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Domestic water hardness, genetic risk, and distinct phenotypes of cardiovascular disease

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Abstract

Aims The study aimed to investigate the association between domestic water hardness and the incidence of AF and the interaction effects between water hardness and genetic susceptibility to incident AF risk. As a secondary objective, its associations with incident heart failure (HF), coronary heart disease (CHD), and stroke were measured.

Methods The UK Biobank is a prospective cohort study comprising over 500,000 participants recruited in the United Kingdom between 2006 and 2010, aged 37 to 73 years. A total of 447,950 participants did not have prevalent AF, and 423,946 participants who were free of HF, CHD, and stroke at baseline were included. Water hardness was assessed by $CaCO_3$ concentration. The genetic risk score for AF was based on the standard polygenic risk score. Cox proportional hazards regression models and restricted cubic spline (RCS) analysis were conducted.

Results During a median follow-up of 13.74 years, 30,726 (6.86%) individuals were diagnosed with AF for the first time. Compared with those with water hardness ≤ 60 mg/L, individuals with domestic water hardness 121–180 mg/L had a 17% lower risk of developing AF (HR 0.83, 95% CI 0.79–0.87), but water hardness of 61-120 mg/L and > 180 mg/L was associated with a higher risk of incident AF (both 1.04, 1.01–1.07). A non-linear relationship between water hardness and incident AF (*P* for non-linear = 0.001) was found. Individuals with water hardness 121-180 mg/L were also significantly associated with a lower risk of incident HF (HR 0.82, 95% CI 0.75–0.89), CHD (HR 0.80, 95% CI 0.76–0.84) and stroke (HR 0.88, 95% CI 0.81–0.95). There were no significant interaction effects between water hardness level and genetic susceptibility to AF, HF, CHD, and stroke risk (all *P* for interaction > 0.05).

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Conclusion Potential U-shaped associations between domestic water hardness and incident AF across varying levels of genetic risk were found. Hard water (121–180 mg/L) may offer the most benefits compared to soft water when considering overall cardiovascular health, including AF, HF, CHD, and stroke.

Keywords Water hardness, Atrial fibrillation, Cardiovascular disease, Genetic risk, UK biobank

Introduction

Atrial fibrillation (AF) is recognized as the predominant clinical cardiac arrhythmia, frequently manifesting as either a cause or a consequence of heart failure (HF) [1]. Both AF and HF, representing two distinct phenotypes of cardiovascular disease (CVD), are linked to an elevated likelihood of cardiovascular complications and mortality, with their prevalence and incidence exhibiting an upward trend globally [2, 3]. Established etiological factors, including lifestyles, genetic predisposition, cardiometabolic factors, etc., only partially account for the population-attributable risk associated with AF [4–6]. Consequently, there is a pressing need to advance our comprehension of the predisposing risk factors for AF, which may facilitate the development of novel preventive interventions.

Water is a common environmental element in daily life, with a growing focus on its effects on health over the past few decades, particularly regarding domestic water hardness, which is measured in terms of calcium carbonate ($CaCO_3$) equivalents [7–9]. Previous studies reported inconsistent relationships between domestic water hardness and various diseases such as eczema [10], atopic dermatitis [11], and all-cause and multiple-cause-specific cancers [9]. The debate regarding the relationship between domestic water hardness and CVD incidence and mortality remains ongoing. A recent meta-analysis indicated a potential 40% reduction in CVD mortality associated with the consumption of hard water [12]. However, among the twenty-five studies included in the meta-analysis, 28% reported no significant relationship between water hardness and CVD prevention and mortality [12].

Previous studies mainly examined the associations of water hardness with coronary heart disease (CHD) and stroke, with limited evidence available on the associations with AF and HF incidence. Additionally, although genome-wide association studies have effectively identified genetic variants linked to various cardiovascular phenotypes, such as AF, HF, CHD, and stroke, there is a lack of understanding regarding the potential interplay between domestic water hardness and genetic predisposition in influencing the risk of these cardiovascular phenotypes.

Using data from the UK Biobank (UKB) large-scale prospective cohort, this study aimed to investigate the potential association between domestic water hardness and incident AF. Additionally, we sought to explore the interaction between water hardness and genetic susceptibility to AF risk. As a secondary objective, we also examined the associations between water hardness and three other cardiovascular phenotypes, including HF, CHD, and stroke.

Methods

Study design and participants

Our study is based on the UK Biobank, a prospective cohort study comprising over 500,000 participants recruited in the United Kingdom between 2006 and 2010, aged 37 to 73 years [13]. A detailed cohort profile and assessment protocol have been published elsewhere [13]. Briefly, data on biological samples, physical measurements, and touch-screen questionnaires were collected at baseline. The UK Biobank study has obtained full ethical approval from the North West Multi-Center Research Ethics Committee, and all the participants provided written informed consent (http://www.ukbiobank.ac.uk/ethics/) [13]. The last accessed date is 19 December 2022.

Among the 502,417 participants included in the study, 46,760 were excluded due to missing information on water hardness at baseline. Of the remaining, 447,950 participants did not have prevalent AF at baseline, with 433,378 having genetic data for AF. Additionally, 423,946 participants were free of HF, CHD, and stroke at baseline, allowing for an analysis of the association between water hardness and these three cardiovascular phenotypes as a secondary objective, with 385,991 having genetic data for HF, 410,272 having genetic data for CHD, and 410,272 having genetic data for stroke (Supplementary Fig. S1).

