

Cardiovascular health and healthy longevity in people with and without cardiometabolic disease: A prospective cohort study

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Summary

Background Existing evidence suggest an association of cardiovascular health (CVH) level with cardiometabolic disease (CMD) and mortality, but the effect of CVH on life expectancy, particularly survival years in CMD patients, has not been well-established. This study aimed to investigate the association of CVH defined using the 7-item tool from the American Heart Association (AHA) with life expectancy in people with and without CMD.

Methods Between 2006 and 2010, a total of 341,331 participants (age 37–73 years) in the UK Biobank were examined and thereafter followed up to 2020. The CVH raised by the AHA included 4 behavioral (smoking, diet, physical activity, body mass index) and 3 biological (fasting glucose, blood cholesterol, blood pressure) metrics, coded on a three-point scale (0, 1, 2). The CVH score was the sum of 7 metrics (score range 0–14) and was then categorized into poor (scores 0–6), intermediate (7–11), and ideal (12–14) CVH. The flexible parametric survival models were applied to estimate life expectancy.

Findings During a median follow-up of 11.4 years, 18,420 (5.4%) deaths occurred. The multivariable-adjusted hazard ratio (HRs) of all-cause mortality were 2.21 (95% CI: 1.77 to 2.75) for male and 2.63 (95% CI: 2.22 to 3.12) for female with prevalent CMD and a poor CVH compared with CMD-free and ideal CVH group, an ideal CVH attenuated the CMD-related risk of mortality by approximately 62% for male and 53% for female. In CMD patients, an ideal CVH compared to poor CVH was associated with additional life years gain of 5.50 (95% CI: 3.94–7.05) for male 4.20 (95% CI: 2.77–5.62) for female at the age of 45 years. Corresponding estimates in those without CMD were 4.55 (95% CI: 3.62–5.48) and 4.89 (95% CI: 3.99–5.79), respectively. Ideal smoking status, fasting glucose and physical activity for male and ideal smoking status, cholesterol level and physical activity for female contributed to the greatest survival benefit.

Interpretation An ideal CVH is associated with a lower risk of premature mortality and longer life expectancy whether in general population or CMD patients. Our study highlights the benefits of maintaining better CVH across the life course and calls attention to the need for comprehensive strategies (healthy behavioral lifestyle and biological phenotypes) to preserve and restore a higher CVH level.

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Keywords: Cardiovascular health; Healthy longevity; Diabetes

Introduction

In 2010, the American Heart Association (AHA) introduced the concept of cardiovascular health (CVH), also referred to as Life's Simple 7—a comprehensive construct incorporating the simultaneous presence of 4

behavioral (smoking, diet, physical activity and obesity) and 3 biological (blood pressure, cholesterol and fasting plasma glucose) metrics.¹ CVH is a global, positive health-oriented construct that has proven widely applicable across clinical settings.² Following the recommendations of the AHA, a large number of community-based studies within the last decade have shown that ideal CVH was associated with lower risks of

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Research in context

Evidence before this study

We searched PubMed for full-text original studies and review articles written in English published up to February 10, 2022, to identify papers on cardiovascular health and life expectancy. The search terms used were “cardiovascular health”, “cardiovascular risk factor”, “cardiovascular disease”, “diabetes”, together with “mortality” and “life expectancy”. Studies were considered eligible if they: reported CVH and life expectancy; CVH and mortality; cardiovascular health and CMD; and had a prospective study design. The most reference lists of the identified papers showed that better CVH level was associated with lower risks of CMD and mortality, however, there was no study to date to present an association between CVH and life expectancy. In particular, CVH level and life expectancy in people with and without CMD has not been well-established.

Added value of this study

To the best of our knowledge, this is one of the largest single cohort studies of its kind to date that quantifies the effect of CVH level on life expectancy. We provide evidence that adherence to AHA 7-item CVH recommendations might be associated with substantially lower risks of premature mortality and longer life expectancy, even in individuals with CMD.

Implications of all the available evidence

These findings have relevant individual, clinical, and public health implications as the results suggest that an ideal CVH is similarly associated with longevity regardless of the presence of CMD. Cardiovascular risk factors are modifiable, making them strategically important prevention targets, which is an important element in tackling the challenge posed by population aging.

cardiovascular disease (CVD) and diabetes.^{3–7} Despite the significance of the CVH score and the modifiable nature of its components, whether and to what extent ideal CVH impacts on longevity in people with cardio-metabolic disease (CMD) is less clear.

Life expectancy estimates are easier to understand for both the public and healthcare professionals and have become a common metric for establishing public health priorities.⁸ Much of the current evidence suggested that combined healthy lifestyles (e.g. no smoking, healthy diet, moderate physical activity and healthy weight, etc.) were likely to confer life expectancy gains.^{8–12} However, no study to date has explored the association of CVH with life expectancy, as well as the difference in life expectancy in those with and without CMD. Quantifying this knowledge gap may have important individual, clinical, and public health implications, in

view of the rapidly increasing trends in the prevalence of CMD.

Therefore, using data from large-scale UK Biobank cohort over a more than 10 years follow-up, our objectives were to (1) examine the association between CVH and life expectancy; (2) determine whether patterns of CVH-related differences in life expectancy among people with CMD are similar to those observed in a general population; (3) evaluate whether and to what extent ideal CVH could offset the detrimental effect of CMD on risk of premature mortality.

Methods

Study design and population

This was a prospective, population-based cohort study of participants enrolled in the UK Biobank cohort. Between April 2006 and December 2010, the UK Biobank recruited 502,528 adults (37–73 years old) from the general population. Participants attended one of 22 assessment centers across England, Scotland, and Wales, where they completed touchscreen and nurse-led questionnaires, had physical measurements taken, and provided biological samples.¹³ The present study sample was restricted to the 377,549 participants who had complete data on CVH metrics. Participants were excluded if they had history of cancer before recruitment ($n = 31,087$) and missing covariates ($n = 5131$), leaving 341,331 participants included in final study (Supplemental Figure S1). All participants gave written informed consent prior data collection. UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). The study was conformed to the STROBE reporting guidelines.

