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# Cardiovascular health and cancer mortality: evidence from US NHANES and UK Biobank cohort studies

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## Abstract

**Background** The American Heart Association recently introduced a novel cardiovascular health (CVH) metric, Life's Essential 8 (LE8), for health promotion. However, the relationship between LE8 and cancer mortality risk remains uncertain.

**Methods** We investigated 17,076 participants from US National Health and Nutrition Examination Survey (US NHANES) and 272,727 participants from UK Biobank, all free of cancer at baseline. The CVH score, based on LE8 metrics, incorporates four health behaviors (diet, physical activity, smoking, and sleep) and four health factors (body mass index, lipid, blood glucose, and blood pressure). Self-reported questionnaires assessed health behaviors. Primary outcomes were mortality rates for total cancer and its subtypes. The association between CVH score (continuous and categorical variable) and outcomes was examined using Cox model with adjustments. Cancer subtypes-related polygenic risk score (PRS) was constructed to evaluate its interactions with CVH on cancer death risk.

**Results** Over 141,526 person-years in US NHANES, 424 cancer-related deaths occurred, and in UK Biobank, 8,872 cancer deaths were documented during 3,690,893 person-years. High CVH was associated with reduced overall cancer mortality compared to low CVH (HR 0.58, 95% CI 0.37–0.91 in US NHANES; 0.51, 0.46–0.57 in UK Biobank). Each one-standard deviation increase in CVH score was linked to a 19% decrease in cancer mortality (HR: 0.81; 95% CI: 0.73–0.91) in US NHANES and a 19% decrease (HR: 0.81; 95% CI: 0.79–0.83) in UK Biobank. Adhering to ideal CVH was linearly associated with decreased risks of death from lung, bladder, liver, kidney, esophageal, breast, colorectal, pancreatic, and gastric cancers in UK Biobank. Furthermore, integrating genetic data revealed individuals with low PRS and high CVH exhibited the lowest mortality from eight cancers (HRs ranged from 0.36 to 0.57) compared to those with high PRS and low CVH. No significant modification of the association between CVH and mortality risk for eight cancers by genetic predisposition was observed. Subgroup analyses showed a more pronounced protective association for overall cancer mortality among younger participants and those with lower socio-economic status.

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**Conclusions** Maintaining optimal CVH is associated with a substantial reduction in the risk of overall cancer mortality. Adherence to ideal CVH correlates linearly with decreased mortality risk across multiple cancer subtypes. Individuals with both ideal CVH and high genetic predisposition demonstrated significant health benefits. These findings support adopting ideal CVH as an intervention strategy to mitigate cancer mortality risk and promote healthy aging.

**Keywords** Life's essential 8, Cardiovascular health, Cancer mortality, Cancer subtypes, Genetic predisposition

## Background

Cancer is a prominent health issue globally and ranks among the leading causes of premature death worldwide [1]. In recent years, there has been increasing attention given to the impact of lifestyle factors on the occurrence and progression of cancer. Adoption of healthy lifestyle practices has shown significant effects, with a remarkable 52% reduction in the risk of cancer mortality compared to individuals with unhealthy lifestyles [2]. Research emphasizes the crucial role of modifiable factors, suggesting that addressing these factors could potentially prevent approximately 40% of cancer cases [3]. Identifying multiple modifiable risk factors not only provides opportunities for preventing or delaying the onset of cancer but also offers pathways for improving the prognosis of cancer patients facing challenging outcomes.

Cardiovascular diseases (CVDs) are also a major cause of death globally, similar to cancer [1, 4]. These conditions share common modifiable risk factors such as smoking, obesity, lack of physical activity, and unhealthy dietary habits, as well as underlying mechanisms like chronic inflammation and oxidative stress [5–9]. To enhance cardiovascular health (CVH), the American Heart Association (AHA) has evolved its assessment approach from the traditional Life's Simple 7 (LS7) score's seven components (smoking, physical activity, obesity, diet, total cholesterol, blood pressure, and blood glucose) to the innovative Life's Essential 8 (LE8) [10, 11]. This updated method integrates sleep health, measured by optimal habitual sleep duration, as a novel component supported by a mounting body of research consistently associating sleep duration with CVH and overall health outcomes [12, 13]. Significantly, sleep duration is closely associated with each of the original seven factors of CVH and contributes independently to overall CVH [13]. The inclusion of sleep health in the LE8 metrics holds great potential for advancing CVH in the general population, although further substantiating data are still warranted.

Previous studies have reported the associations of CVH defined by LE8 score with several important disease outcomes which include CVDs [14], nonalcoholic fatty liver disease [15], dementia [16], chronic kidney disease [17], and all-cause mortality [18]. However, there are limited studies focused on cancer deaths. Although there are several studies reported that adherence to higher LS7-defined CVH is associated with lower cancer incidence [19–23]. However, most studies have been conducted in the United States and have primarily focused on overall cancer incidence without delving into specific cancer subtypes [19–22]. One study carried out in Europe that focused on the correlation between LS7-CVH and overall cancer incidence, involving the French population aged 30–50 rather than general population [23]. Additionally, a single-center study with a limited sample size in the US examined the relationship between LS7-CVH and cancer mortality, yielding non-significance results [24]. However, there is a lack of exploration of evidence supporting the association between LE8-defined CVH and overall and cancer subtype mortality. Genome-wide association study has successfully identified genetic variants associated with specific common cancers [25]. Recent study highlights the dual contribution of genetic factors and lifestyle factors to cancer risk [26]. Thus, further investigation into the combined effects of LE8 score, genetic risk, and susceptibility to various cancer deaths is warranted.

Consequently, we aim to assess the association between LE8-indicated CVH and overall cancer and cancer subtype mortality among adult participants in the US National Health and Nutrition Examination Survey (NHANES) and UK Biobank. Additionally, we seek to delve into the beneficial effects of CVH on cancer death among individuals with different levels of cancer genetic susceptibility in the UK Biobank cohort.