Domestic water hardness

Domestic water hardness data were collected 1 year before the start of baseline recruitment (2005) from local water supply companies in England, Wales, and Scotland by the University of Melbourne, which then provided this category to the UK Biobank (Field IDs: 21100; 21101; 21103; 21104; 21105) [9, 10]. Postcodes were allocated to participant-visit instances according to the approximate location. Subsequently, these assigned postcodes served as a connection to the surveyed locations. 450,000 individual analyses conducted by unforbidden drinking water laboratories in the UK revealed that the hardness of water samples ranged from 1 to 477 mg/L as $CaCO_3$, with a median value of 141.1 mg/L [14]. Water hardness was assessed by $CaCO_3$ concentration, which in this study was classified in three ways: (i) as a continuous variable,

(ii) as a categorical variable, according to the United States Geological Survey (USGS) classification of $CaCO_3$ concentration into four groups: soft water (≤ 60 mg/L), moderately hard water (> 60, ≤ 120 mg/L), hard water (> 120, ≤ 180 mg/L) and very hard water (> 180 mg/L) [9]. In addition, calcium (Ca) and magnesium (Mg) were measured at the water supplies.

Ascertainment of incident AF and three other cardiovascular phenotypes

The incident AF and three other cardiovascular phenotypes were identified from the initial manifestation of health outcomes defined by the 3-character International Statistical Classification of Diseases and Related Health Problems 10th Revision code (ICD-10) (category ID in UKB 1712). The incidents of AF, HF, CHD, and stroke were sourced from death registers, primary care facilities, and hospital records. The definitions of these outcomes based on the ICD-10 specifically were I48 for AF, I50 for HF, I20-I24 for CHD, and I60-I64 and I69 for stroke, as previously described [15].

Genetic risk score for AF and three cardiovascular phenotypes

The genetic risk score for AF, CHD, and stroke was based on the standard polygenic risk score (PRS, field ID 26212, 26227, and 26248 in UK Biobank, respectively) supported by external genome-wide association studies data [16]. The PRS for HF was constructed using single-nucleotide polymorphisms (SNPs) associated with HF with genome-wide association significance in a genome-wide association study, not including UKB participants [17], and 12 SNPs selected for HF have been reported previously [18]. We further classified participants with high (the highest PRS quartile), intermediate (the middle two PRS quartiles), or low (the lowest PRS) genetic risk. As anticipated, PRS and PRS quartiles showed positive associations with the risk of AF, HF, CHD, and stroke (Supplementary Fig. S2).

Covariates

The covariates and their classification considered in the present study were similar to the previous research [4, 5, 15]: age (year, continuous), sex (men or women), ethnicity (White/others), education (university or college degree/others), the Townsend Index (a composite measure of socioeconomic deprivation, continuous), smoking status (never or quit smoking, current smoker), target physical activity or not (≥ 150 min/week of moderate intensity, or ≥ 75 min/week of vigorous-intensity, or an equivalent combination), healthy diet score (score ≥ 4), body mass index (BMI) (continuous), total cholesterol (continuous), ideal HbA1c or not (ideal HbA1c is HbA1c < 5.7%), ideal blood pressure or not (BP < 120/<80 mmHg).

Statistical analyses

IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA) and R (version 4.2.1) were used to perform the analyses. Statistical significance was defined as a two-tailed P value < 0.05. Characteristics of participants at baseline were summarized as the mean (SD) or median (interquartile range) for continuous variables and numbers (percentages) for categorical variables concerning $CaCO_3$ levels of domestic water. Characteristics were compared by domestic water $CaCO_3$ concentration using analysis of variance or Kruskal-Wallis test for continuous variables and Pearson chi-squared test for categorical variables, as appropriate. Follow-up time was calculated from the baseline date to the occurrence of the outcome, death, or the censoring date (19 December 2022), whichever occurred first. Participants who were lost to follow-up were not included in this study.

Cox proportional hazard models with the follow-up time as the time scale were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between water hardness and the primary and secondary outcomes. Several confounders were included in the models, namely age at baseline (continuous), sex, ethnicity (white/others), education (university or college degree/others), the Townsend index (continuous), smoking status (never, former, current), ideal physical activity (yes/no), healthy diet score (yes/no), BMI (continuous), total cholesterol (continuous), ideal HbA1c (yes/no), ideal blood pressure (yes/no). If the information on the above covariates was missing, means (normal distribution) or medians (non-normal distribution) were imputed for continuous variables, or a missing indicator approach was used for categorical variables. Furthermore, we employed another adjustment model to further explore the relationship between $CaCO_3$, Ca, and Mg and four cardiovascular diseases, adjusting for age, sex, ethnicity, education, the Townsend index, smoking status, ideal physical activity, and healthy diet score in the Supplementary Fig. S3.

We measured whether genetic susceptibility to AF and the other three cardiovascular phenotypes modified the association between water hardness and disease risk. We first examined whether the PRS (continuous) and PRS categories were positively associated with AF. The interaction analyses were performed using the likelihood ratio test to compare models with and without a cross-product term. P values were calculated for the interaction and stratified associations by PRS category. Tests for linear trends were performed by including ordinal categories as a continuous variable in the regression model.

Restricted cubic spline (RCS) analyses were performed using a four-knot (with knots at the 5th, 35th, 65th, and 95th percentiles) restricted cubic spline function to further validate the potential non-linear relationships of water hardness with incident AF, HF, CHD, and stroke.

Moreover, stratified analyses were performed by sex, age (< 60 or ≥ 60 years), Townsend index tertiles, race, education, ideal HbA1c, smoking status, total cholesterol level [19] (ideal, < 5.2 mmol/L; and nonideal, ≥ 5.2 mmol/L), BMI (ideal, < 25 kg/ m^2; and nonideal, ≥ 25 kg/ m^2), ideal blood pressure, ideal physical activity status, and ideal diet. The *P* values for the product terms between the water hardness and the stratification variables were used to estimate the significance of interactions using the likelihood ratio test comparing models.