Measurement and definition of CVH

The CVH metrics adopted in this study conformed with the CVH metrics developed by the AHA guideline¹ and consisted of 7 behavioral and biological factors, including smoking status, physical activity, diet pattern, body mass index (BMI), serum cholesterol, blood pressure and fasting plasma glucose. Smoking status (current, past, never), physical activity (hours of moderate and vigorous physical activity per week by the International Physical Activity Questionnaire), and diet (the amount of fish, fruit and vegetable consumption) were assessed using standardized questionnaires. A trained nurse used standard protocols to collect data on BMI (weight/height² in kg/m²), glucose concentration, blood cholesterol concentration, and blood pressure. Systolic and diastolic blood pressure were taken as the mean of two measurements. Blood samples in storage at the UK Biobank (both –80 °C and LN₂) are grouped on storage racks by sample type and by participant in line with the sample processing and storage protocols in place at the

time of sample collection. These measurement methods are described in more detail in the supplementary methods.

Each level of the 7 metrics was categorized as poor (scored as 0), intermediate (scored as 1), and ideal (scored as 2) according to the AHA criteria (Supplemental Table S1). As described previously, we used the sum of each metric to calculate the composite CVH score, ranging from 0 to 14 with higher scores corresponding to better CVH. We categorized this score as poor for scores ranging from 0 to 6 (corresponding to less than one standard deviation (SD) from the mean), intermediate for scores ranging from 7 to 11 (+/-1 SD from the mean), and ideal for scores between 12 and 14 (>1 SD from the mean).¹⁴

Cardiometabolic disease

As part of the baseline assessment, participants were asked whether a physician had diagnosed them with long-term CMD including cardiovascular disease (ischemic heart disease, heart failure, atrial fibrillation, stroke) and diabetes. In addition, these conditions were also identified by linkage to hospital admissions from Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). International Statistical Classification of Diseases 10th Revision (ICD-10) was used to define prevalent and incident CVD (I20-I25, I48, I50, I60-I64) and diabetes (E10-E14), which were separately included before baseline and follow-up period.

Outcomes

The outcomes in the current study were all-cause mortality and mortality from CMD, cancer and respiratory disease. Information on primary cause and date of death were obtained from death certificates held by the National Health Service (NHS) Information centre (England and Wales) and the NHS Central Register Scotland (Scotland). Causes of deaths were coded using the ICD-10. Death date was available up to November 1, 2020. Follow-up for mortality outcomes was censored on this date or the date of death if that occurred earlier.

Covariates

Covariates of our analysis included exact age, sex, ethnicity (White, Black, South Asian, Mixed background), socioeconomic status (Townsend Deprivation Index, continuous), employment status (worked, unemployed, retired, others), education attainment (college or university degree, professional qualifications, others), consumption of alcohol intaking (continuous, g), C-reactive protein (continuous, mg/dL), history of CVD and diabetes. Further details for each variable are available on supplemental methods and the UK Biobank Website (<https://www.ukbiobank.ac.uk/>).

Statistical analysis

We summarized baseline characteristics by CVH category using descriptive statistics, reporting the mean and standard deviation (SD) for continuous variables and proportions for categorical variables. We compared the baseline characteristics by CVH category using Chi-square test for categorical or One-Way ANOVA for continuous variables.

Cox proportional hazard models with age as timescale were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of CVH with all-cause mortality and cause-specific mortality. Schoenfeld's residuals were used to verify the proportional hazards assumption. As we found evidence of effect modification by sex (P for interaction = 0.005), we conducted all analyses in male and female separately. Three incremental models were fitted: model 1 was adjusted for age (timescale); model 2 was further adjusted for ethnicity, educational attainment, employment status, socioeconomic status and alcohol intake; model 3 was further adjusted for C-reactive protein, prevalent cardiovascular disease and diabetes at baseline. Moreover, to explore whether the effect of CVH on mortality varied by CMD, separate models were fitted for those with and without CMD. We created a variable with 6 categories, which combines CMD status (yes, no) with CVH (poor, intermediate, ideal) to investigate their joint effect on risk of mortality. The interaction effect was tested by including an interaction term in Cox model. We then examined the shape of the associations of the continuous CVH score with risk of all-cause and cause-specific mortality by using restricted cubic spline regressions with score 0 as the reference.

The flexible parametric survival models with age as timescale were applied to estimate life expectancy. The calculation of years of life gained (difference in average life expectancy) involved a two-step process. First, residual life expectancy was estimated as the area under the survival curve up to 100 years old, conditional on surviving at ages 40–100 years old (1-year intervals); survival curves were predicted for each individual and averaged over individuals. Second, years of life gained were calculated as the difference between the areas under two survival curves,¹⁵ e.g. the difference between life expectancy for the intermediate or ideal CVH group with the reference of the poor CVH group. All analyses were adjusted for above confounders. In addition, years of life gained were also estimated by CVH group in those with and without CMD.

In the sensitivity analysis, we applied a series of analyses to test the robustness of our findings. First, we additionally adjusted for anti-hypertensive and lipid-lowering medications. Second, we explored the associations of CVH with all-cause and cause-specific mortality and life expectancy after excluding prevalent CMD before baseline. Third, to minimize the potential contribution of reverse causality to these findings, we did a

landmark analysis excluding mortality events occurring within the two years after recruitment. Finally, missing covariates were imputed with multiple imputation procedure using the chained equations method.

All analyses were performed using STATA 15 statistical software, and proportional hazards survival analyses were conducted with the *stpm2* command which uses restricted cubic splines to model the baseline cumulative hazard.¹⁶ All *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participant characteristics

A total of 341,331 participants (mean age 56.2 years; 52.7% female) with complete data were included. During a median follow-up of 11.4 years, 18,420 (5.4%) death cases occurred. Table 1 shows the baseline characteristics of the study population by CVH score. Participants with higher CVH score, denoting better health, were more likely to be female, higher socioeconomic status, lower alcohol consumption and C-reactive protein concentration, and from the higher educational, working groups. Besides, among 7 components of CVH, female have higher proportion of ideal CVH than male, other than ideal physical activity (Supplemental Table S2).

