ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 2903–2913
Published online 14 July 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14446

ORIGINAL ARTICLE

Causality between heart failure and epigenetic age: a bidirectional Mendelian randomization study

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Abstract

Aims Heart failure (HF) is a prevalent age-related cardiovascular disease with poor prognosis in the elderly population. This study aimed to establish the causal relationship between ageing and HF by conducting a bidirectional Mendelian randomization (MR) analysis on epigenetic age (a marker of ageing) and HF.

Methods and results Genome-wide association study data for epigenetic age (GrimAge, HorvathAge, HannumAge, and PhenoAge) and HF were collected and assessed for significant genetic variables. A bidirectional MR analysis was carried out using the random-effects inverse–variance weighted (IVW) method as the primary approach, while other methods (MR–Egger, weighted median, simple mode, and weighted mode) and multiple sensitivity analyses (heterogeneity analysis, leave-one-out sensitivity analysis, and horizontal pleiotropy analysis) were employed to evaluate the impact of epigenetic age on HF and vice versa. Bidirectional MR analysis of two samples revealed that the epigenetic PhenoAge clock increased the risk of HF [IVW odds ratio (OR) 1.015, 95% confidence interval (CI) 1.002–1.028, P = 0.028 and weighted median OR 1.020, 95% CI 1.001–1.038, P = 0.039]. Other results were not statistically significant.

Conclusions The bidirectional MR analysis demonstrated a causal link between genetically predicted epigenetic age and HF in individuals of European descent. Further research into epigenetic age in other populations and additional genetic information related to HF is warranted.

Keywords Epigenetic age; Heart failure (HF); Causality; Bidirectional Mendelian randomization (MR) study; Genome-wide association study (GWAS)

Received: 24 February 2023; Revised: 1 May 2023; Accepted: 8 June 2023
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Introduction

Heart failure (HF) is a common clinical syndrome that results in myocardial injury or overload during the pathogenesis of several diseases, ultimately causing decreased myocardial function.[1] HF is often accompanied by various inflammatory and metabolic disease complications with poor clinical prognosis, including diabetes, atrial fibrillation, and chronic kidney disease.[2] The prevalence of HF is around 26 million people worldwide,[3] with the elderly accounting for 80% of the population, and morbidity and mortality increase with ageing,[4] leading to significant socioeconomic and nursing burdens.[5,6] Cardiovascular ageing is an important risk factor for HF among all risk factors.[7]

The study of ageing-related biomarkers has recently been a hot topic in HF research. While epigenetic modifications are

fundamental mechanisms of biological ageing,[7] these are increasingly implicated in the development of cardiovascular diseases.[8,9] Because there is significant heterogeneity in health outcomes in the elderly,[10] epigenetic age based on DNA methylation (DNAm) is more accurate than chronological age in predicting physiological ageing status in the elderly.[11,12] Each epigenetic clock measures the DNA methylation levels at specific CpG loci to capture the epigenetic ageing profiles. With the advancement of genome-wide methylation research, epigenetic clocks have developed two generations of quantitative models: the first generation (HannumAge[13] and HorvathAge[14]) and the second generation (PhenoAge[15] and GrimAge[16]). Epigenetic age has been shown to be closely associated with atrial fibrillation when factors, such as actual age, are regarded as mediating factors.[17] However, there is a lack of current research on epigenetic age and HF.

Xu *et al.*[18] studied the susceptibility and severity of epigenetic age, such as PhenoAge, GrimAge, HannumAge, and HorvathAge, to novel coronavirus using inverse–variance weighted (IVW), Mendelian randomization (MR)–Egger, weighted median, simple mode, and weighted mode. Similarly, this analysis was used to investigate the causality between epigenetics and HF. To summarize, a bidirectional MR study was conducted using genome-wide association study (GWAS) data for HF and epigenetic clocks to evaluate the causality between them and thus reduce the influence of confounding factors on outcomes through a large sample of clinical genetic data and rule out reverse causality.

Research design and methods

Research design

The research was designed in accordance with the STROBE-MR guideline.[19] In this research, four epigenetic clocks (GrimAge,[16] HannumAge,[13] HorvathAge,[14] and PhenoAge[15]) were included as exposures and HF as outcomes to determine the instrumental variables for bidirectional MR analysis. Subsequently, MR–Egger, Cochran's *Q* analysis, horizontal pleiotropic analysis, and leave-one-out analysis were performed to validate the reliability of causality, with the first two analyses used for heterogeneity analysis and the rest for sensitivity analysis confirmation. MR was then used to examine HF as an exposure factor and epigenetic clock as an outcome factor. In summary, MR studies were required to meet the following three criteria: (i) association hypothesis: instrumental variables closely associated with exposure factors; (ii) independence hypothesis: instrumental variables unrelated to confounding factors associated with exposure and outcome factors; and (iii) exclusivity hypothesis: instrumental variables influenced outcomes through exposure factors only. In this study, bidirectional MR studies were used to examine the bidirectional causality between epigenetic age and HF (*Figure 1*).