In the sensitivity analysis, we used three classification methods of $CaCO_3$ to explore the relationship between CaCO3 and four cardiovascular diseases: (1) as a binary variable (≤ 180 mg/L, > 180 mg/L); (2) as a ternary variable, with cut-off points at 100 and 200 mg/L according to the World Health Organization (WHO) reports [20]; (3) as a quartile variable, with quartiles as cut-off points.

Results

General characteristics of the participants

The baseline characteristics of the study population by the USGS classification of domestic water hardness are presented in Table 1. Of the 447,950 participants (45.07% men; mean age 56.47 years), the proportions of the population with domestic water $CaCO_3$ levels of ≤ 60 mg/L, between > 60 and ≤ 120 mg/L, between > 120 and ≤ 180 mg/L, and > 180 mg/L at baseline were 39.26%, 21.47%, 6.41%, and 32.86%, respectively. During a median follow-up of 13.74 years, 30,726 (6.86%) individuals were diagnosed with AF for the first time. Participants who received higher $CaCO_3$ levels of domestic water were more likely to be younger, women, non-White, non-current smokers, better educated, and have ideal physical activity, body mass index, HbA1c, blood pressure, and diet in baseline (*P* for trend < 0.05).

Associations of water hardness with incident AF and other three cardiovascular phenotypes

Estimated associations between water hardness and incident AF are shown from Cox proportional hazard regression models (Fig. 1). After adjustment for confounders, individuals receiving higher $CaCO_3$ levels (continuous) of domestic water had a higher risk of incident AF and HF and a lower risk of CHD and stroke (Fig. 1). However, using the USGS criteria, individuals with $CaCO_3$ levels of domestic water between > 120 and ≤ 180 mg/L had a 17% lower risk of developing AF (HR 0.83, 95% CI 0.79–0.87), a 20% lower risk of developing CHD (HR 0.80, 95% CI 0.76–0.84), an 18% lower risk of developing HF (HR 0.82, 95% CI 0.75–0.89) and a 12% lower risk of developing stroke (HR 0.88, 95% CI 0.81–0.95) compared with those with $CaCO_3$ levels of ≤ 60 mg/L (Fig. 1). Compared with the individuals with the lowest Ca quartile, those with the highest Ca quartile had a 6% lower risk of developing CHD (HR 0.94, 95% CI 0.92–0.97) and a 10% lower risk of developing stroke (HR 0.90, 95% CI 0.85–0.95). However, individuals with the highest Mg quartile had a 3% higher risk of developing AF (HR 1.03, 95% CI 1.00-1.06),

Table 1 Baseline characteristics of UK biobank participants

	All	$CaCO_3$ category (using USGS)					
		≤ 60 mg/L	> 60, ≤ 120 mg/L	> 120, ≤ 180 mg/L	> 180 mg/L	*P*	*P* for trend
n	447,950	175,857	96,172	28,712	147,209		
Age, year	56.47 (8.08)	56.63 (8.05)	56.80 (7.98)	56.22 (7.92)	56.10 (8.20)	< 0.001	< 0.001
Male gender (%)	201,913 (45.07%)	79,599 (45.26%)	44,366 (46.13%)	12,838 (44.71%)	65,110 (44.23%)	< 0.001	< 0.001
White (%)	422,661 (94.35%)	169,864 (96.59%)	92,648 (96.34%)	27,569 (96.02%)	132,580 (90.06%)	< 0.001	< 0.001
University or college degree (%)	143,232 (31.97%)	52465 (29.83%	25,103 (26.10%)	9684 (33.73%)	55,980 (38.03%)	< 0.001	< 0.001
Townsend deprivation index	-1.26 (3.10)	-1.29 (3.14)	-1.63 (2.82)	-1.82 (2.80)	-0.88 (3.23)	< 0.001	< 0.001
Cholesterol, mmol/L	5.70 (1.11)	5.71 (1.11)	5.71 (1.11)	5.69 (1.09)	5.70 (1.09)	0.004	0.001
Body mass index, kg/m^2	27.42 (4.78)	27.55 (4.80)	27.67 (4.76)	27.54 (4.77)	27.06 (4.75)	< 0.001	< 0.001
Current smoking (%)	47,719 (10.65%)	19,686 (11.19%)	9663 (10.05%)	3057 (10.65%)	15,313 (10.40%)	< 0.001	< 0.001
Physical activity at goal (%)	194,515 (43.42%)	74,756 (42.51%)	41,417 (43.07%)	12,101 (42.15%)	66,241 (45.00%)	< 0.001	< 0.001
Ideal HbA1c (%)	336,377 (75.09%)	130,980 (74.48%)	72,539 (75.43%)	22,186 (77.27%)	110,672 (75.18%)	< 0.001	0.034
Ideal blood pressure (%)	55,166 (12.32%)	20,604 (11.72%)	10,657 (11.08%)	3499 (12.19%)	20,406 (13.86%)	< 0.001	< 0.001
Healthy diet (%)	238,783 (53.31%)	93,497 (53.17%)	51,420 (53.47%)	15,816 (55.08%)	78,050 (53.02%)	< 0.001	0.014
Atrial fibrillation (%)	30,726 (6.86%)	12,531 (7.13%)	7059 (7.34%)	1620 (5.64%)	9516 (6.46%)	< 0.001	< 0.001
Coronary heart disease (%)	33,222 (7.42%)	13,713 (7.80%)	7504 (7.80%)	1743 (6.07%)	10,262 (6.97%)	< 0.001	< 0.001
Heart failure (%)	11,648 (2.60%)	4727 (2.69%)	2671 (2.78%)	587 (2.04%)	3663 (2.49%)	< 0.001	< 0.001
Stroke (%)	10,625 (2.37%)	4511 (2.57%)	2375 (2.47%)	614 (2.14%)	3125 (2.12%)	< 0.001	< 0.001

