studies[8] using AI have depicted the association of abnormal ECG changes, such as AF, conduction blocks, chambers hypertrophy, and enlargement, with groups of patients with a higher HDA. However, this method of risk classification cannot be fully relied upon; since there is evidence of patients with different categories of aging (accelerated, normal, and decelerated) that show no significant difference in various ECG parameters[9]. To clarify, the risk of mortality remains significantly high even in patients with an apparently normal ECG. The precise mechanism by which AI-ECG age predicts adverse cardiovascular events is not yet fully understood. However, one hypothesis suggests that AI may detect subtle variations in low-frequency components of the ECG, such as P and T waves. This supports the idea that AI-ECG age estimation enables a more comprehensive risk assessment, potentially incorporating variables beyond those captured by conventional ECG analysis[9].

Recent advances in AI-powered echocardiography now allow for the estimation of biological age by detecting subtle patterns of myocardial alterations and age-related functional decline[44]. New tools like natural language processing systems for analyzing heart ultrasound reports[45] complements emerging AI-ECG age estimation by enabling large-scale integration of functional cardiac parameters (e.g., ejection fraction, diastolic measures) with HDA. For a brief review of echocardiographic aging markers, see Supplementary Note 2. Future studies could combine HDA with AI-analyzed echocardiograms to build a more complete model of heart aging[44].

Regarding the clinical applications of HDA, it may enhance, if not surrogate, traditional cardiovascular disease risk stratifications like the Framingham Risk Score since physiological data could not be obtained via questionaries[21]. Adding to that, vulnerable patient demographics[15] as well as outpatients and asymptomatic patients can benefit from the simplicity and accessibility of ECG. This is crucial since most cardiovascular diseases have a progressive course and develop silently over many years and patients remain asymptomatic for a long time[46].

While the concept of HDA is fundamentally simple and easily understandable for patients and clinicians, its calculation does require specialized AI-ECG interpretation technology that is not yet universally available. This represents both a current limitation and a future opportunity, as the wider implementation of AI-ECG analysis could make HDA a more accessible risk stratification tool. The true value of HDA lies in its ability to integrate complex physiological information into an intuitive metric that may enhance traditional risk assessment, particularly as AI-ECG technology becomes more widespread.

The absence of a gold standard for measuring biological heart age remains a fundamental challenge in validating HDA's predictive value. While this limitation is shared by all biological age estimators, HDA offers unique advantages such as availability, a reflection of the integrated cardiac pathophysiology, and an intuitive metric (years) for risk communication. Its ECG-based nature offers practical advantages over more complex biological age measures requiring specialized assays or imaging. As demonstrated in this study, HDA's strong associations with outcomes across multiple cohorts suggest clinical utility as a complementary risk tool and a potential solution for risk stratification. To establish comparative validity, future studies could compare HDA against endpoints (e.g., mortality) employing established biological age markers like epigenetic clocks (e.g., DNA methylation), which are strongly associated with cardiovascular mortality[2,47].

Although none of the included studies utilized data from wearable devices, the theoretical potential for HDA derivation from wearable technology exists, as studies have demonstrated the feasibility of AI-based ECG analysis using smartwatch-derived rhythm strips[48,49]. However, important limitations regarding signal quality and clinical validation for age estimation remain to be addressed. Integrating this biomarker with existing health devices could lead to a more comprehensive tool for real-time health monitoring. This integration has the potential to revolutionize personal health management by combining continuous data collection from wearables with advanced analytical algorithms. A recent review suggests that heart age, more than absolute risk, encourages patients to participate more deliberately and carefully in treatment or to take preventive measures, such as lifestyle changes and modification of modifiable risk factors[50], same as when the rate of smoking cessation increased after lung age was presented to smokers[51]. Lastly, HDA could be beneficial in predicting outcomes of cardiac interventions, as examined by the latest studies[52,53]. It could serve as a practical tool for identifying surgery-related adverse events. Integrating HDA into existing surgical risk models—such as those powered by machine learning—could enhance predictive accuracy beyond traditional scoring systems like EuroSCORE II[54]. However, further research is needed to validate its clinical utility and reliability in this context (see Supplementary Note 3 and Supplementary Fig. 6 for further detail).