Data source

In this research, four epigenetic age data sets, GrimAge,[16] HannumAge,[13] HorvathAge,[14] and PhenoAge,[15] were obtained as GWAS data based on 28 cohort studies of 34 710 European ancestry investigators (https://doi.org/10.7488/ds/2834). These data identified 137 ageing-related gene loci.[20] This research provided publicly available large GWAS summary data[21] for HF from the Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium for HF, involving 26 HF cases from 47 309 and 930 014 HF cases from European ancestry and control groups, respectively, stored at the Cardiovascular Disease Knowledge Portal (https://cvd.hugeamp.org/). Details of these studies were presented in *Table 1*.

Tool variable acquisition

A series of parameter controls were performed on gene-associated data for epigenetic age and HF to screen for eligible single-nucleotide polymorphisms (SNPs) in a bidirectional MR analysis of two samples. First, epigenetic age (as the SNP threshold for exposure), kilobase pair (kb), and parameter r^2 were set at a loose threshold $P < 5 \times 10^{-6}$, 5000, and 0.001, respectively. Significant epigenetic age-related SNPs obtained from these thresholds were used to match SNPs for HF outcome data. Moreover, the outcome SNPs that did not meet the threshold were removed. Similarly, according to the above principles, we also set HF as the threshold for significant SNP for exposure. Afterward, the most recent and stringent calculation methods for variance (R^2) and *F*-statistic were performed to avoid weak shifts in instrumental variables. *F*-statistic >10 is considered to avoid shifts caused by weak instrumental variables on MR results.[22] The formula is as follows:

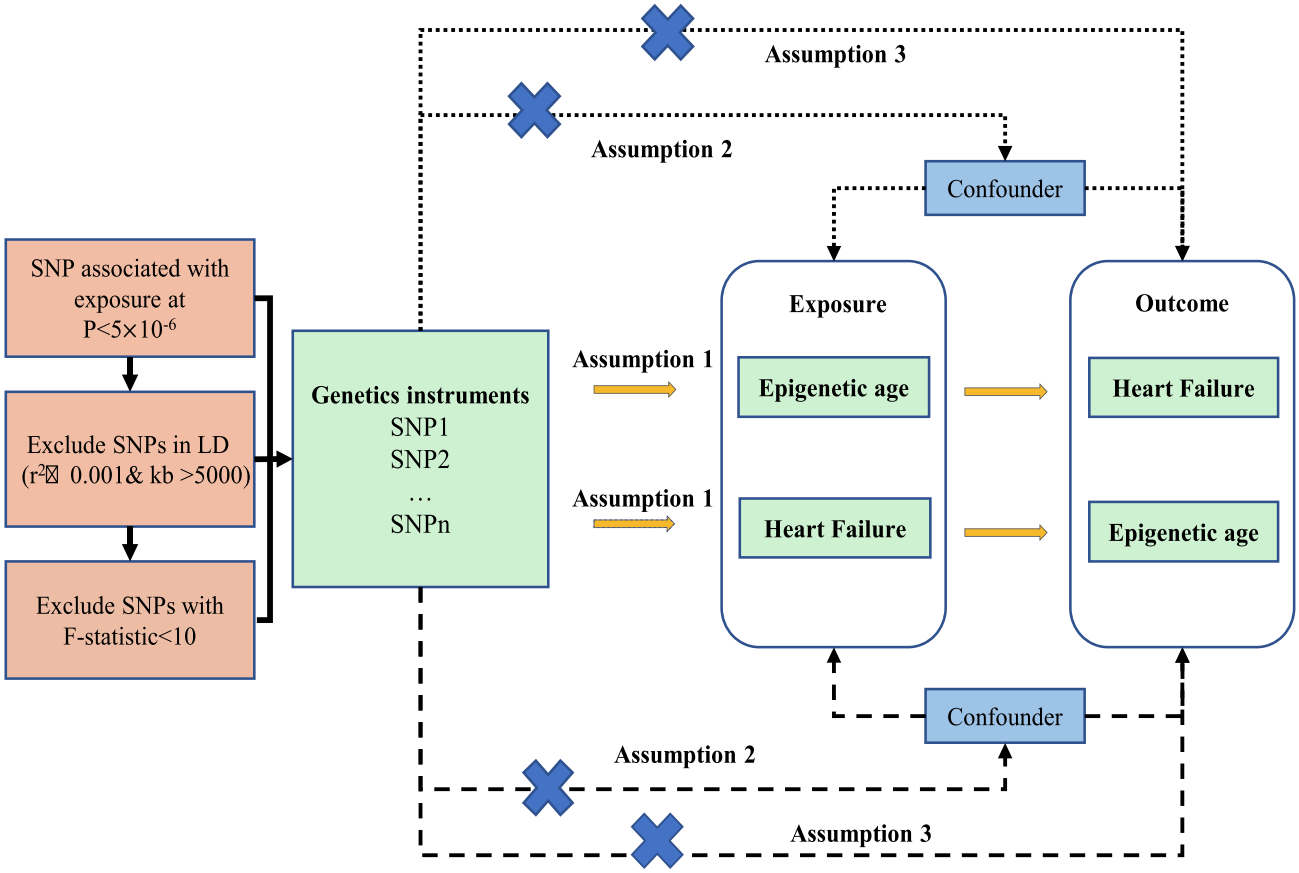
$$R^2 = \frac{2*MAF*(1 - MAF)*\beta^2}{SE^2*N}$$