Participants' characteristics at baseline were summarized as the mean (SD) or median (interquartile range) for continuous variables and numbers (percentages) for categorical variables in terms of $CaCO_3$ levels of domestic water. Characteristics were compared by $CaCO_3$ concentrations of domestic water using analysis of variance or the Kruskal-Wallis test for continuous variables as appropriate and using the Pearson chi-square test for categorical variables. HbA1c, hemoglobin A1c

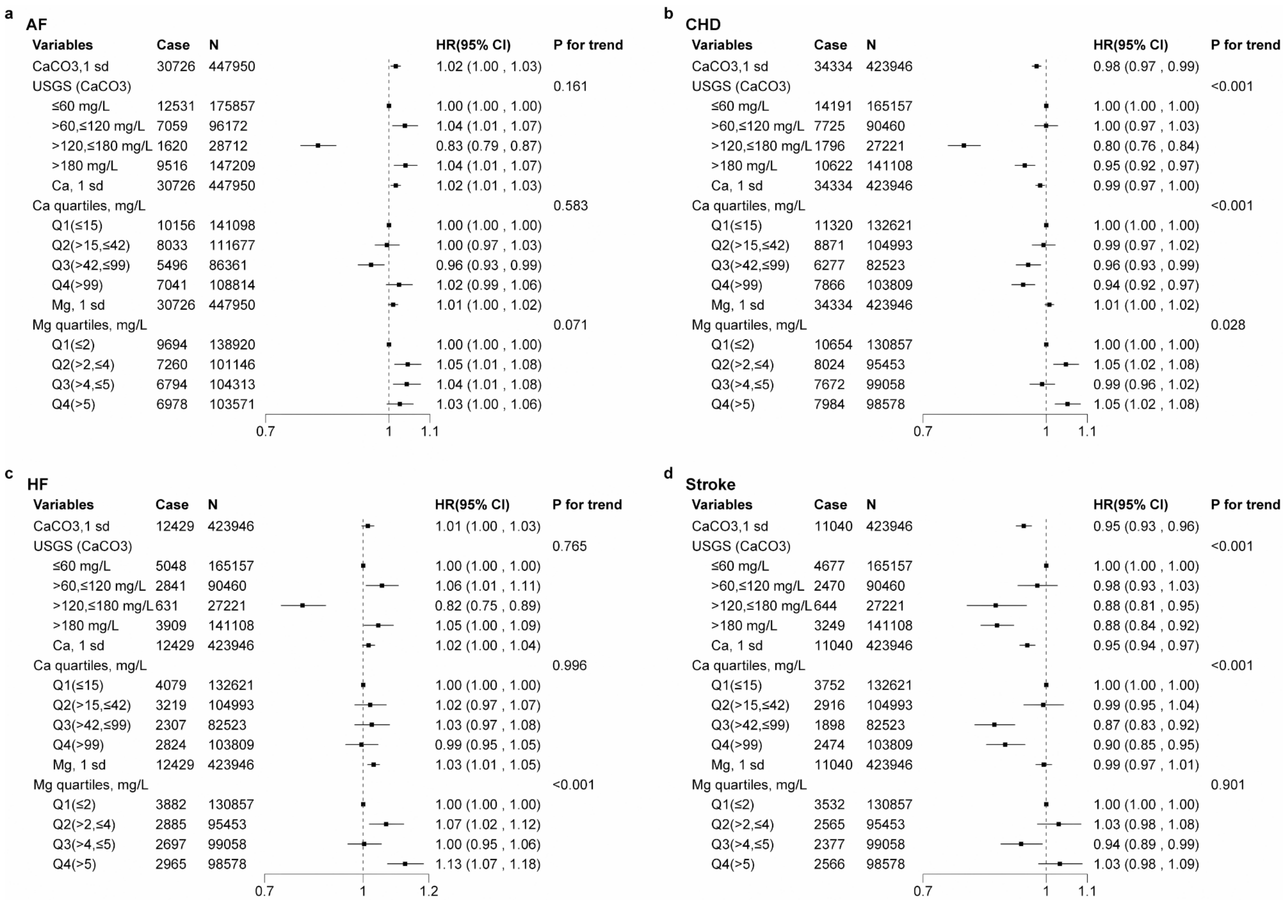

Fig. 1 Associations of water hardness with AF and three other cardiovascular phenotypes incidence. HR of (**a**) AF, (**b**) CHD, (**c**) HF, and (**d**) stroke was adjusted for age, sex, ethnicity, education, the Townsend index, smoking status, ideal physical activity, healthy diet score, BMI, total cholesterol, ideal HbA1c, and ideal blood pressure. HR, hazard ratio; AF, atrial fibrillation; CHD, coronary heart disease; HF, heart failure; USGS, United States Geological Survey; BMI, body mass index; HbA1c, hemoglobin A1c

a 5% higher risk of developing CHD (HR 1.05, 95% CI 1.02–1.08) and a 13% higher risk of developing HF (HR 1.13, 95% CI 1.07–1.18) (Fig. 1). Furthermore, when only adjusting for age, sex, ethnicity, education, the Townsend index, smoking status, ideal physical activity, and healthy diet score, the results are consistent (Supplementary Fig. S3).