## Methods

### Study populations

For both the US NHANES and UK Biobank cohorts, we employed stringent inclusion and exclusion criteria to ensure the reliability of our analysis. Detailed information regarding the study designs and data collection can be found in prior publications (www.cdc.gov/nchs/nhanes/about_nhanes.htm) [27, 28]. In brief, exclusion criteria included individuals lacking complete CVH data, those with prevalent cancer at baseline, participants outside the specified age ranges, and those with missing death data. Figure 1A and B provide an overview of the enrollment process for the US NHANES and UK Biobank cohorts, respectively.

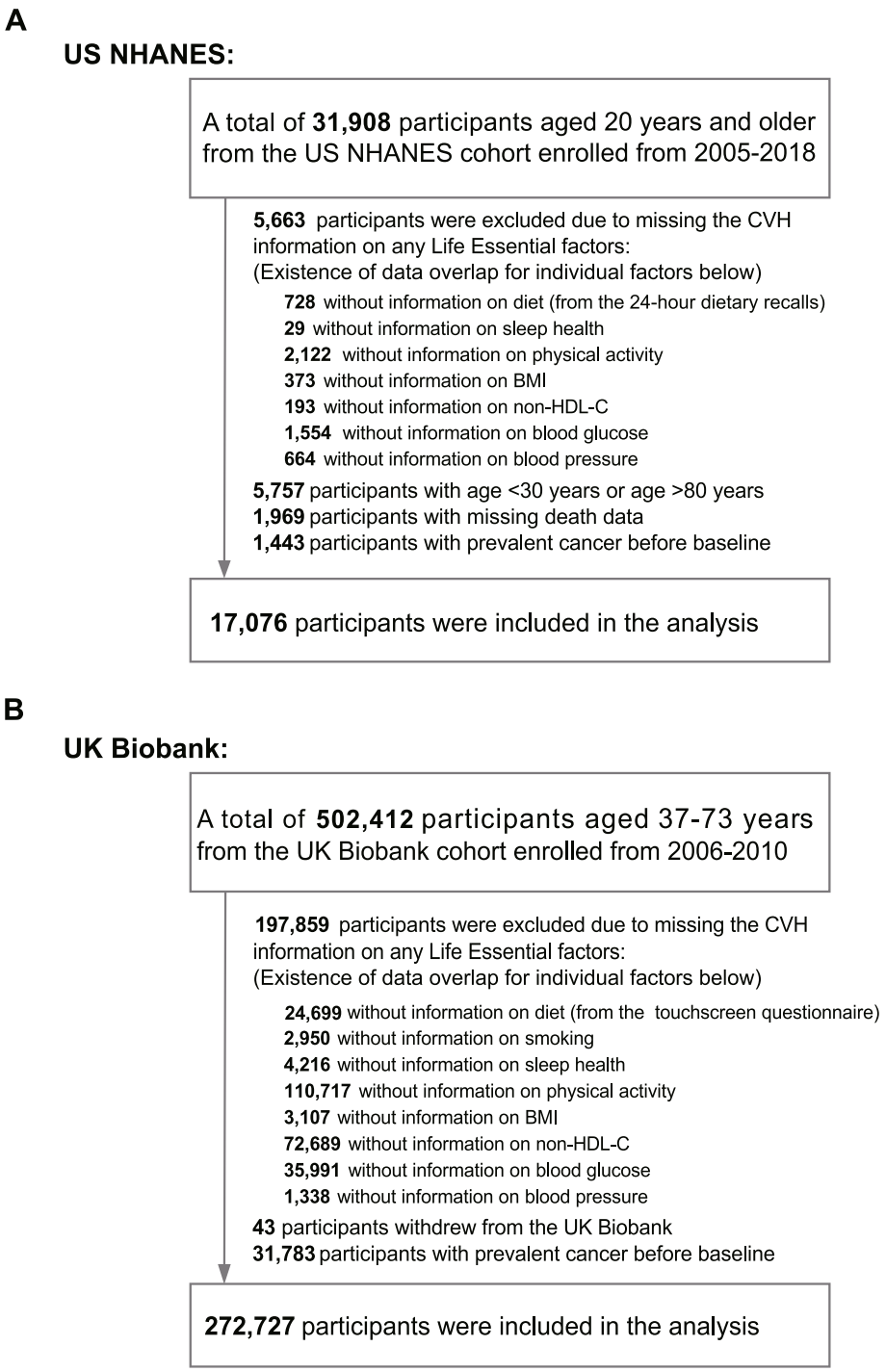


**Fig. 1** Flowchart of participants from US NHANES (**A**) and UK Biobank (**B**) in this study. CVH, cardiovascular health; US, United States; UK, United Kingdom; NHANES, national health and nutrition examination surveys; CVH, cardiovascular health; BMI, body mass index; non-HDL-C, nonhigh-density lipoprotein cholesterol

For the US NHANES cohort, we enrolled a comprehensive cohort of 31,908 participants aged 20 years and older, covering the continuous survey years from 2005 to 2018. After applying the exclusion criteria, our final analytical cohort comprised 17,076 participants.

Similarly, for the UK Biobank cohort, we recruited a total of 502,412 participants aged 37–73 from 2006 to

2010. Following the same exclusion criteria, our final analytical cohort comprised 272,727 participants.

The NHANES protocol was approved by the National Center for Health Statistics' (NCHS) Research Ethics Review Board, and all participants provided written informed consent. Moreover, the UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee. The UK Biobank research was carried out utilizing the UK Biobank Resource under application number 77195.

#### Assessment of updated CVH metrics in LE8

According to the AHA's definition of the LE8 score, an original version for assessing CVH was developed within the US NHANES cohort, while a modified version was implemented within the UK Biobank cohort [10]. In both cohorts, CVH is delineated by eight metrics, comprising four health behaviors (diet, physical activity, nicotine exposure, and sleep) and four health factors (body mass index [BMI], non-high-density lipoprotein cholesterol [HDL-C], blood glucose, and blood pressure).