HDA could offer valuable insights into population-level health variations, enabling comparisons of biological age and its associated factors across different demographic groups. Furthermore, it may aid in identifying underlying risk factors and facilitating lifestyle modifications, particularly for chronic conditions. By supporting proactive health management, HDA encourages preventive measures that enhance overall patient well-being. Additionally, it could be a reliable metric for monitoring intervention outcomes, ultimately leading to more personalized patient care.

To ensure a broader understanding of HDA determinants, large-scale, prospective cohort studies that include diverse ethnic populations are needed, particularly in the elderly[55]. This is particularly important, as some determinants highlighted in this review were reported in only one study. Future research should prioritize evaluating the modifiability of predicted risk outcomes and assessing their practical utility in clinical settings. Moreover, clinical trials may utilize HDA as a surrogate biomarker, directly comparing it with traditional cardiovascular risk scores to determine its relative effectiveness and potential advantages. Overall, the next steps beyond this study would be validating HDA across diverse populations, standardizing cut-offs, integrating it with existing risk models to enhance clinical utility, and investigating the potential for a causal relationship between HDA and cardiovascular outcomes through well-designed longitudinal and interventional studies.

Our results indicated that the use of antihypertensive medications and lipid-lowering medications contributed to elevated HDA. This association likely reflects confounding by indication, as these patients inherently have higher cardiovascular[7,10]. However, direct ECG effects of these medications (e.g., autonomic modulation by beta-blockers) cannot be ruled out, though current evidence is limited[19]. This highlights the need for future studies to differentiate medication-related ECG changes from true biological aging, while clinically, elevated HDA in treated patients should prompt closer risk assessment.

Several questions remain unanswered, including the specific ECG characteristics that define accelerated aging compared to normal or decelerated aging. Similarly, the exact mechanisms through which AI models estimate ECG age are not yet fully understood. Given the inconsistencies in HDA cut-offs across studies included in this review, we advocate for the development of a standardized system to ensure more consistent reporting and interpretation.

A key strength of this systematic review lies in its comprehensive synthesis of potential HDA determinants and outcomes, consolidated into a single study. Additionally, the robust methodology—including the absence of language restrictions and the use of a visually intuitive quality assessment table—enhances the credibility of our findings.

However, certain limitations should be acknowledged regarding the quality of evidence. First, our meta-analysis was based on a limited number of studies, which may affect the generalizability of the results. Second, variations in the classification of HDA across studies posed a challenge in conducting a meta-analysis. To address this, we treated the different cut-off values as a single variable, allowing for pooled results despite minor variations that are likely negligible in clinical practice. Third, differences in the covariates used across studies may have influenced the effect sizes obtained. Fourth, publication bias led to missing articles, which may have reduced the statistical power of our analysis. Fourth, while our analysis shows HDA predicts adverse outcomes, this association does not establish that HDA directly causes these outcomes. Finally, we were unable to obtain detailed statistical data (e.g., odds ratios, *p*-values, and adjustments) from several studies examining potential determinants and outcomes of HDA. Consequently, we relied on a qualitative synthesis rather than a fully quantitative analysis. Lastly, several studies adopted the same AI model developed either by Attia et al.[19] or from the CODE study[9]. While both models were developed using extensive ECG datasets—CODE being the largest publicly accessible digital ECG database—their foundation in specific populations raises concerns about generalizability. This could potentially affect the interpretation of results. Moreover, the lack of a gold standard for calculating biological age, particularly heart age, limits the ability to compare HDA's predictive value with other assessment tools. The unique technical aspects of the AI-ECG age further complicate the ability to draw definitive causal conclusions. Additionally, our findings may have been influenced by publication bias, as conference abstracts and preprints were excluded from this review.