Non-linear associations between water hardness with incident AF and other three cardiovascular phenotypes

We utilized non-linear spline models to analyze the estimated associations between domestic water hardness and cardiovascular phenotype outcomes. As illustrated in Fig. 2, the results indicated a non-linear relationship between water hardness and the incidence of AF (*P* for non-linear = 0.001) and a potential non-linear relationship with the incidence of HF (*P* for non-linear = 0.078). Furthermore, domestic water hardness was inversely associated with the incidence of CHD and stroke, and the non-linear association was not found (both *P* for overall < 0.001, *P* for non-linear > 0.1).

Associations of water hardness with incident AF and other three cardiovascular phenotypes across genetic risk status

In subgroup analyses, individuals with $CaCO_3$ (> 120, ≤ 180 mg/L) had a lower risk of AF among low, intermediate, and high genetic risk groups (Fig. 3a). In addition, we did not observe any interaction between the categories of PRS and $CaCO_3$ (*P* for interaction > 0.4) (Fig. 3a). Similar associations of water hardness with HF, CHD, and stroke across genetic risk status were also observed (Fig. 3b-d).

Stratification analysis on the associations of water hardness with incident AF and other three cardiovascular phenotypes

We further conducted stratified analyses to evaluate whether there was a different association between water hardness and incident AF risk by different risk factor statuses. We found a significant interaction between water hardness and age and HbA1c for incident AF risk (*P* for interaction = 0.017 and 0.019, respectively; Table 2). Among participants aged < 60 or ≥ 60 years, those who

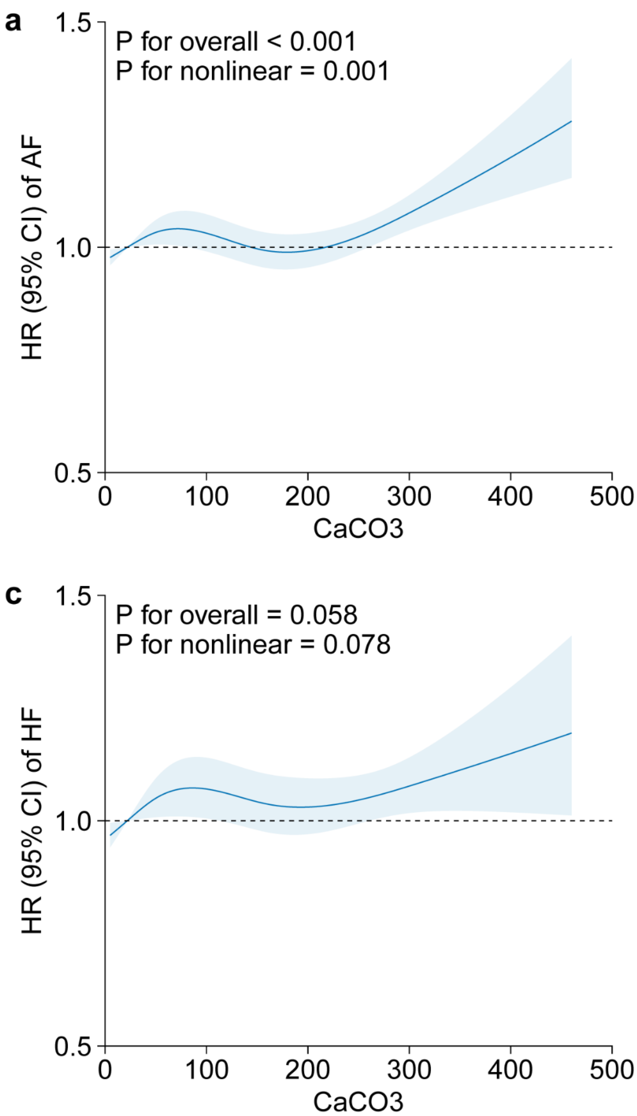

Fig. 2 Restricted cubic spline for testing the hypothesis of non-linear correlation between $CaCO_3$ and incident AF and three other cardiovascular phenotypes. Spline curves represent hazard ratios of (**a**) AF, (**b**) CHD, (**c**) HF, and (**d**) stroke adjusted for age, sex, ethnicity, education, the Townsend index, smoking status, ideal physical activity, healthy diet score, BMI, total cholesterol, ideal HbA1c, and ideal blood pressure. HR, hazard ratio; AF, atrial fibrillation; CHD, coronary heart disease; HF, heart failure; BMI, body mass index; HbA1c, hemoglobin A1c

received $CaCO_3$ levels of domestic water between > 120 and ≤ 180 mg/L had a 23% (HR 0.77, 95% CI 0.70–0.85) and 15% (HR 0.85, 95% CI 0.80–0.90) lower risk of developing AF, respectively. Among participants with ideal HbA1c, those with $CaCO_3$ (> 120, ≤ 180 mg/L) had a 20% (HR 0.80, 95% CI 0.75–0.85) and 10% (HR 0.90, 95% CI 0.82-1.00) lower risk of developing AF in participants with ideal and nonideal HbA1c, respectively (Table 2). A significant interaction between water hardness and age was also found for CHD risk, rather than HF and stroke risk (Supplementary Tables S1–S3). However, we did not find a significant interaction between water hardness and HbA1c for the risk of CHD, HF, and stroke (Supplementary Tables S1–S3).