$$F - statistic = \frac{R^2*(N - k - 1)}{k^2(1 - R^2)}$$

where *MAF* is the minor allele frequency, β is the effect size, *SE* is the standard error, *N* is the sample size, and *k* is the number of tool variables.

Subsequently, exposed SNP from previous thresholds was extracted, integrated, and combined with outcome data, such that the effect value of the effector allele of the outcome was consistent with that of the exposure.

Figure 1 The flow chart of this study. LD, linkage disequilibrium; SNPs, single–nucleotide polymorphisms.



Statistical analysis

First, based on the results of the MR analysis, Cochran's *Q* test <0.05 was considered heterogeneous and a random-effects model was used; otherwise, a fixed-effects model was used. IVW was used as the primary method[23] for MR analysis and could reach robust conclusions. Meanwhile, MR–Egger,[24] weighted median,[25] simple mode, and weighted mode were used to assess the robustness of MR results. Second, the MR–Egger intercept was calculated to assess heterogeneity and horizontal pleiotropy, and the MR–Egger intercept <0.05 was considered horizontal pleiotropy. Third, a 'leave-one-out' sensitivity analysis was used to examine whether a single SNP affected MR-level pleiotropy. Subsequently, forest plots and funnel plots were generated directly for horizontal pleiotropy testing. Finally, causal estimates (i.e. beta coefficients) were assessed and converted into random numbers [odds ratio (OR)]. The above approaches would provide the highest statistical effect based on the MR analysis of exposure to outcomes satisfying three key assumptions in the methodology section. Overall, these methods ensure the reliability of the causality between exposure and outcome. For multiple testing, the false discovery rate (FDR) is considered to be effective and robust.[26,27] In this study, FDR is implemented based on the R package 'fdrtool'.

All statistical analyses were performed using the TwoSampleMR (Version 0.5.6) package of R software 4.2.1. $P < 0.05$ was considered statistically significant.

Results

Tool variable extraction

When utilizing epigenetic age as the exposure factor, extracted epigenetic age with GWAS data was significantly correlated SNP ($P < 5 \times 10^{-6}$), and linkage disequilibrium (LD) was removed ($r^2 < 0.001$, 5000 kb). Parallelly, we also eliminated palindromic SNPs (SNPs whose alleles consisted of one base and its complementary base). Eventually, an epigenetic age of SNP (instrumental variable: GrimAge = 26,

Table 1 Data description of epigenetic age and heart failure

Type	Phenotype	Population	SNP	Sample size	*n*_cases	*n*_controls	Release date	Access address	DOI
Epigenetic age	PhenoAge	European	PhenoAge (7567585)	34 710	—	—	1 July 2020	https://datashare.ed.ac.uk/handle/10283/3645	https://doi.org/10.7488/ds/2834
	GrimAge		GrimAge (7567701)	34 710	—	—	2 July 2020	https://datashare.ed.ac.uk/handle/10283/3646	https://doi.org/10.7488/ds/2835
	HannumAge		HannumAge (7565045)	34 710	—	—	3 July 2020	https://datashare.ed.ac.uk/handle/10283/3647	https://doi.org/10.7488/ds/2836
	HorvathAge		HorvathAge (7567532)	34 710	—	—	4 July 2020	https://datashare.ed.ac.uk/handle/10283/3648	https://doi.org/10.7488/ds/2837
Heart failure	Heart failure	European	Heart failure (8281262)	964 057	47 309	930 014	9 January 2020	https://cvd.hugeamp.org/downloads.html	https://doi.org/10.1038/s41467-019-13690-5

DOI, digital object identifier; SNP, single-nucleotide polymorphism.