Our meta-analysis highlights the predictive value of AI-ECG age and HDA in mortality and other cardiovascular outcomes. HDA, derived from ECG analysis using AI models, has the potential to serve as an intuitive metric alongside other clinical variables, particularly for identifying at-risk patients in primary healthcare settings. Integrating HDA into standard ECG reports during routine patient assessments could enhance screening for asymptomatic individuals and facilitate early prevention strategies, given the widespread availability of ECGs in most healthcare clinics.

Methods

Search strategy and selection criteria

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[56] (Supplementary Table 1). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration ID CRD42023470198.

For this review, studies with the following criteria were included: 1) Using AI methods to estimate patients' biological heart age from ECG; 2) Studies with measured HDA (ECG-derived biological age - chronological age); 3) Studies reporting all-cause mortality, cardiovascular diseases, major adverse cerebro-cardiovascular events (e.g., cardiovascular-related death, heart failure (HF), coronary artery disease, ischemic stroke), or cardiovascular risk factors (e.g., hypertension (HTN), diabetes mellitus (DM), smoking, and dyslipidemia) between the groups.

We defined AI models as algorithms, such as neural networks, that can learn and make decisions based on patterns and improve their performance as exposed to more data over time. In this manner, studies that included traditional statistical methods like Bayesian statistics and traditional regression models were excluded. Furthermore, reviews, case reports, case series, conference abstracts, book chapters, letters, editorials, animal studies, and studies investigating participants after a cardiac intervention were not included in this review.

SM and AV systematically searched four databases (PubMed, Embase, Web of Science, and Scopus) from inception to September 27, 2024, without restrictions on language, country, or publication source. The search strategy and the keywords formulated for this review are outlined in Supplementary Table 2.

Duplicates were removed, and the remaining studies were screened by title and abstract. Full texts of the remaining studies were then obtained for further eligibility assessment and articles meeting the eligibility criteria were included in the review. A comprehensive review was conducted on the references of relevant articles to ascertain the presence of any additional suitable articles. Finally, with input from ZG the two investigators compared their search results and to ensure accuracy and address any potential discrepancies, AS was consulted for further verification.

Data extraction

Cardiovascular variables were divided into two groups: 1) HDA outcomes: Variables such as cardiovascular-related outcomes or mortality that were recorded during a specific follow-up period for patients and reported with hazard ratios (HR) along with 95% confidence intervals (CI). 2) HDA determinants: Common cardiovascular risk factors and variables that have an impact and influence on HDA, recorded with other measures of effect (e.g., odds ratio (OR), regression coefficient).

Additional data, including authors, publication year, country, study design, data collection period, AI method of ECG age estimation, population, age and sex proportions, and HDA cutoffs, were extracted from the studies.

Quality assessment

We assessed the risk of bias in the included studies with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist[57] (Supplementary Table 3). We established the following criteria for each of the four domains: "Complete Information" if adequate information on the checklist item was provided; "No Information" if there was no information on the checklist item; "Incomplete Information" if the reported data was insufficient for judgment; and "Not applicable" for items that could not be examined in the study context. The data extraction and critical appraisal process was conducted by two independent authors (SM and AV), and two other authors (AS and ZG) cross-checked the extracted data and the critical appraisal.

Data synthesis and meta-analysis

We calculated the pooled HR and the corresponding 95% CI to evaluate the relationship between the higher HDA group with mortality outcomes. An HR greater than 1 indicated a significantly higher mortality for patients with higher HDA, provided the 95% CI did not include 1.

To quantify the heterogeneity among studies and determine whether to apply fixed-effects or random-effects methods, we calculated the I2 statistic. If I2 > 40%, the random-effects model was used; otherwise, the fixed-effects model was applied. To evaluate publication bias, we employed graphical and statistical methods, including the funnel plot for visual inspection and Begg's test. Additionally, we utilized the trim-and-fill method for sensitivity analysis and to address missing studies.