Sensitivity analyses

In the sensitivity analyses, the associations of $CaCO_3$ with incident AF and other three cardiovascular phenotypes were further examined using three methods of classification of $CaCO_3$ (Supplementary Fig. S4). Compared with the individuals with $CaCO_3$ levels of ≤ 180 mg/L, those with $CaCO_3$ levels > 180 mg/L had a 4% higher risk of developing AF (HR 1.04, 95% CI 1.02–1.07). Similarly, compared with the individuals with the lowest $CaCO_3$ quartile (≤ 42 mg/L), those with the highest CaCO3 quartile (> 253 mg/L) had a 4% higher risk of developing AF (HR 1.04, 95% CI 1.01–1.08). However, compared with the individuals with $CaCO_3$ levels of < 100 mg/L, those with $CaCO_3$ levels between ≥ 100 and ≤ 200 mg/L had a

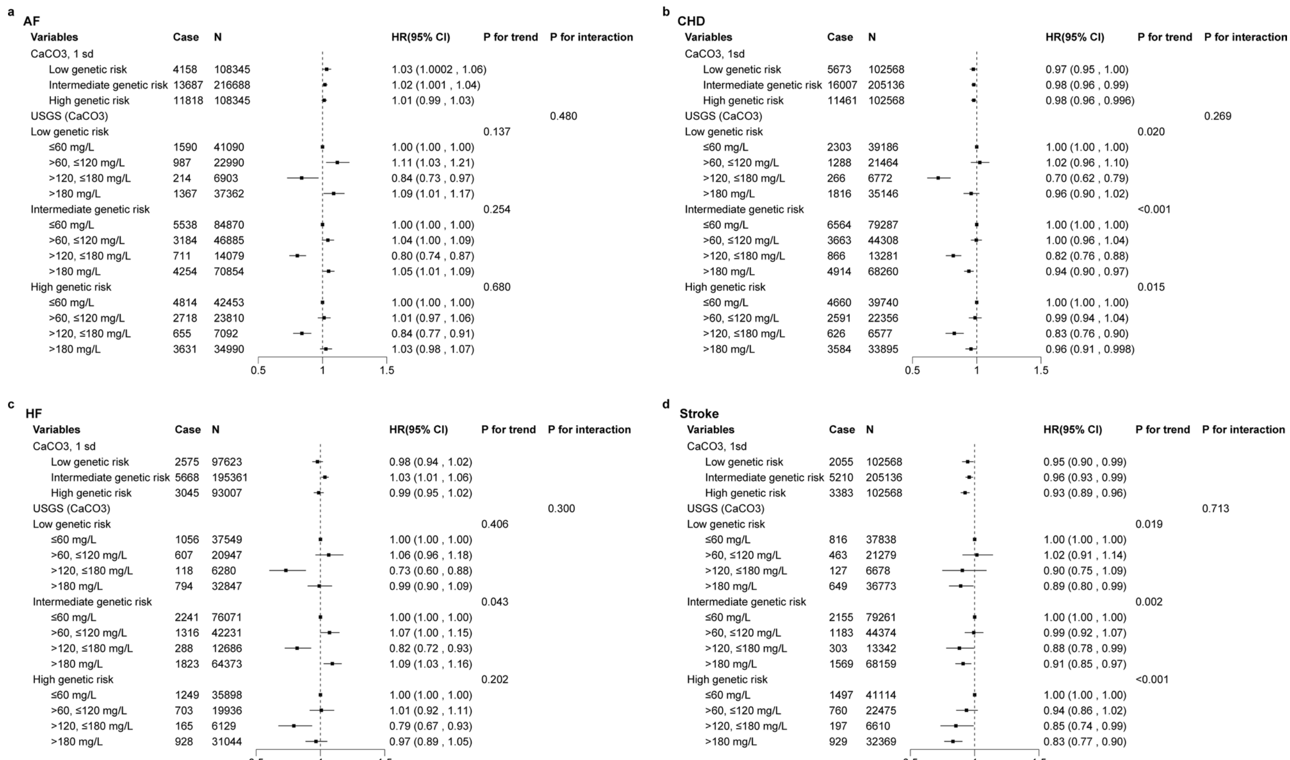

Fig. 3 Multivariable-adjusted HRs (95%CIs) of incident AF and three other cardiovascular phenotypes associated with $CaCO_3$ (continuous and categorical) stratified by genetic risk. HR of (**a**) AF, (**b**) CHD, (**c**) HF, and (**d**) stroke was adjusted for age, sex, ethnicity, education, the Townsend index, smoking status, ideal physical activity, healthy diet score, BMI, total cholesterol, ideal HbA1c, and ideal blood pressure. HR, hazard ratio; AF, atrial fibrillation; CHD, coronary heart disease; HF, heart failure; BMI, body mass index; HbA1c, hemoglobin A1c

10% lower risk of developing AF (HR 0.90, 95% CI 0.86–0.94), and those with $CaCO_3$ levels > 200 mg/L had a 3% higher risk of developing AF (HR 1.03, 95% CI 1.00-1.05).

Discussion

In this large-scale cohort with an over 10-year follow-up time, the following were observed: (i) using the USGS criteria, individuals with $CaCO_3$ levels of domestic water (> 120, ≤ 180 mg/L) had a lower risk of developing AF, HF, CHD, and stroke. (ii) Non-linear relationships were identified between domestic water hardness and the incidence of AF and HF. (iii) The associations between water hardness and the four phenotypes of CVDs, including AF, HF, CHD, and stroke, remained significant across varying levels of genetic risk.

Few studies evaluated the association between domestic hard water and the incidence of AF, although previous studies predominantly concentrated on the relationships between domestic water hardness and CVD mortality. A recent meta-analysis demonstrated a significant correlation between total water hardness and a protective effect against CVD mortality [12]. However, few large-scale cohort studies explored the associations between water hardness and the incidence of CVD. One case-control study involving 1,021 individuals suggested a protective role of hard water consumption in the incidence of CVD without considering phenotypic variations [21]. Additionally, an ecological study reported an inverse relationship between water hardness and the incidence of CHD [22]. Our study builds upon these previous findings by identifying an inverse and linear association between water hardness and the incidence of CHD and stroke. Furthermore, we disclosed U-shaped relationships between water hardness and the incidence of AF and HF, indicating a potentially beneficial association with hard water (> 120, ≤ 180 mg/L).