The original Dietary Approaches to Stop Hypertension (DASH) diet score, applied in the US NHANES cohort, and its modified counterpart in the UK Biobank, were both based on the DASH-style eating pattern proposed by the AHA [10, 29] (Additional file 1: Table S1). While the UK Biobank maintained the original seven-factor classifications, all eight metrics in the US NHANES cohort were derived from the original version. Detailed information and scoring algorithms for each CVH metric in these cohorts can be found in Additional file 1: Table S2. The total CVH score was obtained by summing these eight components and dividing them by 8, with each component ranging from 0 to 100 points. Higher scores indicate better CVH. In addition to considering CVH continuous variables, our study also incorporated CVH categorical variables. Following AHA recommendations [10], overall CVH was categorized into low (< 50 points), moderate (50–79 points), and high (≥ 80 points) based on the LE8 score.

In both the US NHANES cohort and the UK Biobank cohort, various essential health metrics were assessed using standardized methodologies.

For the US NHANES cohort, the original DASH eating pattern served as the basis for evaluating diet metrics [10] (Additional file 1: Table S1). This involved gathering dietary intake data from two 24-h recall interviews to calculate DASH scores. Additionally, self-report questionnaires were utilized to collect data on physical activity, smoking status, sleep patterns, diabetes history, and medication usage. Physical examinations included measurements of blood pressure, height, and weight, from which BMI was derived. Blood samples were collected and analyzed for blood lipids, plasma glucose, and hemoglobin A1c (HbA1c) levels using established laboratory procedures.

Similarly, in the UK Biobank cohort, participants reported their daily intake of a DASH-style eating pattern, which was adjusted using available dietary variables within the dataset [10, 29] (Additional file 1: Table S1). Baseline assessments included touch screen questionnaires to ascertain the frequency and duration of moderate and vigorous physical activity, nicotine exposure, sleep duration, and medication usage. Height and weight measurements were taken during the initial assessment center visit, and BMI was calculated accordingly. Laboratory analyses involved determining total cholesterol levels through CHO-POD analysis and measuring HDL-C levels using enzyme immunoinhibition methods on a Beckman Coulter AU5800 instrument. HbA1c levels were assessed using high-performance liquid chromatography on a Bio-Rad VARIANT II Turbo system. Blood pressure measurements were obtained using an Omron device, with averaged values utilized for subsequent analyses.

#### Outcome ascertainment

Outcomes were classified using ICD-10 (international classification of diseases, 10th revisions) codes. The primary outcomes were total cancer mortality (ICD-10 codes, C00–C97, in US NHANES and UK Biobank cohort), and the secondary outcome encompassed cancer subtype mortality (in UK Biobank cohort only). These subtypes included lip, oral cavity and pharynx, esophagus, stomach, colorectum, liver, pancreas, lung, soft tissue, melanoma, breast, uterus, ovary, prostate, kidney, bladder, brain, lymphoma, and leukemia cancers; subtypes with small case numbers (< 100) were excluded from the analysis to avoid results of limited statistical power. The detailed ICD-10 revision codes are provided in Additional file 1: Table S3.

In the US NHANES cohort, baseline data from NHANES 2005–2018 were linked with causes of death data extracted from the National Death Index death certificate records until December 31, 2019. This process employed an enhanced linkage methodology to accurately ascertain participants' mortality status. Specifically, the enhanced linkage methodology, rooted in the Fellegi-Sunter paradigm, was adopted to account for changes in the survey data collection process. The enhanced linkage algorithm was designed to enhance match quality while minimizing both type I (false positive) and type II (false negative) linkage errors. Further details of the matching method are available from the NCHS (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm).

In the UK Biobank cohort, mortality data were systematically compiled from records maintained by the National Health Service (NHS) England (England & Wales) and the NHS Central Register, National Records of Scotland (Scotland) up to December 19, 2022. Additional details about the linkage procedure are available online at UK Biobank (https://www.ukbiobank.ac.uk/).

#### Assessment of covariates

We evaluated potential confounders by using a comprehensive array of health-related data, including questionnaires, physical examinations, biochemical index examinations, and medical history in both the US NHANES cohort and the UK Biobank cohort.

Variables with the potential for confounding included the following: age (continuous), sex (female/male), race/ethnicity (White/non-White), marital status (married/other status, US NHANES only), education level (college or above/high school or equivalent/less than high school), assessment center (22 assessment centers, UK Biobank only), Townsend deprivation index (continuous, derived from the postcode of residence using aggregated data on unemployment, car and homeownership, and household overcrowding; a higher score indicates worse socioeconomic status (SES) [30], UK Biobank only), family income level (continuous, operationalized using the family poverty to income ratio [31], US NHANES only), first 10 principal components of ancestry at baseline (continuous, UK Biobank only), comorbidities (Charlson comorbidity index [CCI] score used to evaluate overall comorbidity status of participants in the UK Biobank; Baseline hypertension, diabetes, and CVD used to evaluate the overall comorbidity status of participants in the US NHANES).

The CCI was calculated by summarizing the presence of 15 medical conditions and their weight scores based on severity [32]; SES in the NHANES cohort was measured by family income to poverty ratios and divided into three categories: high ($\geq 3.5$), medium ($>1.3$ to $<3.5$), and low ($\leq 1.3$) [33]. SES in the UK Biobank cohort was measured by the Townsend deprivation index categorized into three categories: high (Q1), medium (Q2), and low (Q3). The variables and codes used for disease diagnosis and Charlson comorbidities are detailed in Additional file 1: Table S4 and Additional file 1: Table S5.

#### Calculation of the polygenic genetic risk score (PRS)

Genotyping was conducted by the UK Biobank team using two similar arrays: the UK BiLEVE Axiom Array and the UK Biobank Axiom Array. Detailed information is available at http://www.ukbiobank.ac.uk/scientists-3/genetic-data/.