This meta-analysis was conducted using STATA software version 17.0 (StataCorp, College Station, Texas), and all statistical calculations were performed with this tool. AM and MY performed the data analysis.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability

Data extracted from included studies and data used for all analyses are provided in Tables 1 and 2 and Supplementary Tables 5 and 6.

Received: 7 February 2025; Accepted: 16 May 2025;
Published online: 29 May 2025

References

1. Silva, N. et al. Measuring healthy ageing: current and future tools. *Biogerontology* https://doi.org/10.1007/s10522-023-10041-2 (2023).
2. Raisi-Estabragh, Z. et al. Estimation of biological heart age using cardiovascular magnetic resonance radiomics. *Sci. Rep.* **12**, 12805 (2022).
3. Raghu, V. K., Weiss, J., Hoffmann, U., Aerts, H. & Lu, M. T. Deep learning to estimate biological age from chest radiographs. *JACC Cardiovasc. Imaging* **14**, 2226–2236 (2021).
4. Ansari, M. Y. et al. Estimating age and gender from electrocardiogram signals: a comprehensive review of the past decade. *Artif. Intell. Med.* **146**, 102690 (2023).
5. Ryu, J. S. et al. Deep learning algorithms for estimation of demographic and anthropometric features from electrocardiograms. *J. Clin. Med.* **12**, https://doi.org/10.3390/jcm12082828 (2023).
6. Ball, R. L., Feiveson, A. H., Schlegel, T. T., Starc, V. & Dabney, A. R. Predicting "heart age" using electrocardiography. *J. Pers. Med.* **4**, 65–78 (2014).
7. Hirota, N. et al. Cardiovascular events and artificial intelligence-predicted age using 12-lead electrocardiograms. *Int. J. Cardiol. Heart Vasc.* **44**, 101172 (2023).
8. Chang, C. H., Lin, C. S., Luo, Y. S., Lee, Y. T. & Lin, C. Electrocardiogram-based heart age estimation by a deep learning model provides more information on the incidence of cardiovascular disorders. *Front. Cardiovasc. Med.* **9**, 754909 (2022).
9. Lima, E. M. et al. Deep neural network-estimated electrocardiographic age as a mortality predictor. *Nat. Commun.* **12**, 5117 (2021).
10. Ladejobi, A. O. et al. The 12-lead electrocardiogram as a biomarker of biological age. *Eur. Heart J. Digit Health* **2**, 379–389 (2021).
11. Brant, L. C. C. et al. Association between electrocardiographic age and cardiovascular events in community settings: the Framingham Heart Study. *Circ. Cardiovasc. Qual. Outcomes* **16**, e009821 (2023).
12. Jylhävä, J., Pedersen, N. L. & Hägg, S. Biological age predictors. *EBioMedicine* **21**, 29–36 (2017).
13. Zhang, C. et al. Association of lifestyle with deep learning predicted electrocardiographic age. *Front. Cardiovasc. Med.* **10**, 1160091 (2023).
14. Shelly, S. et al. Accelerated aging in LMNA mutations detected by artificial intelligence ECG-derived age. *Mayo Clin. Proc.* **98**, 522–532 (2023).
15. Lorenz, E. C. et al. Physiological age by artificial intelligence-enhanced electrocardiograms as a novel risk factor of mortality in kidney transplant candidates. *Transplantation* **107**, 1365–1372 (2023).
16. Lindow, T. et al. Heart age gap estimated by explainable advanced electrocardiography is associated with cardiovascular risk factors and survival. *Eur. Heart J. Digit Health* **4**, 384–392 (2023).