As far as we know, this study is the first to investigate the interaction between water hardness and the PRS on incident AF. Our findings revealed that participants exposed to hard water (> 120, ≤ 180 mg/L) had the lowest risk of incident AF across different levels of genetic risk. Similar results were also observed regarding the risk of incident HF and CHD. These results indicate that hard water exposure may benefit various cardiovascular conditions, such as AF, HF, and CHD, irrespective of genetic predisposition, if the observed associations are causal. However, in stratified analyses, significant interaction effects of age on the associations between water hardness and incident AF and CHD were identified. The protective effect of hard water (> 120, ≤ 180 mg/L) on

Table 2 Stratification analysis on the associations of water hardness with incident AF

	$CaCO_3$ category (using USGS)				*P* for trend	*P* for interaction
	≤60 mg/L	>60, ≤120 mg/L	>120, ≤180 mg/L	>180 mg/L		
Sex [a]						
Women	Ref.	1.04 (0.99, 1.09)	0.84 (0.77, 0.91)	1.08 (1.03, 1.13)	0.011	0.222
Men	Ref.	1.04 (1.00, 1.08)	0.82 (0.77, 0.88)	1.02 (0.98, 1.05)	0.813	
Age						
<60	Ref.	1.03 (0.98, 1.09)	0.77 (0.70, 0.85)	0.99 (0.94, 1.04)	0.169	0.017
≥60	Ref.	1.04 (1.01, 1.08)	0.85 (0.80, 0.90)	1.06 (1.03, 1.09)	0.015	
Townsend deprivation index						
Tertile 1	Ref.	1.07 (1.02, 1.13)	0.83 (0.77, 0.91)	1.07 (1.02, 1.13)	0.08	0.216
Tertile 2	Ref.	1.03 (0.98, 1.08)	0.80 (0.73, 0.87)	1.05 (1.01, 1.10)	0.214	
Tertile 3	Ref.	1.02 (0.97, 1.08)	0.86 (0.78, 0.95)	1.01 (0.97, 1.06)	0.949	
Race [a]						
White	Ref.	1.04 (1.01, 1.07)	0.83 (0.78, 0.87)	1.04 (1.01, 1.07)	0.167	0.704
others	Ref.	0.91 (0.73, 1.14)	0.95 (0.68, 1.33)	1.07 (0.91, 1.26)	0.214	
Education [a]						
University or college degree	Ref.	1.05 (0.99, 1.12)	0.84 (0.76, 0.93)	1.03 (0.98, 1.09)	0.616	0.77
Others	Ref.	1.04 (1.00, 1.07)	0.82 (0.77, 0.87)	1.05 (1.02, 1.09)	0.087	
HbA1c[a]						
Ideal	Ref.	1.04 (1.00, 1.08)	0.80 (0.75, 0.85)	1.04 (1.00, 1.07)	0.516	0.019
Nonideal	Ref.	1.01 (0.95, 1.07)	0.90 (0.82, 1.00)	1.02 (0.96, 1.07)	0.841	
Smoking [a]						
Ideal	Ref.	1.05 (1.01, 1.08)	0.83 (0.78, 0.88)	1.05 (1.02, 1.08)	0.071	0.257
Nonideal	Ref.	0.97 (0.89, 1.06)	0.82 (0.71, 0.96)	1.01 (0.93, 1.09)	0.797	
Cholesterol						
Ideal	Ref.	1.05 (1.00, 1.10)	0.82 (0.75, 0.89)	1.04 (0.99, 1.08)	0.546	0.786
Nonideal	Ref.	1.03 (0.99, 1.07)	0.84 (0.78, 0.89)	1.04 (1.01, 1.08)	0.181	
BMI						
Ideal	Ref.	1.02 (0.95, 1.08)	0.77 (0.69, 0.86)	0.98 (0.93, 1.04)	0.199	0.253
Nonideal	Ref.	1.05 (1.01, 1.08)	0.84 (0.80, 0.89)	1.05 (1.02, 1.09)	0.046	
Blood pressure [a]						
Ideal	Ref.	0.99 (0.87, 1.14)	0.94 (0.76, 1.17)	0.93 (0.82, 1.04)	0.177	0.354
Nonideal	Ref.	1.04 (1.01, 1.07)	0.82 (0.78, 0.87)	1.05 (1.02, 1.08)	0.081	
Physical activity [a]						
Ideal	Ref.	1.04 (1.00, 1.09)	0.87 (0.80, 0.94)	1.05 (1.01, 1.09)	0.106	0.535
Nonideal	Ref.	1.02 (0.97, 1.07)	0.79 (0.73, 0.87)	1.02 (0.98, 1.07)	0.947	
Diet [a]						
Ideal	Ref.	1.04 (1.00, 1.09)	0.83 (0.77, 0.89)	1.05 (1.01, 1.09)	0.155	0.784
Nonideal	Ref.	1.03 (0.99, 1.08)	0.82 (0.76, 0.89)	1.03 (0.99, 1.08)	0.514	

Model: adjusted for age, sex, ethnicity, education, the Townsend index, smoking status, ideal physical activity, healthy diet score, BMI, total cholesterol, ideal HbA1c, and ideal blood pressure

In the analysis stratified by marked categorical variable, the corresponding variable was excluded from the model

AF, atrial fibrillation; USGS, United States Geological Survey; BMI, body mass index; HbA1c, hemoglobin A1c

incident AF and CHD was more pronounced in younger individuals. This implies earlier exposure to an optimal water hardness environment may confer greater benefits in preventing AF and CHD. Although women generally have a lower prevalence of atrial fibrillation than men [23], we did not find a significant sex-different association between water hardness and AF, which implies that both women and men were suggested to be exposed to an optimal water hardness environment for preventing AF. Nonetheless, these secondary findings warrant further investigation.