CVH and all-cause and cause-specific mortality

CVH score showed an inverse dose-response association with all-cause mortality for both male and female (P for linearity < 0.001) (Figure 1), the shapes for cause-specific mortality were generally consistent (Supplemental Figure S2). Compared with reference group (poor CVH), ideal CVH group was associated with 49% (HR = 0.51, 95% CI: 0.45–0.57) and 51% (HR = 0.49, 95% CI: 0.45–0.54) lower risk of all-cause mortality in the fully adjusted model (Figure 1, Supplemental Table S3). The HRs of CMD, cancer and respiratory mortality were also significantly lower for those with ideal CVH, ranging from HR 0.38 to 0.51 in male and 0.31 to 0.58 in female (Supplemental Table S4).

An ideal CVH, CMD and all-cause mortality

When CMD status and CVH groups were combined, there was a monotonic association with increasing CMD risk and an increasingly unfavorable CVH (P for

trend < 0.001) (Figure 2). The multivariate-adjusted HRs (95% CIs) of all-cause mortality were 2.21 (1.77 to 2.75) for male and 2.63 (2.22 to 3.12) for female with CMD and a poor CVH, 4.17 (3.64 to 4.78) for male and 4.48 (4.01 to 5.01) for female with CMD and an ideal CVH, compared with CMD-free and ideal CVH group. These results suggested that an ideal CVH attenuated the CMD-related risk of premature mortality by approximately 62% for male and 53% for female (Supplemental Table S5).

CVH and life expectancy

Life expectancy rose as the level of CVH increased. Using flexible parametric survival models after adjusted for potential confounders, we projected a life expectancy at age 45 years of 42.0 years (95% CI 41.3 to 42.7) for male and 43.7 years (95% CI 42.7 to 44.6) for female who had a poor CVH. In contrast, for those who had an ideal CVH, we projected a life expectancy at age 45 years of 46.7 years (95% CI 45.9 to 47.5) for male and 48.1 years (95% CI 47.3 to 48.8) for female (Figure 3). Equivalently, female with an ideal CVH could gain 4.40 years (95% CI 3.70 to 5.10) of life expectancy on average, and male could gain 4.67 years (95% CI 3.90 to 5.43) of life expectancy compared with those with a poor CVH (Supplemental Table S6). The pattern of results was similar at the age of 65 years.

Individual CVH metrics and life expectancy

The associations between individual CVH metrics and survival are presented in Table 2. The largest survival difference was observed for the risk factor smoking for both male and female. The adjusted all-cause mortality in participants with non-smoking compared with current smoking was 58% lower (HR = 0.42, 95% CI 0.40 to 0.44) in male and 63% lower (HR = 0.37, 0.35 to 0.40) in female. At the age of 45 years, an ideal smoking status was associated with a gain of 6.48 (95% CI 5.87 to 7.09) and 6.91 (95% CI 6.17 to 7.64) additional life years compared to poor CVH for male and female, respectively. Ideal fasting glucose for male and ideal cholesterol level for female was associated with the second highest survival benefit, ideal physical activity was associated with the third highest survival benefit for both male and female. The years of life gained were shorter for other CVH metrics.

CVH and life expectancy with and without CMD

At the age of 45 years, participants with CMD had, on average, a life expectancy of 5.37 (95% CI 4.95 to 5.78) for male and 5.88 (95% CI 5.38 to 6.38) for female lower than participants without CMD; the corresponding estimates at the age of 65 years was 4.56 (95% CI 4.21 to 4.91) and 5.19 (95% CI 4.75 to 5.62) years (Supplemental Figure S3).

Characteristics	Total	Cardiovascular health (CVH)			P value
		Poor	Intermediate	Ideal	
Total	341,331	40,330 (11.8)	253,196 (74.2)	47,805 (14.0)	
Sex					<0.001
Male	161,506 (47.3)	26,591 (65.9)	123,819 (48.9)	11,096 (23.2)	
Female	179,825 (52.7)	13,739 (34.1)	129,377 (51.1)	36,709 (76.8)	
Age (mean, SD)	56.2 (8.1)	57.1 (7.8)	56.4 (8.1)	54.4 (8.1)	<0.001
Townsend deprivation index	-1.39 (3.02)	-0.54 (3.34)	-1.45 (2.99)	-1.82 (2.76)	<0.001
Ethnicity					<0.001
White	323,640 (94.8)	37,846 (93.8)	239,852 (94.7)	45,942 (96.1)	
Black	5332 (1.6)	744 (1.8)	4140 (1.6)	448 (0.9)	
South Asian	7318 (2.1)	1071 (2.7)	5489 (2.2)	758 (1.6)	
Mixed background	5041 (1.5)	669 (1.7)	3715 (1.5)	657 (1.4)	
Employment status					<0.001
Worked	203,468 (59.6)	21,508 (53.3)	151,025 (59.7)	30,935 (64.7)	
Retired	108,269 (31.7)	12,998 (32.2)	82,344 (32.5)	12,927 (27.0)	
Unemployed	24,593 (7.2)	5287 (13.1)	16,239 (6.4)	3067 (6.4)	
Others	5001 (1.5)	537 (1.3)	3588 (1.4)	876 (1.8)	
Education level					<0.001
College or university degree	115,475 (33.8)	8596 (21.3)	84,973 (33.6)	21,906 (45.8)	
Professional qualifications	173,141 (50.7)	21,331 (52.9)	129,548 (51.2)	22,262 (46.6)	
Others	52,715 (15.4)	10,403 (25.8)	38,675 (15.3)	3637 (7.6)	
Alcohol intake (g/day; mean, SD)	15.0 (18.4)	16.5 (22.9)	15.3 (18.5)	12.2 (12.9)	<0.001
C-reactive protein (mg/dL; mean, SD)	2.51 (4.18)	4.18 (5.37)	2.46 (4.08)	1.34 (2.90)	<0.001
CMD	77,445 (22.7)	19,684 (48.8)	53,722 (21.2)	4039 (8.5)	<0.001
CVD	60,339 (17.7)	12,740 (31.6)	43,820 (17.3)	3779 (7.9)	<0.001
Diabetes	28,958 (8.5)	12,896 (32.0)	15,713 (6.2)	349 (0.7)	<0.001

Table 1: Baseline characteristics of participants by cardiovascular health.