To construct the PRS for eight specific cancers, we obtained standard PRS for five specific cancers—colorectal cancer (Field ID: 26,218), breast cancer (Field ID: 26,220), ovarian cancer (Field ID: 26,232), melanoma (Field ID: 26,252), and prostate cancer (Field ID: 26,267)—from genomics data in the UK Biobank.

Weighted PRSs for lung, esophageal, and pancreatic cancers were calculated using single nucleotide polymorphisms (SNPs) identified from genome-wide association studies. Specifically, 9 SNPs were used for lung cancer, 14 SNPs for esophageal cancer, and 54 SNPs for pancreatic cancer. The coding for each SNP is 0, 1, or 2 based on the number of risk alleles. The weight for lung cancer PRS was determined using the formula: $PRS = (\beta 1 \times SNP1 + \beta 2 \times SNP2 + \ldots + \beta 9 \times SNP9)$. Similarly, PRS for esophageal or pancreatic cancer was created using their corresponding SNPs identified from the PRS for each cancer. A higher PRS indicates a greater genetic predisposition to specific cancers. Participants were classified into low (Q1), moderate (Q2), and high (Q3) categories based on the tertiles of each cancer PRS. Details on the sources and components of the PRS scores for the eight cancers are provided in Additional file 1: Table S6.

#### Statistical analysis

In both the US NHANES and UK Biobank cohorts, baseline characteristics of participants were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and percentages for categorical variables. Cox proportional hazard models were used to estimate hazard ratios (HRs) and their corresponding 95% confidence interval (CI) for the association between LE8 score and the risk of overall cancer and subtype cancer. The proportional hazards assumptions of the Cox model were tested using the Schoenfeld residual method and found to be satisfied [34]. Furthermore, a correlation matrix analysis was performed to evaluate collinearity between all included covariates, and no multicollinearity was detected. To correct for multiple testing, the Benjamin-Hochberg method was applied to adjust the *P* values using the false discovery rate (FDR) [35].

In both the US NHANES and UK Biobank cohorts, Kaplan–Meier survival curves were generated for the calculation of cumulative total cancer mortality using three categories of CVH (low, moderate, high), and comparisons were using the log-rank test. Model 1 was a crude model. Model 2 was adjusted for sex, age, and race/ethnicity. Model 3 was further controlled for assessment center, education levels, SES, comorbidities, and first 10 principal components of ancestry. The analyses for behavior and biological subscale scores were repeated with mutual adjustment for each other in the

model. Restricted cubic spline models with three knots (10th, 50th, and 90th percentiles) were conducted to estimate the dose–response association of total CVH score with the mortality of subtype cancers, with 50 points of CVH score as the reference.

In the UK Biobank cohort, we examined the associations of PRS categories, CVH categories, and their combined impact on the mortality of subtype cancers. To explore whether the genetic predisposition could be mitigated by CVH, we tested the interaction between CVH categories and the PRS categories of subtype cancers in the model. Additionally, we examined the relationship between CVH and outcomes by introducing interaction terms between CVH and age, sex, or SES into the model. This allowed us to evaluate whether the association between CVH and outcomes was influenced by sex differences, age variations, or differences in SES. Several subgroup analyses were conducted using Cox regression model to test the difference between subgroups by socio-demographic features, including age ($<65$ vs. $\geq 65$ years), sex (male vs. female), and SES status (low SES vs. high SES, defined by Townsend deprivation index, where low SES indicates high deprivation and high SES indicates less deprivation).

In the UK Biobank cohort, we conducted several sensitivity analyses to ensure the reliability and robustness of our results. Firstly, the 24-h dietary recall questionnaire was distributed to participants who provided email addresses during the initial visit to the UK biobank. In our included participants, we utilized diet data from the 24-h dietary recall questionnaire instead of from the touch screen questionnaires in this sensitivity analysis, which were used to calculate the original DASH diet score proposed by AHA. Subsequently, we computed the original LE8 score and analyzed the association of CVH with cancer outcomes ($N=122{,}303$). Secondly, we excluded events that occurred within two years at baseline to address any concerns regarding reverse causality ($N=266{,}261$). Thirdly, we performed the main analyses exclusively among participants with complete covariate data to minimize potential biases resulting from missing information ($N=232{,}035$). Fourthly, we conducted the main analyses among participants without CCI scores greater than one score to assess the potential impact of these comorbidities on the association between CVH and cancer mortality ($N=252{,}114$). Finally, based on the main model, we further corrected for more confounders, including hormone replacement therapy and C-reactive protein ($N=272{,}727$).

To account for any missing covariate values in the analysis, we employed the "missForest" R package for multiple imputations, ensuring statistical power and minimizing inferential bias [36]. Detailed missing rates for the covariates used in this study are provided in Additional file 1: Table S7.

All statistical analyses were conducted using R software version 4.2. All statistical tests were two-sided, and a significant level of $P<0.05$ was considered statistically significant.

## Results

### Baseline characteristics of study participants in US NHANES and UK Biobank cohorts

Descriptive characteristics of participants, stratified by CVH categories, are presented in Additional file 1: Table S8 for both the US NHANES and UK Biobank cohorts.

In the US NHANES cohort, consisting of 17,076 participants with a mean age of 53.3 (14.6) years (50.8% female, 45.9% non-Hispanic White American background), 2,959 (17.3%) had low CVH, 11,611 (68.0%) had moderate CVH, and 2,506 (14.7%) had high CVH. Participants with higher CVH tended to be younger, female, highly educated, married, of higher SES, and had a lower prevalence of comorbidities. Excluded participants, due to missing information, were aged $<30$ or age $>80$, or had prevalent cancer, were younger and more likely to be female, non-White, of lower SES, highly educated, unmarried, and had better health status compared to the included participants (Additional file 1: Table S9).