17. Meenakshi-Siddharthan, D. V. et al. Artificial intelligence-derived electrocardiogram assessment of cardiac age and molecular markers of senescence in heart failure. *Mayo Clin. Proc.* **98**, 372–385 (2023).
18. Toya, T. et al. Vascular aging detected by peripheral endothelial dysfunction is associated with ECG-derived physiological aging. *J. Am. Heart Assoc.* **10**, e018656 (2021).
19. Attia, Z. I. et al. Age and sex estimation using artificial intelligence from standard 12-lead ECGs. *Circ. Arrhythm. Electrophysiol.* **12**, e007284 (2019).
20. Leung, R. et al. Association between deep neural network-derived electrocardiographic-age and incident stroke. *Front. Cardiovasc. Med.* **11**, https://doi.org/10.3389/fcvm.2024.1368094 (2024).
21. Baek, Y. S. et al. Artificial intelligence-estimated biological heart age using a 12-lead electrocardiogram predicts mortality and cardiovascular outcomes. *Front. Cardiovasc. Med.* **10**, 1137892 (2023).
22. Iakunchykova, O. et al. Machine-learning-derived heart and brain age are independently associated with cognition. *Eur. J. Neurol.* **30**, 2611–2619 (2023).
23. Diez Benavente, E. et al. Studying accelerated cardiovascular ageing in Russian adults through a novel deep-learning ECG biomarker [version 1; peer review: 1 approved with reservations]. *Wellcome Open Res*. **6**, https://doi.org/10.12688/wellcomeopenres.16499.1 (2021).
24. Libiseller-Egger, J. et al. Deep learning-derived cardiovascular age shares a genetic basis with other cardiac phenotypes. *Sci. Rep.* **12**, 22625 (2022).
25. Rodríguez-Rodero, S. et al. Aging genetics and aging. *Aging Dis.* **2**, 186–195 (2011).
26. Zhang, J., Wang, S. & Liu, B. New insights into the genetics and epigenetics of aging plasticity. *Genes* **14**, 1–19 (2023).
27. Hodes, R. J. et al. Disease drivers of aging. *Ann. N. Y. Acad. Sci.* **1386**, 45–68 (2016).
28. Lu, W. H. Effect of modifiable lifestyle factors on biological aging. *JAR Life* **13**, 88–92 (2024).
29. Salih, A., Nichols, T., Szabo, L., Petersen, S. E. & Raisi-Estabragh, Z. Conceptual overview of biological age estimation. *Aging Dis.* **14**, 583–588 (2023).
30. Khane, R. S., Surdi, A. D. & Bhatkar, R. S. Changes in ECG pattern with advancing age. *J. Basic Clin. Physiol. Pharm.* **22**, 97–101 (2011).
31. Tanveer, M. et al. Deep learning for brain age estimation: a systematic review. *Inf. Fusion* **96**, 130–143 (2023).
32. Cole, J. H. & Franke, K. Predicting age using neuroimaging: innovative brain ageing biomarkers. *Trends Neurosci.* **40**, 681–690 (2017).
33. Levin, M. G. et al. Genome-wide association and multi-trait analyses characterize the common genetic architecture of heart failure. *Nat. Commun.* **13**, 6914 (2022).
34. Buniello, A. et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res.* **47**, D1005–d1012 (2019).
35. Worman, H. J. & Michaelis, S. Prelamin A and ZMPSTE24 in premature and physiological aging. *Nucleus* **14**, 2270345 (2023).
36. Wang, X. et al. Distinct roles of telomerase activity in age-related chronic diseases: an update literature review. *Biomed. Pharmacother.* **167**, 115553 (2023).
37. Guo, J. et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. *Signal Transduct. Target Ther.* **7**, 391 (2022).
38. Ollila, L. et al. Clinical disease presentation and ECG characteristics of LMNA mutation carriers. *Open Heart* **4**, e000474 (2017).
39. Belfiori, M., Lazzari, L., Hezzell, M., Angelini, G. D. & Dong, T. Transcriptomics, proteomics and bioinformatics in atrial fibrillation: a descriptive review. *Bioengineering* **12**, 149 (2025).
40. Vicent, L. & Martínez-Sellés, M. Electrocardiogeriatrics: ECG in advanced age. *J. Electrocardiol.* **50**, 698–700 (2017).