Data are n (%), unless otherwise specified. CMD, cardiometabolic disease; CVH, cardiovascular health; CVD, cardiovascular disease; SD, standard deviation.

In male aged 45 years with CMD, intermediate and ideal CVH were associated with an average 2.80 (95% CI 2.28 to 3.32) and 5.50 (95% CI 3.94 to 7.05) of additional life years gained, respectively, compared to poor CVH; corresponding estimates in those without CMD were 2.41 (95% CI 1.81 to 3.01) and 4.55 (95% CI 3.62 to 5.48) additional life years gained, respectively (Figure 4). In female aged 45 years with CMD, an ideal CVH was associated with a gain of 4.20 (95% CI 2.77 to 5.62) additional life years compared to poor CVH. Corresponding estimates in female without CMD were 4.89 (95% CI 3.99 to 5.79) years (Supplemental Table S7).

Sensitivity analyses

The robustness of the associations of CVH with mortality and life expectancy was examined by several sensitivity analyses. First, we further adjusted for anti-hypertensive and lipid-lowering medications, the associations between CVH and mortality were almost not altered (Supplemental Table S8). Next, we repeated the main analysis among participants with at least 2 years of follow-up, the projected life expectancy at age 45 years was on average 4.73 years (95% CI 3.88 to 5.58) and 5.09

(95% CI 4.31 to 5.87) longer among male and female with ideal CVH compared with those with poor CVH (Supplemental Table S9, Figure S4). Although years of life gained were slightly greater comparing ideal versus poor CVH groups, the main results were largely confirmed after excluding participants with CMD at baseline (Supplemental Table S10, Figure S5). The consistent associations of CVH with all-cause and cause-specific mortality and life expectancy were identified when imputing missing data (Supplemental Table S11).

Discussion

In this prospective cohort study of 341,331 individuals with a 11-year median follow-up period, we found an inverse dose-response association between CVH score and all-cause mortality and mortality from CMD, cancer and respiratory disease. An ideal CVH could attenuate the CMD-related risk of mortality by approximately 62% for male and 53% for female. Those who had an ideal CVH comparing a poor CVH was associated with an average life expectancy gained of 4.67 years for male and 4.40 years for female at the age of 45 years. Even

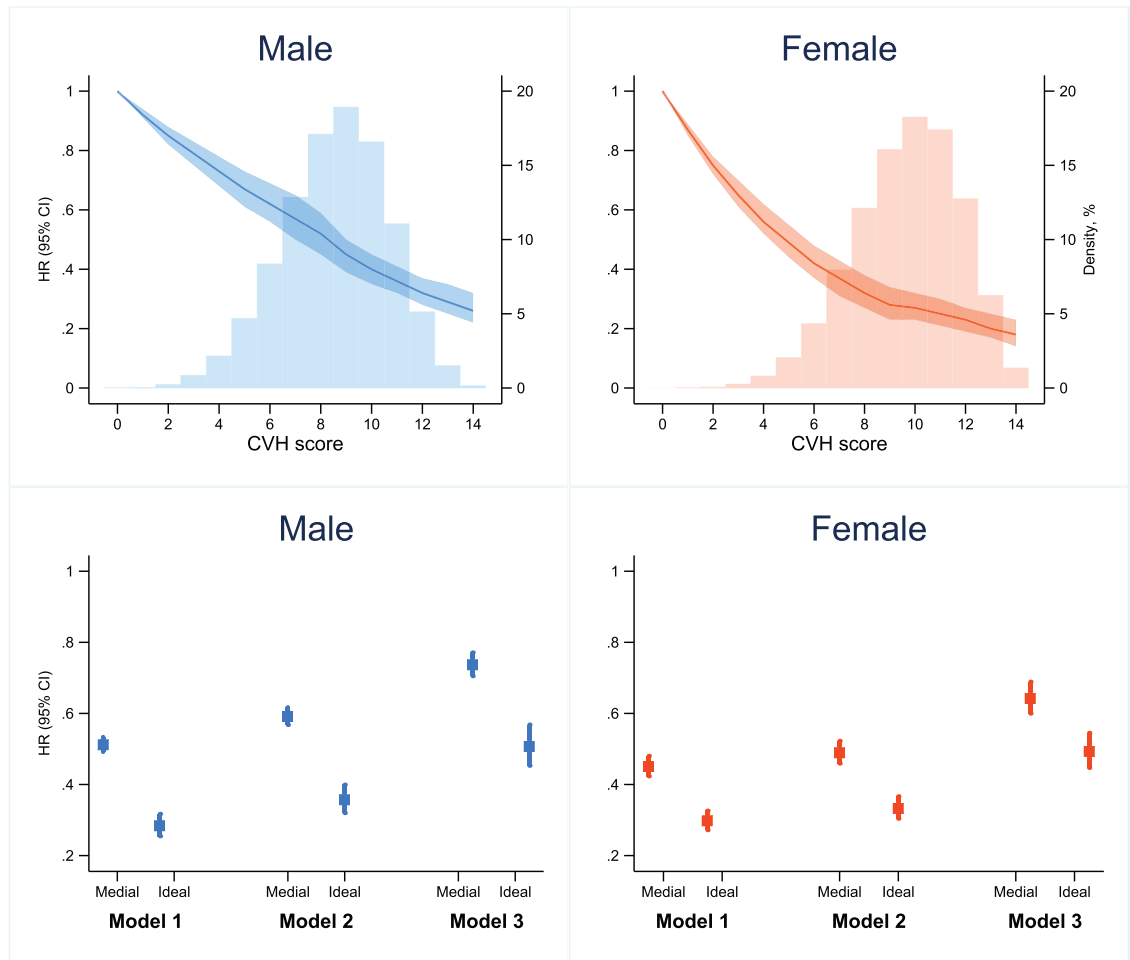


Figure 1. The distribution of cardiovascular health and its association with all-cause mortality. Restricted cubic spline models were adjusted for age, ethnicity, educational attainment, employment status, socioeconomic status, alcohol intake, C-reactive protein, history of cardiovascular disease and diabetes. The model 1 was adjusted for age (timescale); model 2 was further adjusted for ethnicity, educational attainment, employment status, socioeconomic status, alcohol intake and C-reactive protein; model 3 was further adjusted for prevalent cardiovascular disease and diabetes at baseline.

though in people with prevalent CMD, the corresponding years of life gained was 5.50 years in male and 4.20 years in female. These findings have relevant individual, clinical, and public health implications as the results suggest that an ideal CVH is similarly associated with longevity regardless of the presence of CMD.