In the UK Biobank cohort, comprising of 272,727 participants with a mean age of 56.5 (8.2) years (51.6% female, 95.5% White European background), 15,364 (5.6%) had low CVH, 220,571 (80.9%) had moderate CVH, and 36,792 (13.5%) had high CVH. Participants with higher CVH were generally younger, female, highly educated, of higher SES, and had a lower prevalence of comorbidities. Excluded participants, due to missing information or prevalent cancer, compared to the included participants, were older and more likely to be female, of lower SES, highly educated, and had worse health status compared to the included participants (see Additional file 1: Table S9).

The UK Biobank cohort demonstrates an older age, a higher proportion of females, individuals of White ethnicity, and a higher CVH score compared to the US NHANES cohort. However, the baseline characteristics of the CVH groups between the two cohorts are similar. Additional file 1: Table S10 presents the baseline characteristics of the included, categorized based on whether they experienced cancer-related mortality in the two cohorts.

### Association of LE8 score with overall *cancer* mortality in US NHANES and UK Biobank cohorts

In the US NHANES cohort, a total of 424 cancer deaths were recorded during a mean follow-up of 8.3 (3.4) years. The total cancer death rates per 1,000 person-years among participants with CVH at moderate and high levels were significantly lower than those with a low level (as shown in Table 1). The cumulative mortality of total cancer exhibited a graded relationship based on the levels of CVH categories during follow-up in the US NHANES cohort ($P<0.001$ for the log-rank test, as illustrated in Fig. 2A).

After adjusting for potential covariates, including age, sex, race, education level, marital status, SES, and history of comorbidities, a significant inverse association between CVH and cancer mortality was observed in the US NHANES cohort ($P_{trend}=0.012$). Compared to participants with low CVH, the HRs (95%CI) of cancer mortality were 0.81 (0.64–1.02, $P=0.069$) and 0.58 (0.37–0.91, $P=0.019$) for the moderate CVH and high CVH groups in the US NHANES cohort, respectively. Additionally, per SD increment in LE8 score was associated with a 19% decrease in risk (HR, 0.81, 95% CI 0.73–0.91, $P<0.001$) for cancer mortality in the US NHANES cohort.

Furthermore, the subscale of the CVH scores in the US NHANES study, specifically the behavior subscale, showed a significant association with reduced risks of cancer mortality. This finding supports the LE8 score, suggesting that behaviors have a vital role in lowering the risk of cancer-related deaths. Notably, the behavior scale exhibited enhanced magnitudes of association, particularly in nicotine exposure score. Although there were non-significant associations for diet, physical activity, and sleep health scores, a similar trend was observed with higher scores being associated with a reduced risk of cancer mortality, while the biological scale, as well as the other health factors of the LE8, did not reach statistical significance in this regard (as shown in Table 1 and Additional file 1: Table S11).

In the UK Biobank cohort, a total of 8872 cancer deaths were recorded during a mean follow-up of 13.5 (1.8) years. The total cancer death rates per 1,000 person-years among participants with CVH at the moderate and high levels were significantly lower than those with low level (as shown in Table 1). The cumulative mortality of total

**Table 1** Associations of CVH score with overall cancer mortality in US NHANES and UK Biobank cohort

| All cancer mortality | *N* | Event/person-years | Model 1 HR (95%CI) [a]; *P*-value | Model 2 HR (95%CI) [b]; *P*-value | Model 3 HR (95%CI) [c]; *P*-value |
|---|---|---|---|---|---|
| US NHANES | | | | | |
| Low CVH | 2,959 | 108/23,916 | Ref | Ref | Ref |
| Moderate CVH | 11,611 | 290/96,783 | 0.66 (0.53–0.82); < 0.001 | 0.71 (0.57–0.89); 0.003 | 0.81 (0.64–1.02); 0.069 |
| High CVH | 2,506 | 26/20,827 | 0.28 (0.18–0.42); < 0.001 | 0.46 (0.30–0.71); < 0.001 | 0.58 (0.37–0.91); 0.019 |
| *P* for trend | | | < 0.001 | < 0.001 | 0.012 |
| Per SD increase in CVH | 17,076 | 424/141,526 | 0.70 (0.64–0.77); < 0.001 | 0.77 (0.70–0.86); < 0.001 | 0.81 (0.73–0.91); < 0.001 |
| Per SD increase in CVH subscale [d] | | | | | |
| Behavior scale | 17,076 | 424/141,526 | 0.71 (0.65–0.78); < 0.001 | 0.70 (0.64–0.77); < 0.001 | 0.75 (0.68–0.82); < 0.001 |
| Biological scale | 17,076 | 424/141,526 | 0.80 (0.73–0.88); < 0.001 | 1.02 (0.91–1.13); 0.790 | 1.03 (0.91–1.17); 0.602 |
| UK biobank | | | | | |
| Low CVH | 15,364 | 851/203,525 | Ref | Ref | Ref |
| Moderate CVH | 220,571 | 7,378/2,982,590 | 0.59 (0.55–0.63); < 0.001 | 0.60 (0.56–0.65); < 0.001 | 0.65 (0.60–0.70); < 0.001 |
| High CVH | 36,792 | 643/504,778 | 0.30 (0.27–0.33); < 0.001 | 0.45 (0.41–0.50); < 0.001 | 0.51 (0.46–0.57); < 0.001 |
| *P* for trend | | | < 0.001 | < 0.001 | < 0.001 |
| Per SD increase in CVH | 272,727 | 8,872/3,690,893 | 0.72 (0.70–0.73); < 0.001 | 0.78 (0.77–0.80); < 0.001 | 0.81 (0.79–0.83); < 0.001 |
| Per SD increase in CVH subscale [d] | | | | | |
| Behavior scale | 272,727 | 8,872/3,690,893 | 0.79 (0.77–0.80); < 0.001 | 0.77 (0.75–0.78); < 0.001 | 0.79 (0.77–0.80); < 0.001 |
| Biological scale | 272,727 | 8,872/3,690,893 | 0.78 (0.76–0.79); < 0.001 | 0.91 (0.89–0.94); < 0.001 | 0.89 (0.85–0.92); < 0.001 |