41. Krittayaphong, R. et al. Electrocardiographic predictors of cardiovascular events in patients at high cardiovascular risk: a multicenter study. *J. Geriatr. Cardiol.* **16**, 630–638 (2019).
42. Starc, V. et al. Can functional cardiac age be predicted from the ECG in a normal healthy population?. In 2012 Computing in Cardiology, 101–104. IEEE, 2012.
43. Oehler, A., Feldman, T., Henrikson, C. A. & Tereshchenko, L. G. QRS-T angle: a review. *Ann. Noninvasive Electrocardiol.* **19**, 534–542 (2014).
44. Chowdhury, M. A. et al. The heart of transformation: exploring artificial intelligence in cardiovascular disease. *Biomedicines* **13**, 427 (2025).
45. Dong, T. et al. Development and evaluation of a natural language processing system for curating a trans-thoracic echocardiogram (TTE) database. *Bioengineering* **10**, 1307 (2023).
46. Townsend, N. et al. Cardiovascular disease in Europe: epidemiological update 2016. *Eur. Heart J.* **37**, 3232–3245 (2016).
47. Chen, L. et al. Modeling biological age using blood biomarkers and physical measurements in Chinese adults. *EBioMedicine* **89**, 104458 (2023).
48. Tison, G. H. et al. Passive detection of atrial fibrillation using a commercially available smartwatch. *JAMA Cardiol.* **3**, 409–416 (2018).
49. Selder, J. L. et al. Accuracy of a standalone atrial fibrillation detection algorithm added to a popular wristband and smartwatch: prospective diagnostic accuracy study. *J. Med. Internet Res.* **25**, e44642 (2023).
50. Bonner, C. et al. Interventions using heart age for cardiovascular disease risk communication: systematic review of psychological, behavioral, and clinical effects. *JMIR Cardio* **5**, e31056 (2021).
51. Parkes, G., Greenhalgh, T., Griffin, M. & Dent, R. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *Bmj* **336**, 598–600 (2008).
52. Saleh, G. et al. Artificial intelligence electrocardiogram-derived heart age predicts long-term mortality after transcatheter aortic valve replacement. *JACC Adv.* **3**, 101171 (2024).
53. Park, H. et al. Artificial intelligence estimated electrocardiographic age as a recurrence predictor after atrial fibrillation catheter ablation. *npj Digital Med.* **7**, 234 (2024).
54. Sinha, S. et al. Comparison of machine learning techniques in prediction of mortality following cardiac surgery: analysis of over 220 000 patients from a large national database. *Eur. J. Cardiothorac. Surg.* **63**, https://doi.org/10.1093/ejcts/ezad183 (2023).
55. Shafiee, A. & van Bodegom, D. The necessity for research on the elderly in iran. *J. Tehran Heart Cent.* **7**, 40 (2012).
56. Page, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71 (2021).
57. Vandenbroucke, J. P. et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Epidemiology* **18**, 805–835 (2007).

Acknowledgements

This study was not funded by any public, private, or nonprofit organization.

Author contributions

A.S. conceptualized and administered the study. A.V. and S.M. with assistance from Z.G. developed the search strategy, conducted the literature search, and extracted the data from the relevant articles. S.M. and A.V. performed the critical appraisal of the included studies. A.S. and Z.G. cross-checked and validated the extracted data and the critical appraisal. A.M. and M.Y. performed the data analysis. S.M. and A.V. prepared the original draft of the manuscript. A.S. and F.A. supervised the study. All authors participated in a critical review, provided valuable intellectual input to the final manuscript, had full access to all the data in the study, and took ultimate responsibility for the decision to submit it for publication.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41746-025-01727-7.

Correspondence and requests for materials should be addressed to Akbar Shafiee.