To the best of our knowledge, this is the first study to examine the effect of CVH on life expectancy. Our findings have important implications, as currently there is limited research regarding the most commonly occurring clusters of cardiovascular risk factors and on their impact on life expectancy to quantify their burden. Previous studies mostly reported the risk of mortality by CVH scale. Using Framingham Heart Study data, there were multiple prospective studies examining cardiovascular risk factors and mortality with over 50 years of follow-up.¹⁷ A meta-analysis including 6 longitudinal

studies summarized a strong inverse linear dose-response relationship between ideal CVH metrics and both all-cause and cardiovascular disease-related mortality.¹⁸ A recent study from Finland showed that an ideal CVH was associated with 67% lower risk of all-cause mortality for men.¹⁹ The consistent findings were also suggested among middle-aged and older Amerindian adults.²⁰ Despite so many studies about CVH-mortality association, the effect of an ideal CVH on difference in life expectancy remained unclear. Nevertheless, several previous studies have quantified the difference in life expectancy by healthy lifestyle, which were important components of CVH scale. For instance, a previous study including 44,052 Chinese showed adherence to 4–5 healthy lifestyle factors (healthy diet, nonsmoking status, light to moderate alcohol drinking, being physically active and optimal BMI) versus none could achieve

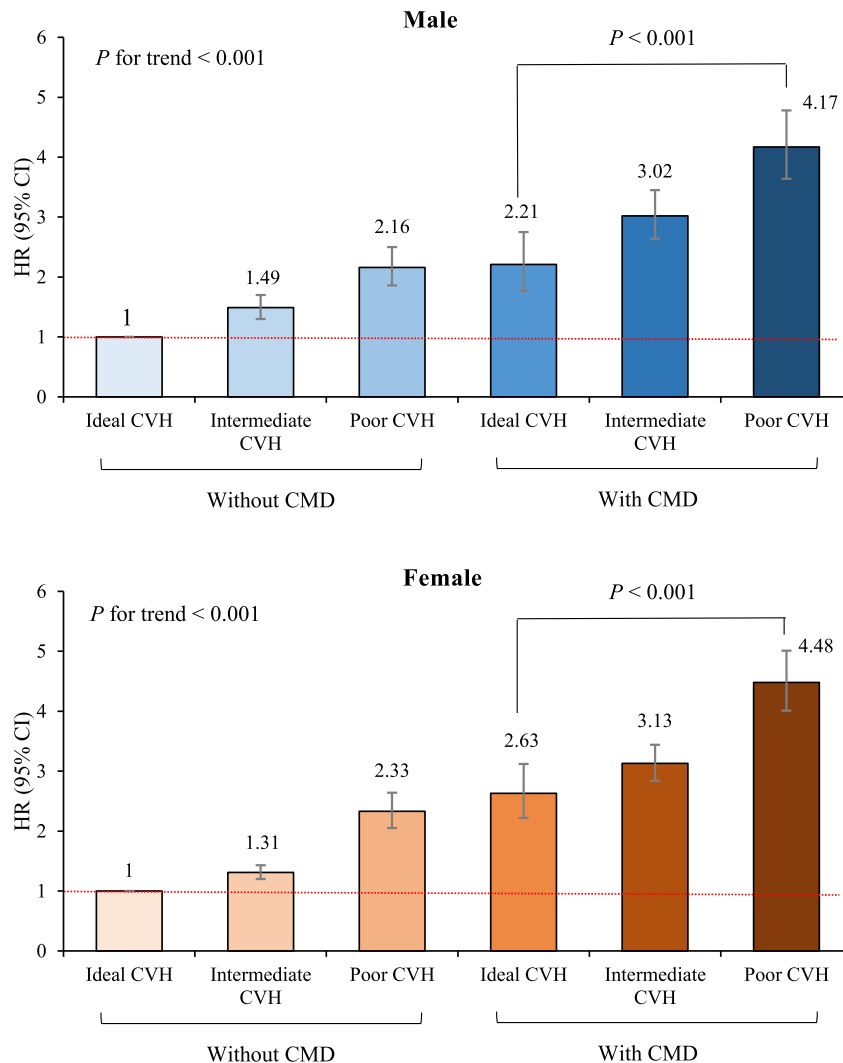


Figure 2. The hazard ratios (HRs) of the associations between cardiovascular health and all-cause mortality in participants with and without cardiometabolic disease. Models were adjusted for age, ethnicity, educational attainment, employment status, socioeconomic status, alcohol intake and C-reactive protein.

a gain of 8.1 years in women and 6.6 years in men for the life expectancy at 50 years.¹¹ Evidence from The Nurses' Health Study suggested that residual life expectancy at age 50 increased with increasing number of 5 healthy lifestyle factors: from 31.7 years to 41.1 years in women and from 31.3 years to 39.4 years in men.²¹ In our study, we estimated that the an ideal CVH could prolong life expectancy at 45 years by 4.67 (residual life expectancy from 42.0 to 46.7) years in women and 4.40 years (from 43.7 to 48.1) in men. Our estimates of life expectancy gains were somewhat different because of different definitions of ideal CVH metrics and study population characteristics. Our results that the adverse associations of CVH score with all-cause and cause-

specific mortality were consistent with previous studies.^{18,19,22–25}

Our study also estimated the association between CVH and life expectancy with and without CMD, we found that even though in people with prevalent CMD, the years of life gained of ideal CVH comparing poor CVH was 5.50 years in male and 4.20 years in female. Results were generally consistent in those without CMD. A recent study found that participants with cardiometabolic multimorbidity at 45 years had the average life expectancy gains of about 2.53 years for men and 5.81 years for women with the healthiest lifestyle score compared to those reporting the lowest lifestyle score.²⁶ Similarly, a previous study including 3 cohorts showed