*US* United States, *UK* United Kingdom, *NHANES* national health and nutrition examination surveys, *HR* Hazard ratio, *CI* Confidence interval, *CVH* Cardiovascular health, *SD* Standard deviation

[a] Mode1 1: crude model

[b] Model 2: adjusting sex, age and race/ethnicity

[c] Model 3: model 2 + additional adjusting education level, Townsend deprivation index (ratio of family income to poverty in NAHANES), Charlson comorbidity index (diabetes, hypertension and cardiovascular disease history in NAHANES), and the first 10 principal components of ancestry (UK Biobank only)

[d] Behavior factor including diet, physical activity, tobacco/nicotine exposure, and sleep health. Biological factor including body mass index, blood lipids, blood glucose, and blood pressure. Behavior scale and biological scale were further mutually adjusted for subscale analyses

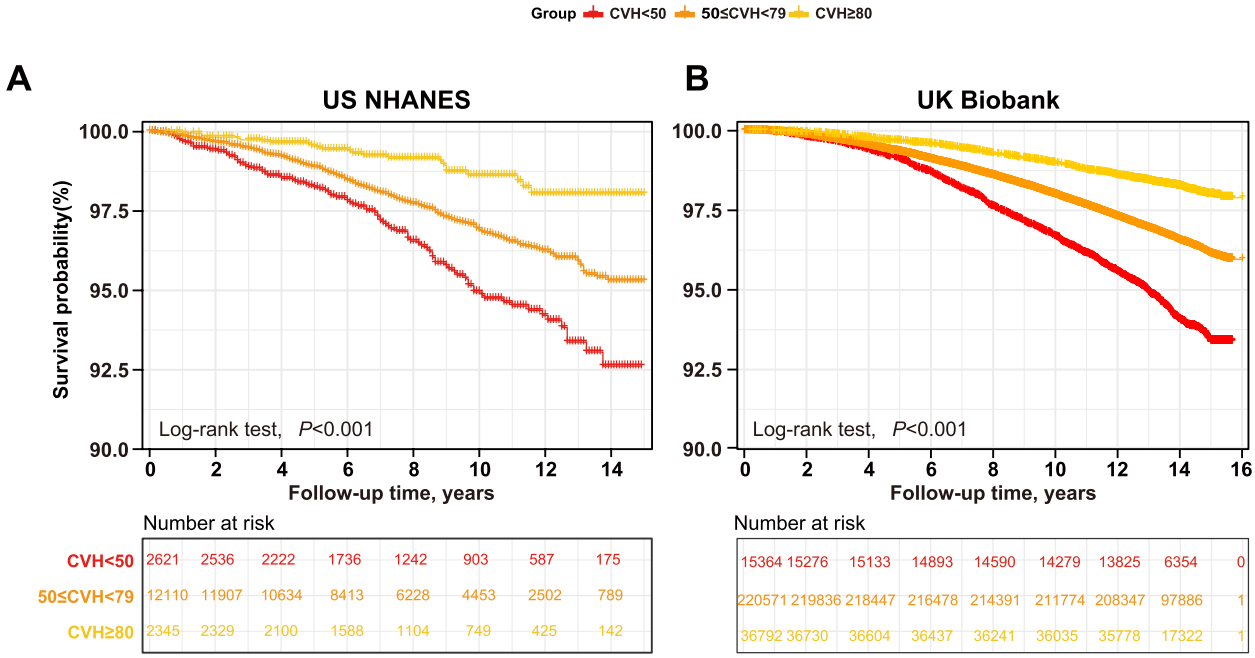


**Fig. 2** Cumulative Survival probability of overall cancer according to CVH categories defined by LE8 in US NHANES (**A**) and UK Biobank (**B**) cohort. US, United States; UK, United Kingdom; NHANES, national health and nutrition examination surveys; CVH, cardiovascular health; Life's Essential 8, LE8

cancer demonstrated a graded relationship based on the levels of CVH categories during the follow-up in the UK Biobank cohort ($P<0.001$ for the log-rank test, as illustrated in Fig. 2B).

After adjusting for potential covariates, including age, sex, race, education level, SES, assessment centers, history of comorbidities, and first 10 principal components of ancestry, similarly, a significant negative association between CVH and cancer mortality was observed in the UK Biobank cohort ($P_{trend}<0.001$). The HRs (95%CI) were 0.65 (0.60–0.70, $P<0.001$) and 0.51 (0.46–0.57, $P<0.001$) in the UK Biobank study, respectively. Additionally, per SD increment in LE8 score was associated with a 19% decrease in risk (HR, 0.81, 95% CI 0.79–0.83, $P<0.001$) for cancer mortality.

Furthermore, for the subscales of the CVH in the UK Biobank study, both the behavior and biological subscale scores remained significantly associated with lower risks of cancer mortality, similar to the overall LE8 score. However, there was a greater magnitude of association observed in the behavior scale, while the magnitudes in the biological scale was attenuated (as shown in Table 1). When we analyzed the individual component of LE8 and simultaneously included all the metrics in the model, we found that higher scores of diets, sleep health, nicotine exposure, body mass index, blood glucose, and blood pressure were significantly associated with a reduced risk of overall cancer mortality (all $P_{trend}<0.01$). Conversely, a higher score of blood lipid was significantly associated with an increased risk of cancer mortality. Although there were non-significant associations for physical activity, a similar trend was observed, with higher scores being associated with a reduced risk of outcomes (as shown in Additional file 1: Table S11).