The mechanisms underlying the association between domestic water hardness and the susceptibility to AF are complex and not fully elucidated. The health implications of water hardness are primarily attributed to the presence of dissolved salts, specifically calcium [24, 25]. The physiological impact of calcium ions may elucidate the potential relationship between water hardness and AF risk. The possible explanations were: (I) disrupted intracellular calcium cycling during AF underlies impaired atrial contractility and excitability. During cell depolarization, Ca^{2+} influx via L-type Ca^{2+} channels triggers a substantial release of Ca^{2+} from adjacent sarcoplasmic reticulum (SR) sites through ryanodine receptor 2 (RyR2) channels, driving myocyte contraction [26]. (II) Mechanisms such as Ca^{2+}-mediated oxidative stress, inflammatory signaling, and calcium overload contribute to AF development [27]. (III) The decreased corrosive nature of hard water on plumbing systems may contribute to the observed effects on AF by preventing the release of harmful substances such as lead into the water supply [28]. Inversely, as it was reported by WHO, soft water (< 100 mg/L) may have a low buffering capacity and so be more corrosive for water pipes [20]. Our results also showed that compared with the individuals with CaCO3 levels of < 100 mg/L, those with CaCO3 levels (between ≥ 100 and ≤ 200 mg/L) had a lower risk of developing AF. Further experimental studies will be needed to verify our findings and reveal the underlying mechanisms.

Meta-analyses had suggested an inverse relationship between dietary magnesium intake and CVD risk [29, 30]. However, the current study presented intriguing findings that elevated magnesium levels in domestic water are associated with a higher risk of AF, CHD, and HF. Similarly, a recent study observed a positive association between magnesium levels in tap water and AF risk [31], aligning with the results of our study. These discrepancies may arise from the substantial differences between dietary magnesium and magnesium intake from tap water. It has been reported that tap water contributes only 2% to the daily magnesium intake among adults aged 55–69 in the Netherlands, where no overall association was found between magnesium in tap water and mortality from ischemic heart disease or stroke [32]. Another prospective study involving men from 24 British towns indicated a positive, rather than inverse, association between magnesium intake from tap water and CHD incidence [33].

The current study has significant implications for public health in the primary prevention of AF and the optimal water hardness for cardiovascular health. A systematic review has indicated distinct risk factors for AF compared to other cardiovascular diseases [34], and recent guidelines have highlighted the limited focus on primary AF prevention [35]. Our findings suggest that hard water (> 120, ≤ 180 mg/L) may be most beneficial for cardiovascular health, particularly in preventing AF, although previous studies showed increased water hardness was associated with a decreased risk of CHD, stroke, and CVD mortality [12, 36]. In addition, water is a fundamental necessity for sustaining life, and achieving the globally recognized objective of providing safe and managed domestic water would result in significant public health benefits. As water hardness levels exceeding 180 mg/L may elevate the likelihood of developing kidney stones [37], eczema [10], and even all-cause cancer [9], water with a hardness level between > 120 and ≤ 180 mg/L may be the most advisable option.

Although the current study has several strengths, such as large-scale sample size and extended follow-up duration, the implementation of standardized data collection protocols, and diverse resources for disease diagnosis, certain limitations persist. First, measurements of domestic water hardness were conducted before the baseline, raising concerns about the potential for exposure level fluctuations over time due to variables such as alterations in water sources and treatment procedures or missing information on participants relocating to different addresses, potentially influencing our risk estimates. Second, the lack of data on other water contaminants within the UK Biobank, such as nitrate, metals, and disinfection by-products, restricts the capacity to investigate potential modifications of the association between hard water and cardiovascular phenotypes by these contaminants. Third, the identification of incident cardiovascular phenotypes was based on medical records obtained during follow-up, potentially leading to biased incidences due to the individuals who did not exhibit recorded symptoms. However, it was reported that only about one-tenth of AF cases were undiagnosed [15, 38]. Fourth, the study primarily consisted of participants of White British descent from the UK, thereby restricting the generalizability of the results to other races or geographic regions. Fifth, definitive causation cannot be established due to the inherent constraints of observational research. Therefore, further investigation into the underlying causality and mechanisms is warranted.

In summary, the current study observed potential U-shaped associations between domestic water hardness and incident AF and HF across varying levels of genetic risk within the UKB population. Furthermore, higher levels of water hardness may potentially reduce the occurrence of CHD and stroke. When considering overall cardiovascular health, including AF, HF, CHD, and stroke, hard water (> 120, ≤ 180 mg/L) may offer the most benefits compared to soft water. However, further basic research and prospective studies in other populations are necessary to validate these results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01166-7.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions
N.W., H.W. and X.P. conceptualized and revised the manuscript; F.T., G.Y., and M.Y. conducted data analysis and drafted the manuscript; Z.G. and S.Y. verified the results and reviewed the manuscript; H.W. and X.P. assisted with data acquisition and critically revised it for significant intellectual content. All authors approved the final manuscript.

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Data availability
The dataset used and analyzed during the current study is available from UK Biobank (www.ukbiobank.ac.uk). This research has been conducted using the UK Biobank Resource under Application Number 77740.

Declarations

Competing interests
The authors declare no competing interests.

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