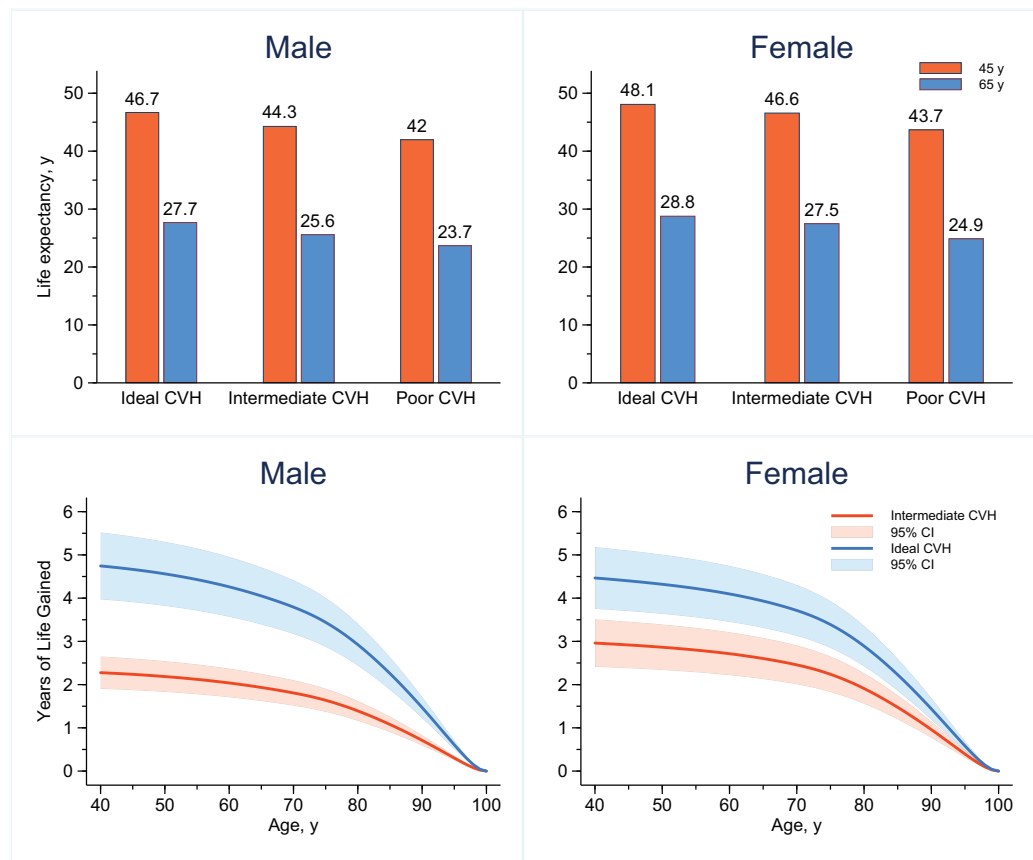


Figure 3. Residual life expectancy and years of life gained at age 45 and 65 years by cardiovascular health (CVH). Reference group is the poor CVH group. Models were adjusted for age, ethnicity, educational attainment, employment status, socioeconomic status, alcohol intake, C-reactive protein, cardiovascular disease and diabetes.

that individual and combined healthy lifestyle were associated with longer life expectancy in participants with CVD.⁹ As no previous studies were regarded CVH as exposures, we were unable to directly compare our findings with the available evidence. In addition, our study suggested that an ideal CVH could attenuate the CMD-related risk of mortality by approximately 62% for male and 53% for female, which has important clinical and public health implications for promoting CMD patients to maintain an ideal CVH. Public health recommendations about an ideal CVH to reduce the risk of mortality and prolong life expectancy equally apply to individuals who have already CVD and diabetes.

By combining lifestyle and biomarkers using the AHA 7-item tool, we investigated an extended risk factors profile. Moreover, the effects individual CVH metrics on life expectancy were also examined, we found that no smoking had the largest impact on life expectancy regardless of people with and without CMD, similar to studies from the general population.²⁷ This emphasizes the importance of smoking cessation. Ideal intensity of physical activity can moderately prolong the life expectancy both in men and women, which were in

line with previous studies that meeting the recommended level of physical activity was associated with a longer life expectancy in people with and without cardiometabolic multimorbidity.^{28,29} In addition to cardiovascular risk factors that are related to lifestyle, genetic risk factors may also be associated with CMD and mortality. A previous study including 3584 elderly American men of Japanese ancestry showed that the longevity-associated alleles of FOXO3 were associated with significantly longer lifespan in CMD patients, with haplotype HR of 0.81 (95% CI: 0.72–0.91), which suggested that FOXO3 longevity genotype increases lifespan only in at-risk individuals by protection against cardiometabolic stress.³⁰ Kuakini Honolulu Heart Program cohort similarly reported that FOXO3 genotype is an important risk factor for CVD mortality in older populations.³¹

Notable strengths of the present study included its prospective design and its relatively large sample size, which provided us with modest statistical power to assess the association of CVH with life expectancy for subgroup analysis by sex. Most importantly, this is the first study to investigate the effects of ideal CVH on life expectancy. Despite these strengths, several limitations