In summary, our study demonstrated a protective association of high CVH with total cancer deaths in two cohorts, namely the US NHANES and UK Biobank cohorts. Notably, the association was found to be more significant in the UK Biobank cohort. Building upon these findings, we further examined the relationship between CVH and cancer-specific deaths, with a particular focus on the combinations and interaction of genetic predisposition and CVH in relation to subtype-specific cancer deaths.

### Association of LE8 score with subtype-specific *cancer* mortality in the UK Biobank cohort

In the UK Biobank cohort, we examined the impact of the LE8 score on subtype-specific cancer mortality, as detailed in Table 2. The analysis revealed a compelling association between higher CVH scores and reduced mortality risks across various cancer subtypes.

For lung, bladder, liver, kidney, esophagus, breast, colorectum, and pancreas cancers, participants with higher CVH scores exhibited significantly lower mortality risks (HRs ranged from 0.20 to 0.58, all adjusted *P*

**Table 2** Associations of CVH score with cancer subtype mortality in the UK Biobank cohort

| Cancer subtype mortality | Low CVH | Moderate CVH | *P*-value [a] | High CVH | *P*-value [a] | Per SD increment in CVH score | *P*-value [a] |
|---|---|---|---|---|---|---|---|
| ***N* all participants** | 15,364 | 220,571 | | 36,792 | | 272,727 | |
| **Lip, oral cavity and pharynx** | | | | | | | |
| Event/person-years | 14/203,525 | 85/2,982,590 | | 8/504,778 | | 107/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.55 (0.31–0.98); 0.044 | 0.099 | 0.47 (0.19–1.14);0.096 | 0.173 | 0.80 (0.65–0.98); 0.027 | 0.049 |
| **Esophagus** | | | | | | | |
| Event/person-years | 56/203,525 | 378/2,982,590 | | 26/504,778 | | 460/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.55 (0.41–0.73); < 0.001 | < 0.001 | 0.40 (0.25–0.63); < 0.001 | 0.001 | 0.70 (0.64–0.78); < 0.001 | < 0.001 |
| **Stomach** | | | | | | | |
| Event/person-years | 25/203,525 | 219/2,982,590 | | 18/504,778 | | 262/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.68 (0.45–1.04); 0.073 | 0.146 | 0.55 (0.30–1.02); 0.056 | 0.111 | 0.82 (0.72–0.94); 0.003 | 0.007 |
| **Colorectum** | | | | | | | |
| Event/person-years | 83/203,525 | 789/2,982,590 | | 71/504,778 | | 943/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.67 (0.53–0.84); < 0.001 | 0.002 | 0.50 (0.36–0.69); < 0.001 | < 0.001 | 0.85 (0.79–0.91); < 0.001 | < 0.001 |
| **Liver** | | | | | | | |
| Event/person-years | 37/203,525 | 282/2,982,590 | | 17/504,778 | | 336/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.60 (0.42–0.85); 0.004 | 0.013 | 0.33 (0.18–0.59); < 0.001 | 0.001 | 0.71 (0.63–0.80); < 0.001 | < 0.001 |
| **Pancreas** | | | | | | | |
| Event/person-years | 77/203,525 | 659/2,982,590 | | 68/504,778 | | 804/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.62 (0.49–0.79); < 0.001 | < 0.001 | 0.58 (0.42–0.81); 0.001 | 0.005 | 0.83 (0.77–0.89); < 0.001 | < 0.001 |
| **Lung** | | | | | | | |
| Event/person-years | 246/203,525 | 1,275/2,982,590 | | 57/504,778 | | 1,578/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.45 (0.39–0.51); < 0.001 | < 0.001 | 0.20 (0.15–0.27); < 0.001 | < 0.001 | 0.60 (0.57–0.63); < 0.001 | < 0.001 |
| **Soft tissue** | | | | | | | |
| Event/person-years | 16/203,525 | 283/2,982,590 | | 21/504,778 | | 320/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 1.33 (0.80–2.20); 0.274 | 0.448 | 1.03 (0.53–1.98); 0.937 | 0.979 | 1.06 (0.94–1.20); 0.355 | 0.419 |
| **Melanoma** | | | | | | | |
| Event/person-years | 9/203,525 | 105/2,982,590 | | 15/504,778 | | 129/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.80 (0.40–1.59); 0.527 | 0.593 | 0.91 (0.39–2.11); 0.822 | 0.979 | 1.09 (0.90–1.31); 0.373 | 0.419 |
| **Kidney** | | | | | | | |
| Event/person-years | 25/203,525 | 205/2,982,590 | | 12/504,778 | | 242/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.63 (0.41–0.95); 0.028 | 0.085 | 0.36 (0.18–0.71); 0.004 | 0.010 | 0.75 (0.65–0.86); < 0.001 | < 0.001 |
| **Bladder** | | | | | | | |
| Event/person-years | 18/203,525 | 183/2,982,590 | | 6/504,778 | | 207/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.78 (0.48–1.28); 0.325 | 0.487 | 0.29 (0.11–0.72); 0.008 | 0.018 | 0.74 (0.64–0.86); < 0.001 | < 0.001 |
| **Brain** | | | | | | | |
| Event/person-years | 29/203,525 | 376/2,982,590 | | 57/504,778 | | 462/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.92 (0.63–1.35); 0.667 | 0.706 | 1.11 (0.71–1.76); 0.644 | 0.828 | 1.00 (0.90–1.10); 0.962 | 0.962 |
| **Lymphoma** | | | | | | | |
| Event/person-years | 25/203,525 | 301/2,982,590 | | 30/504,778 | | 356/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.87 (0.58–1.32); 0.512 | 0.593 | 0.84 (0.49–1.43); 0.516 | 0.714 | 0.92 (0.82–1.02); 0.121 | 0.168 |
| **Leukemia** | | | | | | | |
| Event/person-years | 17/203,525 | 247/2,982,590 | | 24/504,778 | | 288/3,690,893 | |
| HR (95% CI) [b]; *P*-value | Ref | 1.10 (0.66–1.83); 0.719 | 0.719 | 1.01 (0.53–1.91); 0.979 | 0.979 | 0.99 (0.87–1.12); 0.847 | 0.896 |
| **N (Females)** | 5954 | 109,132 | | 25,719 | | 140,805 | |
| **Breast** | | | | | | | |
| Event/person-years | 24/79,853 | 292/1,486,725 | | 47/353,770 | | 363/1,920,348 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.65 (0.43–0.99); 0.044 | 0.099 | 0.48 (0.29–0.79); 0.004 | 0.010 | 0.85 (0.77–0.95); 0.003 | 0.007 |
| **Uterus** | | | | | | | |
| Event/person-years | 9/79,853 | 132/1,486,725 | | 17/353,770 | | 158/1,920,348 | |