Table 2 Heterogeneity and pleiotropy of epigenetic age and heart failure

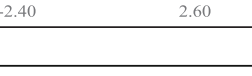
		Q-statistics		Pleiotropic test	
Exposure	Outcome	MR–Egger	IVW	Egger_intercept	*P* value
GrimAge	HF	$Q = 1.74E+01, P = 6.88E-01$	$Q = 1.75E+01, P = 7.37E-01$	−2.12E − 03	7.65E − 01
HannumAge	HF	$Q = 3.23E+01, P = 5.01E-01$	$Q = 3.24E+01, P = 5.44E-01$	−1.73E − 03	7.35E − 01
HorvathAge	HF	$Q = 5.50E+01, P = 2.28E-01$	$Q = 5.50E+01, P = 2.59E-01$	6.33E − 05	9.90E − 01
PhenoAge	HF	$Q = 3.20E+01, P = 1.85E-01$	$Q = 3.92E+01, P = 2.12E-01$	2.05E − 03	6.64E − 01
HF	GrimAge	$Q = 1.47E+01, P = 1.18E-02$	$Q = 1.93E+01, P = 3.64E-03$	1.67E − 01	2.65E − 01
HF	HannumAge	$Q = 4.18E+01, P = 1.74E-05$	$Q = 4.44E+01, P = 1.32E-05$	−5.58E − 02	4.31E − 01
HF	HorvathAge	$Q = 1.35E+01, P = 3.67E-03$	$Q = 1.42E+01, P = 6.62E-03$	7.04E − 02	7.16E − 01
HF	PhenoAge	$Q = 9.95E+00, P = 6.91E-03$	$Q = 1.03E+01, P = 1.65E-02$	−9.67E − 02	8.28E − 01

IVW, inverse-variance weighted; MR, Mendelian randomization.

Figure 2 Inverse–variance weighted (IVW) was used as the main method to analyse the two-way causal relationship between epigenetic age (GrimAge, HannumAge, HorvathAge, and PhenoAge) and heart failure. The forest map visualizes the causal effect of exposure on outcome risk by IVW method [when the outcome is heart failure, i.e. the dichotomy variable, the standard line is the 'X = 1' line (orange dashed line); when the outcome is epigenetic age, i.e. the continuity variable, the standard line is the 'X = 0' line (orange dashed line)], and the blue markers represent positive results with $P < 0.05$. Beta, risk index; CI, confidence interval; OR, odds ratio; Se, standard error; SNPs, single–nucleotide polymorphisms.