Individual CVH metric	Male			Female		
	Poor	Intermediate	Ideal	Poor	Intermediate	Ideal
Behavioral CVH metrics						
Smoking status						
No. of deaths/participants	2426/19,676	4988/49,300	4100/92,530	1189/15,443	2276/44,438	3441/119,944
HR (95% CI), all-cause mortality	Reference	0.65 (0.61–0.68)	0.42 (0.40–0.44)	Reference	0.54 (0.51–0.59)	0.37 (0.35–0.40)
Years of life gained, 45 y	Reference	3.40 (2.91–3.89)	6.48 (5.87–7.09)	Reference	4.51 (3.83–5.18)	6.91 (6.17–7.64)
Years of life gained, 65 y	Reference	2.89 (2.48–3.31)	5.54 (5.02–6.06)	Reference	3.86 (3.29–4.43)	5.98 (5.35–6.60)
Body mass index						
No. of deaths/participants	3604/40,440	5259/80,096	2651/40,970	2076/41,120	2492/65,917	2338/72,788
HR (95% CI), all-cause mortality	Reference	0.96 (0.92–1.00)	1.10 (1.04–1.17)	Reference	0.93 (0.88–0.99)	1.03 (0.96–1.10)
Years of life gained, 45 y	Reference	0.29 (–0.03–0.61)	–0.72 (–1.13––0.31)	Reference	0.40 (0.04–0.76)	–0.19 (–0.59–0.20)
Years of life gained, 65 y	Reference	0.24 (–0.02–0.51)	–0.60 (–0.95––0.26)	Reference	0.37 (0.04–0.69)	–0.17 (–0.54–0.19)
Physical activity						
No. of deaths/participants	2370/23,402	3316/46,862	5828/91,242	1659/30,781	1933/54,037	3314/95,007
HR (95% CI), all-cause mortality	Reference	0.91 (0.86–0.96)	0.83 (0.79–0.87)	Reference	0.85 (0.79–0.91)	0.78 (0.73–0.83)
Years of life gained, 45 y	Reference	0.68 (0.28–1.08)	1.33 (0.95–1.70)	Reference	0.98 (0.57–1.39)	1.47 (1.08–1.87)
Years of life gained, 65 y	Reference	0.57 (0.24–0.91)	1.12 (0.80–1.44)	Reference	0.90 (0.53–1.28)	1.36 (1.00–1.72)
Diet pattern						
No. of deaths/participants	1310/17,784	4865/71,001	5339/72,721	532/10,933	2758/77,351	3616/91,541
HR (95% CI), all-cause mortality	Reference	0.98 (0.92–1.04)	0.92 (0.86–0.98)	Reference	0.83 (0.75–0.91)	0.80 (0.73–0.89)
Years of life gained, 45 y	Reference	0.16 (–0.28–0.61)	0.61 (0.16–1.06)	Reference	1.12 (0.53–1.72)	1.29 (0.69–1.89)
Years of life gained, 65 y	Reference	0.14 (–0.24–0.51)	0.51 (0.13–0.89)	Reference	1.03 (0.48–1.57)	1.18 (0.63–1.73)
Biological CVH metrics						
Serum cholesterol						
No. of deaths/participants	3094/33,882	6992/104,117	1428/23,507	509/7452	3816/88,654	2581/83,719
HR (95% CI), all-cause mortality	Reference	0.91 (0.86–0.95)	0.97 (0.91–1.04)	Reference	0.77 (0.70–0.85)	0.75 (0.67–0.83)
Years of life gained, 45 y	Reference	0.71 (0.38–1.04)	0.22 (–0.29–0.72)	Reference	1.58 (0.96–2.21)	1.73 (1.06–2.41)
Years of life gained, 65 y	Reference	0.60 (0.32–0.88)	0.18 (–0.24–0.61)	Reference	1.45 (0.88–2.02)	1.59 (0.98–2.21)
Blood pressure						
No. of deaths/participants	4242/50,675	6706/98,863	564/11,958	2022/40,434	4063/103,294	821/36,085
HR (95% CI), all-cause mortality	Reference	0.93 (0.89–0.96)	0.99 (0.90–1.08)	Reference	0.96 (0.91–1.02)	0.98 (0.90–1.06)
Years of life gained, 45 y	Reference	0.54 (0.26–0.82)	0.09 (–0.55–0.73)	Reference	0.21 (–0.11–0.54)	0.12 (–0.40–0.63)
Years of life gained, 65 y	Reference	0.45 (0.22–0.69)	0.08 (–0.46–0.62)	Reference	0.19 (–0.10–0.47)	0.10 (–0.35–0.56)
Fasting serum glucose						
No. of deaths/participants	1625/10,305	3341/35,981	6548/115,220	576/6934	2020/38,074	4310/134,817
HR (95% CI), all-cause mortality	Reference	0.79 (0.74–0.85)	0.74 (0.69–0.80)	Reference	0.95 (0.86–1.05)	0.93 (0.83–1.03)
Years of life gained, 45 y	Reference	1.70 (1.16–2.24)	2.18 (1.60–2.75)	Reference	0.29 (–0.32–0.90)	0.43 (–0.20–1.06)
Years of life gained, 65 y	Reference	1.42 (0.97–1.87)	1.83 (1.34–2.31)	Reference	0.27 (–0.30–0.83)	0.39 (–0.18–0.97)

Table 2: . The hazard ratio and years of life gained of individual cardiovascular health metrics.