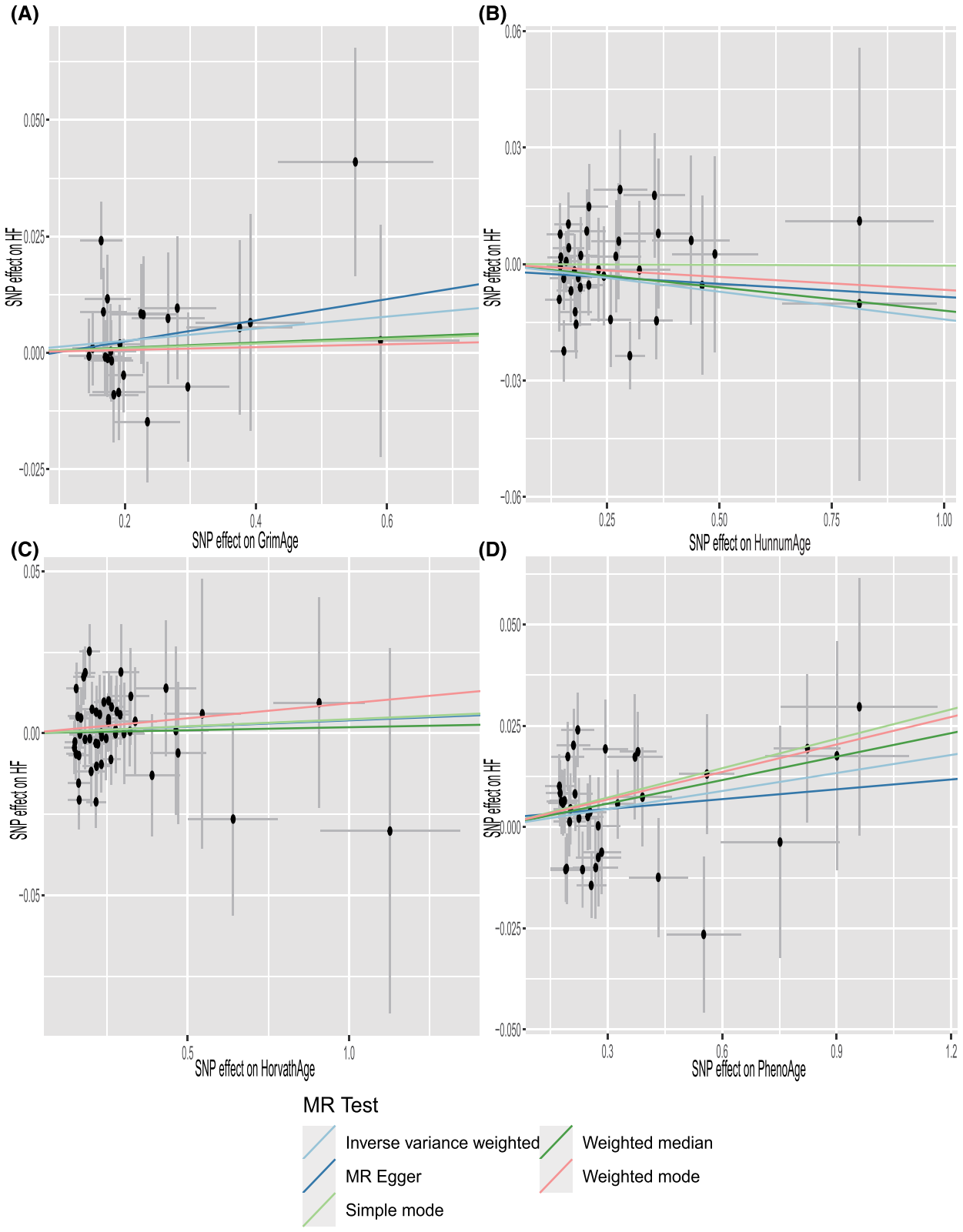
Exposure	Outcome	Method	nSNP	Beta	Se	P	OR(95%CI)
GrimAge	Heart Failure	MR Egger	23	0.023	0.034	0.510	1.02(0.96-1.09)
		Weighted median	23	0.006	0.014	0.695	1.01(0.98-1.03)
		Inverse variance weighted	23	0.013	0.010	0.215	1.01(0.99-1.03)
		Simple mode	23	0.005	0.025	0.841	1.00(0.96-1.05)
		Weighted mode	23	0.003	0.024	0.901	1.00(0.96-1.05)
HunnumAge	Heart Failure	MR Egger	35	-0.007	0.023	0.776	0.99(0.95-1.04)
		Weighted median	35	-0.012	0.012	0.310	0.99(0.97-1.01)
		Inverse variance weighted	35	-0.014	0.008	0.081	0.99(0.97-1.00)
		Simple mode	35	0.000	0.025	0.987	1.00(0.95-1.05)
		Weighted mode	35	-0.007	0.025	0.796	0.99(0.95-1.04)
HorvathAge	Heart Failure	MR Egger	50	0.004	0.021	0.856	1.00(0.96-1.05)
		Weighted median	50	0.002	0.009	0.831	1.00(0.98-1.02)
		Inverse variance weighted	50	0.004	0.006	0.519	1.00(0.99-1.02)
		Simple mode	50	0.004	0.019	0.823	1.00(0.97-1.04)
		Weighted mode	50	0.009	0.017	0.600	1.01(0.97-1.04)
PhenoAge	Heart Failure	MR Egger	34	0.008	0.017	0.634	1.01(0.98-1.04)
		Weighted median	34	0.019	0.009	0.039	1.02(1.00-1.04)
		Inverse variance weighted	34	0.015	0.007	0.028	1.01(1.00-1.03)
		Simple mode	34	0.024	0.018	0.192	1.02(0.99-1.06)
		Weighted mode	34	0.023	0.014	0.115	1.02(1.00-1.05)

Exposure	Outcome	Method	nSNP	Beta	Se	P	Beta(95%CI)
Heart Failure	GrimAge	MR Egger	7	-2.370	2.677	0.417	-2.37(-7.62-2.88)
		Weighted median	7	1.405	0.401	0.000	1.41(0.62-2.19)
		Inverse variance weighted	7	0.940	0.494	0.057	0.94(-0.03-1.91)
		Simple mode	7	1.579	0.507	0.021	1.58(0.58-2.57)
		Weighted mode	7	1.519	0.486	0.020	1.52(0.57-2.47)
Heart Failure	HunnumAge	MR Egger	13	1.143	1.315	0.403	1.14(-1.44-3.72)
		Weighted median	13	0.448	0.363	0.217	0.45(0.26-1.16)
		Inverse variance weighted	13	0.114	0.381	0.764	0.11(-0.63-0.86)
		Simple mode	13	1.385	0.819	0.117	1.38(-0.22-2.99)
		Weighted mode	13	1.250	0.553	0.043	1.25(0.17-2.33)
Heart Failure	HorvathAge	MR Egger	5	-0.259	3.794	0.950	-0.26(-7.70-7.18)
		Weighted median	5	1.581	0.563	0.005	1.58(0.48-2.68)
		Inverse variance weighted	5	1.225	0.691	0.076	1.22(-0.13-2.58)
		Simple mode	5	1.600	0.635	0.065	1.60(0.36-2.84)
		Weighted mode	5	1.589	0.608	0.059	1.59(0.40-2.78)
Heart Failure	PhenoAge	MR Egger	4	3.566	9.770	0.750	3.57(-15.58-22.71)
		Weighted median	4	1.934	0.708	0.006	1.93(0.55-3.32)
		Inverse variance weighted	4	1.170	0.968	0.226	1.17(-0.73-3.07)
		Simple mode	4	2.020	0.845	0.097	2.02(0.36-3.68)
		Weighted mode	4	2.009	0.874	0.105	2.01(0.30-3.72)



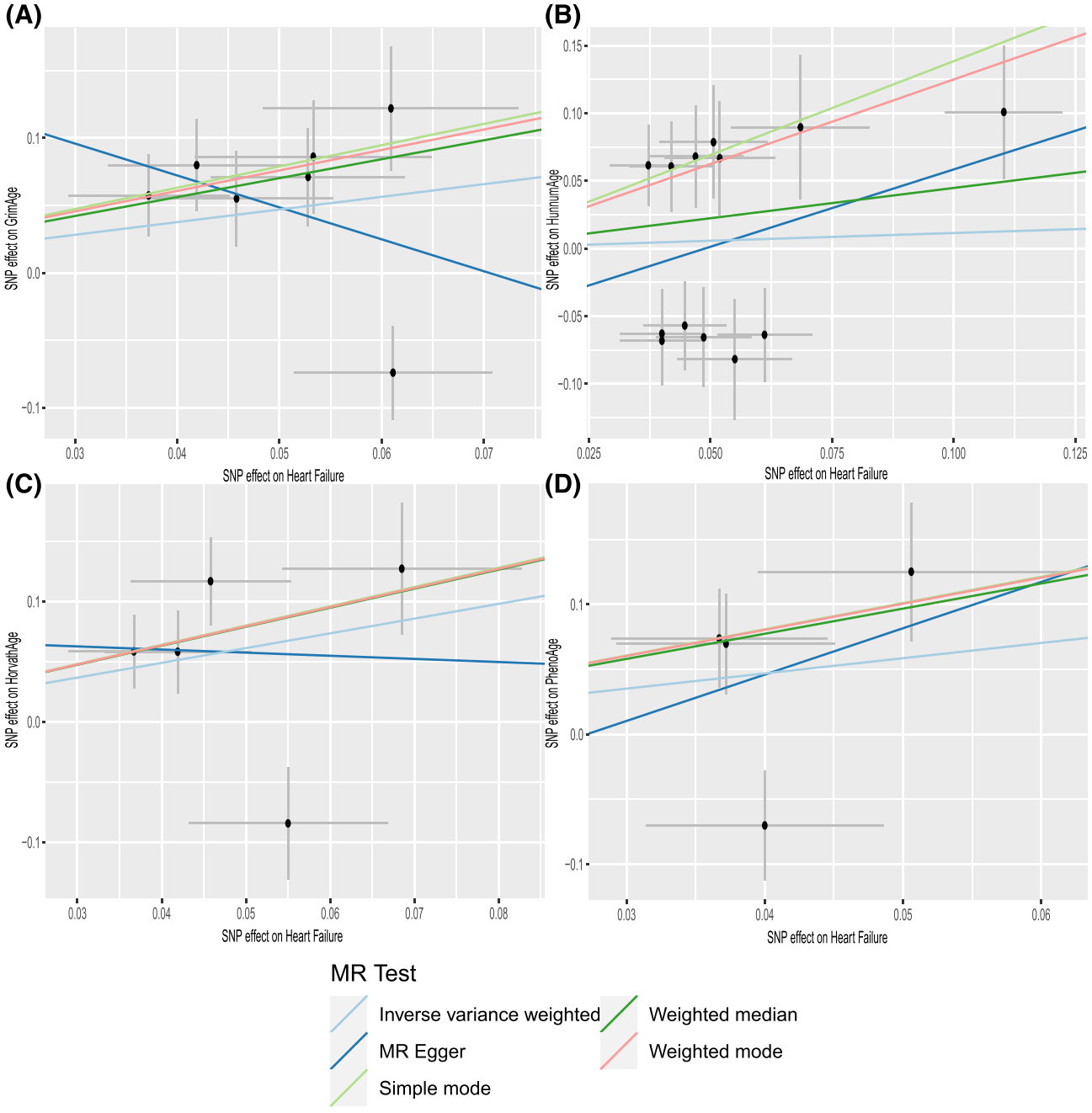
R^2 = 1.89%, F-statistic = 25.73; instrumental variable: HannumAge = 42, R^2 = 3.54%, F-statistic = 30.25; instrumental variable: HorvathAge = 59, R^2 = 6.25%, F-statistic = 39.14; and instrumental variable: PhenoAge = 37, R^2 = 3.34%, F-statistic = 32.35) (Supporting Information, *Table S1*) satisfying the genome >2 for MR analysis was obtained. Correspondingly, when HF was the exposure factor, the number of instrumental variables was 54, R^2 = 0.15%, and F-statistic = 27.00. The number of instrumental variables also met the requirements for MR analysis (Supporting Information, *Table S2*). In MR studies, F-statistic was employed to evaluate the strength of instrumental variables. Generally,