All models were adjusted for age, ethnicity, educational attainment, employment status, socioeconomic status, alcohol intake, C-reactive protein, prevalent cardiovascular disease and diabetes at baseline, and each CVH metrics were adjusted for each other.

of our study need to be considered. First, the study sample was recruited from a community setting but there is evidence of participation bias with study participants being more affluent and healthier than the average UK population.³² Therefore, UK Biobank is not a representative sample of the UK population, we should be cautious in generalizing summary statistics to the general population. However, it can be used to provide valid estimates of exposure–disease relationships due to its large sample size and multitude of exposures.^{32,33} Estimated relative risks derived from UK Biobank are consistent

with more representative population cohorts.³³ Second, although participants who died within the first 2 years of follow-up were examined to reduce the risk of reverse causation in the sensitivity analyses, it is still possible that participants with CMD may generally be less well, which could result in unhealthy behaviors and a higher mortality rate, or adherence to a healthier lifestyle may be associated to a greater adherence to medications. However, we conducted another sensitivity analyses that participants with prevalent CMD at baseline were excluded, which did not violate our main results. Third,

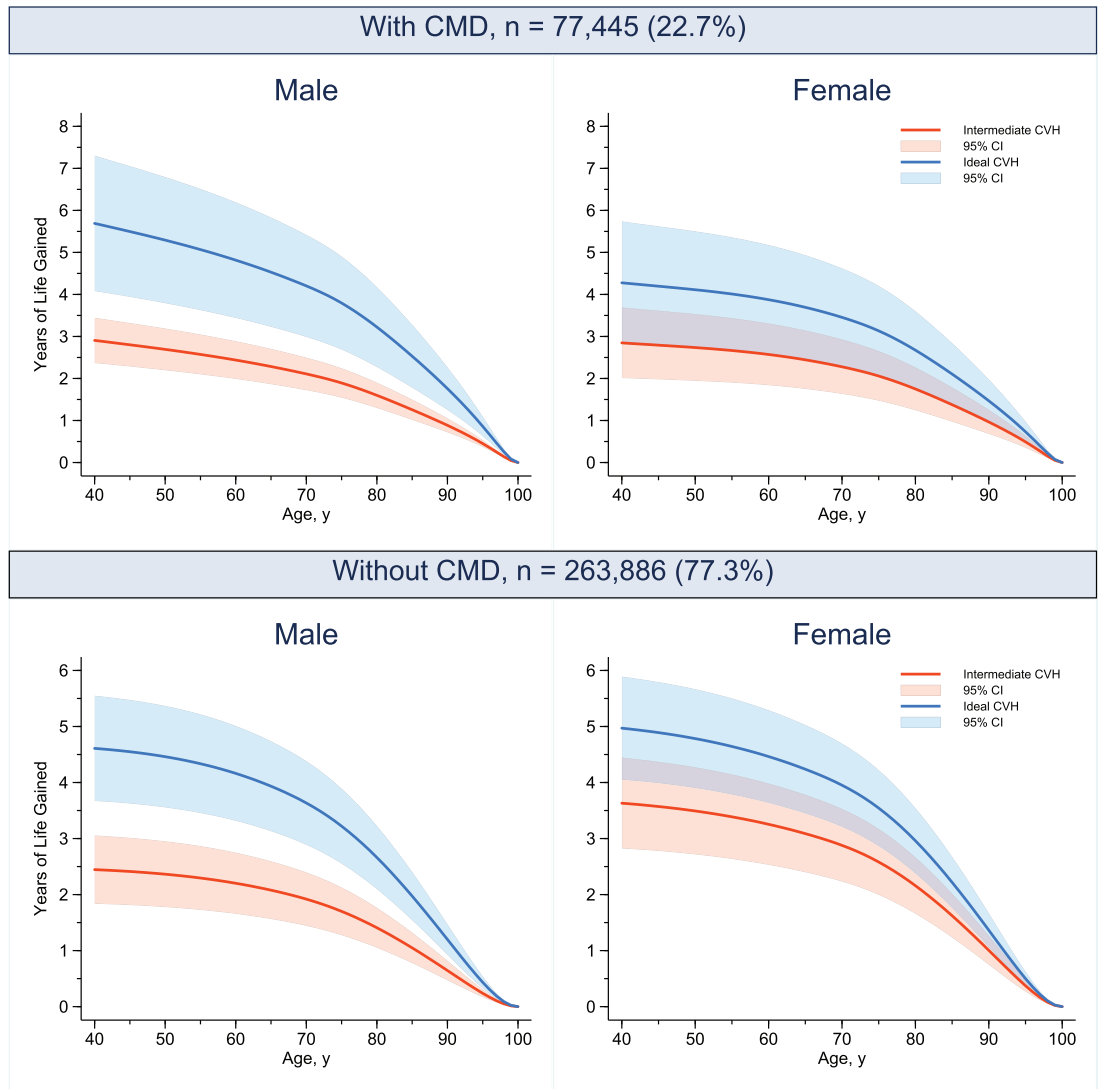


Figure 4. Years of life gained associated with intermediate and ideal cardiovascular health (CVH) when compared to the poor CVH group for participants with and without cardiometabolic disease (CMD). Models were adjusted for age, ethnicity, educational attainment, employment status, socioeconomic status, alcohol intake, C-reactive protein.

although analyses were adjusted for known potential sources of bias and participants were followed up for a median of 11 years, the possibility of unmeasured confounding and reverse causation remains. Fourth, as in many large prospective studies, healthy lifestyle information (e.g. physical activity, diet metrics) was subjectively measured by self-reported, which are known to cause possible recall bias. However, recall-based assessment methods remain reasonable representations for health behaviors with alternative biases and problems inherent in observed assessment methods. Fifth, CVH metrics were obtained only at baseline, and changes over time were not accounted for in this study. Sixth, the CVH score was established by the sum of each CVH

metrics grading, which was not fully taking the weight of different CVH metrics into account. Finally, the current study was an observational study, and causality cannot be inferred.

In this large population-based sample, we found that ideal CVH could substantially attenuate the CMD-related risk of premature mortality, and improve greater life expectancy regardless of the presence of CMD. Our study highlights the benefits of maintaining better CVH across the life course and calls attention to the need for comprehensive strategies (healthy behavioral lifestyle and biological phenotypes) to preserve and restore a higher CVH score to prolong life expectancy.

Data sharing statement

The data that support the findings of this study are available from UK Biobank project site, subject to registration and application process. Further details can be found at <https://www.ukbiobank.ac.uk>.

Contributors

ZC contributed to the idea and conceptual design. CX have full access to the data and were responsible for the raw data of this study. CX analyzed the data and completed all results, with the help of PZ. ZC and CX wrote the first and successive drafts of the manuscript. All authors reviewed the manuscript. ZC took the decision to submit the manuscript for publication after got an approval of all authors.

Declaration of interests

The authors declare that they have no competing interests.

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Supplementary materials

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