Figure 3 Scatter plot of epigenetic age and HF. Horizontal ordinate: single–nucleotide polymorphisms (SNPs) effect on 'exposure'; vertical coordinates: SNP effect on 'outcome'. (A) Exposure: GrimAge; outcome: HF. (B) Exposure: HannumAge; outcome: HF. (C) Exposure: HorvathAge; outcome: HF. (D) Exposure: PhenoAge; outcome: HF. MR, Mendelian randomization.



DOI: 10.1002/ehf2.14446

Figure 4 Scatter plots of HF and epigenetic age. Horizontal ordinate: single–nucleotide polymorphisms (SNPs) effect on 'exposure'; vertical coordinates: SNP effect on 'outcome'. (A) Exposure: HF; outcome: GrimAge. (B) Exposure: HF; outcome: HannumAge. (C) Exposure: HF; outcome: HorvathAge. (D) Exposure: HF; outcome: PhenoAge. MR, Mendelian randomization.



an *F*-statistic >10 can rule out shifts caused by weak instrumental variables on MR results. In this study, the bidirectional MR had an *F*-statistic >10 (range 20.73–239.73), and no weak instrumental variables were present. Therefore, these instrumental variables help determine the causality of exposure to outcomes.

Mendelian randomization analysis of epigenetic age on heart failure

Cochran's *Q* test ($P > 0.05$) indicated no heterogeneity, so IVW analysis was performed using a fixed-effects model (*Table 2*). The IVW model suggested a causality between

DOI: 10.1002/ehf2.14446

PhenoAge and HF [IVW OR 1.015, 95% confidence interval (CI) 1.001–1.028, $P = 0.028$]. And similar results were seen with the weighted median method (OR 1.020, 95% CI 1.001–1.038, $P = 0.039$). The OR and 95% CI of other epigenetic clocks and HF were not statistically significant (*Figure 2*) (GrimAge and HF: OR 1.013, 95% CI 0.992–1.034, $P = 0.215$; HannumAge and HF: OR 0.986, 95% CI 0.970–1.002, $P = 0.081$; HorvathAge and HF: OR 1.004, 95% CI 0.992–1.017, $P = 0.519$). The generated scatter plots were used to demonstrate the genetic visualization estimates of epigenetic age on HF (*Figure 3*). Results from other analytical methods and forest plots of MR analyses of individual SNPs were located in Supporting Information, *Figure S1*. IVW ($P = 0.212$) and MR–Egger regression ($P = 0.185$) showed no significant heterogeneity between epigenetic age and MR analysis of HF. Egger_intercept of MR–Egger and zero were not statistically significant ($P = 0.664$). SNPs were not horizontally pleiotropic (*Table 2*). There were no SNPs in the study data that had a significant impact on the results, so the results have a high level of confidence (Supporting Information, *Figure S2*). Therefore, we can also draw the conclusion that the results were robust.

Mendelian randomization analysis of heart failure on epigenetic age

There is no clear evidence of causality between HF and epigenetic age (GrimAge IVW beta = 0.940, 95% CI −0.029 to 1.908, $P = 0.057$; HannumAge IVW beta = 0.114, 95% CI −0.632 to 0.861, $P = 0.764$; HorvathAge IVW beta = 0.200, 95% CI −0.129 to 2.579, $P = 0.076$; and PhenoAge IVW beta = 1.170, 95% CI −0.726 to 3.607, $P = 0.226$) (*Figure 2*). Visual estimation plots of the genetic variance are displayed in *Figure 4* and forest plots of individual SNPs for reverse MR in Supporting Information, *Figure S3*. The diagram of HF and epigenetic age was shown in Supporting Information, *Figure S4*.

Discussion

Ageing is a risk factor in an ageing society, causing increased morbidity and mortality in various diseases. The mechanism of ageing is the focus of human physiological and pathological mechanism research.[28] Although the epigenetic age is not exactly comparable with the traditional age, epigenetic clocks can help researchers better understand the biological mechanisms of human health and ageing using different training samples and populations.[12] Investigating the causality between epigenetic age and cardiovascular disease is a novel and challenging research topic.

To the best of our knowledge, this is the first study to look into the bidirectional causality between epigenetic age and HF. In this research, the epigenetic clock PhenoAge was found to increase the risk of HF. On the other hand, HF also increased the risk of the epigenetic HorvathAge clock. In our study, no causality between other epigenetic clocks and HF was found.

We investigated the mechanism by which the epigenetic clock PhenoAge increases the risk of HF. As an epigenetic biomarker, PhenoAge can effectively combine blood DNAm indicating that epigenetic age, with a correlation coefficient with the heart of 0.66, can specifically assess the ageing characteristics of cardiovascular disease[15] and can better capture 'preclinical ageing'. Second, it has been demonstrated that pathway enrichment of genes involved in PhenoAge positively correlates with the activation of pro-inflammatory pathways such as response to lipopolysaccharide and nuclear factor-κB (NF-κB). Lipopolysaccharide is a toxic component produced by Gram-negative cocci with immunostimulatory and immunomodulatory effects.[29] Increased plasma concentrations of lipopolysaccharide have been reported in patients with chronic HF.[30] They may reach the blood and cause the release of pro-inflammatory factors such as tumour necrosis factor-α (TNF-α) by altering the intestinal barrier.[31] Lipopolysaccharide reactivity has also been demonstrated to be an independent predictor of mortality in HF.[32] NF-κB activates myocardial senescence[33] and is closely related to cardiomyocyte survival and inflammatory regulation.[34] Prolonged activation of NF-κB promotes inflammatory pathway signalling causing HF. Several studies[35–37] have shown that inhibiting NF-κB pathway activity helps delay cardiomyocyte senescence and reduce age-related HF, with the underlying mechanism possibly associated with apoptosis[38] and mitochondrial oxidative stress.[39] The findings of the preceding studies are consistent with the findings of this study regarding the causality of HF and epigenetic age.[40] We investigated why HF can accelerate the ageing of epigenetic clock (HorvathAge) malfunction due to HF's effect on telomere length and DNA methylation modifications.[41]

However, our study does have inevitable limitations. First, the data in our study were primarily obtained from the European populations, and despite a large number of populations, genetic studies on epigenetic age and HF between ethnic groups are still lacking. This may cause discrepancies between observations and the actual situation. Second, because epigenetic age is intrinsically associated with environmental exposures rather than genetic factors, this highlights the limitations of MR in this context. Finally, the OR values of our findings were low; thus, they should be interpreted cautiously. We look forward to future research that will explain the relationship between epigenetic age and HF.

Conclusions

In this study, epigenetic age had a bidirectional causality with HF. PhenoAge, an epigenetic clock, increased the risk of HF. Moreover, the underlying mechanism may be related to

inflammatory pathways. HF accelerated the epigenetic clock HorvathAge. This research explored the causality between epigenetic age and HF via MR analysis. However, more research into the mechanisms between epigenetic age and HF in different ethnic groups is needed.

Acknowledgements

We thank statisticians and GWAS data providers for their efforts in this study. Meanwhile, we thank Dr Guangli Sun, Chief Physician, Department of Traditional Chinese Medicine, Laixi City Hospital, for her financial assistance with this study. We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This study was supported by the Natural Science Foundation of Shandong Province (ZR2020QH306) and the Department of Science and Technology of Sichuan Province of China (23QYCX0040).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Mendelian randomization effects forest plots for individual SNPs with epigenetic age as the exposure, Heart Failure as the outcome. (A) exposure: GrimAge, outcome: Heart Failure; (B) exposure: HannumAge, outcome: Heart Failure; (C) exposure: HovarthAge, outcome: Heart Failure; (D) exposure: PhenoAge, outcome: Heart Failure; The red marker points indicated All-MR Egger and All-IVW.
Figure S2. MR leave-one-out sensitivity analysis "outcome" on "Heart Failure". (A) exposure: GrimAge, outcome: Heart Failure; (B) exposure: HannumAge, outcome: Heart Failure; (C) exposure: HovarthAge, outcome: Heart Failure; (D) exposure: PhenoAge, outcome: Heart Failure.
Figure S3. Mendelian randomization effects forest plots for individual SNPs with heart failure as the exposure, epigenetic age as the outcome. (A) exposure: Heart Failure, outcome: GrimAge; (B) exposure: Heart Failure, outcome: HannumAge; (C) exposure: Heart Failure, outcome: HorvathAge; (D) exposure: Heart Failure, outcome: PhenoAge. The red marker points indicated All-MR Egger and All-IVW.
Figure S4. MR leave-one-out sensitivity analysis "outcome" on "Epigenetic age". (A) exposure: Heart Failure, outcome: GrimAge; (B) exposure: Heart Failure, outcome: HannumAge; (C) exposure: Heart Failure, outcome: HovarthAge; (D) exposure: Heart Failure, outcome: PhenoAge.
Table S1. Epigenetic age instrumental variables and R2 and F-statistics.
Table S2. Heart failue instrumental variables and R2 and F-statistics.
Data S1. Supporting Information.

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