**Table 2** (continued)

| Cancer subtype mortality | Low CVH | Moderate CVH | *P*-value [a] | High CVH | *P*-value [a] | Per SD increment in CVH score | *P*-value [a] |
|---|---|---|---|---|---|---|---|
| HR (95% CI) [b]; *P*-value | Ref | 0.79 (0.40–1.57); 0.504 | 0.593 | 0.63 (0.28–1.43); 0.267 | 0.401 | 0.86 (0.73–1.02); 0.077 | 0.116 |
| **Ovary** | | | | | | | |
| Event/person-years | 12/79,853 | 263/1,486,725 | | 36/353,770 | | 311/1,920,348 | |
| HR (95% CI) [b]; *P*-value | Ref | 1.22(0.68–2.18); 0.506 | 0.593 | 0.99 (0.51–1.92); 0.979 | 0.979 | 0.94 (0.83–1.06); 0.301 | 0.388 |
| **N (Male)** | 9410 | 111,439 | | 11,073 | | 131,922 | |
| **Prostate** | | | | | | | |
| Event/person-years | 40/123,672 | 417/1,495,865 | | 28/151,008 | | 485/1,770,545 | |
| HR (95% CI) [b]; *P*-value | Ref | 0.82 (0.59–1.14); 0.238 | 0.428 | 0.68 (0.41–1.11); 0.119 | 0.194 | 0.91 (0.82–1.00); 0.052 | 0.085 |

*UK*, United Kingdom; *HR*, hazard ratio; *CI*, confidence interval; *CVH*, cardiovascular health; *SD*, standard deviation

[a] Adjusted *P* values were corrected via the false discovery rate by using the Benjamin-Hochberg method

[b] Model was controlled for age, sex, and ethnicity, assessment center, education levels, Townsend deprivation index, Charlson comorbidity index, and first 10 principal components of ancestry

values < 0.05). Moreover, per SD increment in CVH demonstrated an inverse association with mortality across the same eight subtype-specific cancers (HRs ranged from 0.60 to 0.85, all adjusted *P* values < 0.05). Beyond the initially highlighted cancer types, per SD increment in CVH was linked to decreased mortality risks for lip, oral cavity, and pharynx cancer (HR 0.80, 95% CI 0.65–0.98, $P_{adjusted} < 0.05$) and stomach cancer (HR 0.82, 95% CI 0.72–0.94, $P_{adjusted} < 0.01$). While there were no statistically significant associations between CVH scores and mortality risks for soft tissue cancer, melanoma, uterus cancer, ovary cancer, prostate cancer, brain cancer, lymphoma, and leukemia, a consistent protective trend was observed.

Notably, the graphical representation in Additional file 1: Fig. S1 highlights a steep linear association for mortality across nine cancer subtypes with CVH, all exhibiting significant linear trends (all $P_{non\text{-}linear} > 0.05$). No evidence of linear associations was found for mortality caused by the other nine cancer subtypes in relation to CVH.

### Combined association and interaction of genetic risk with LE8 score on multiple subtype-specific *cancer* mortality in the UK Biobank cohort

In the UK Biobank cohort, we successfully constructed the PRS for eight subtype cancers, as outlined in Additional file 1: Table S12. The joint impact of the LE8 score and corresponding PRS on multiple subtype-specific cancer mortality is visually presented in Fig. 3. Notably, participants with high CVH and low PRS exhibited the most favorable outcomes for each subtype-specific cancer mortality. Compared to those who had low CVH and high PRS, participants with high CVH and low PRS showcased the lowest mortality risks across a spectrum of cancers, including ovary, prostate, colorectum, lung, pancreas, esophagus, breast, and melanoma (HRs ranged from 0.36 to 0.57, with all *P* values < 0.001).

Detailed subgroup analyses, stratified by PRS, are presented in Additional file 1: Table S13. Notably, the genetic predisposition to the eight cancer subtypes did not significantly alter the association between the LE8 Score and mortality risk. However, within each genetic risk category, a consistent and compelling observation emerged. Higher CVH was consistently associated with a significantly reduced risk of death across multiple cancer sites in the UK population. This emphasizes the potential of elevated CVH as a protective factor mitigating mortality risks associated with various cancer subtypes.

### Subgroup and sensitivity analysis

After conducting subgroup analyses on CVH and total cancer mortality, a significant protective effect was identified, the protective effect was significantly enhanced in individuals younger than 65 years and those with lower SES ($P_{interaction} < 0.05$). While no significant differences in the associations of the CVH score with multiple cancer subtype-specific mortalities were observed across subgroups, notable distinctions emerged in some cancer subtypes. A statistically significant difference was noted in the association between the CVH score and prostate cancer mortality within age subgroups. The protective association demonstrated a notably heightened magnitude in individuals younger than 65 years ($P_{interaction} = 0.011$). Similarly, a statistically significant difference in the associations of the CVH score with esophagus cancer mortality was observed within sex subgroups. The protective association demonstrated a notably heightened magnitude in the male population ($P_{interaction} = 0.001$) (Additional file 1: Fig. S2–Fig. S4).

To ensure the robustness of our findings, we conducted several sensitivity analyses, all of which

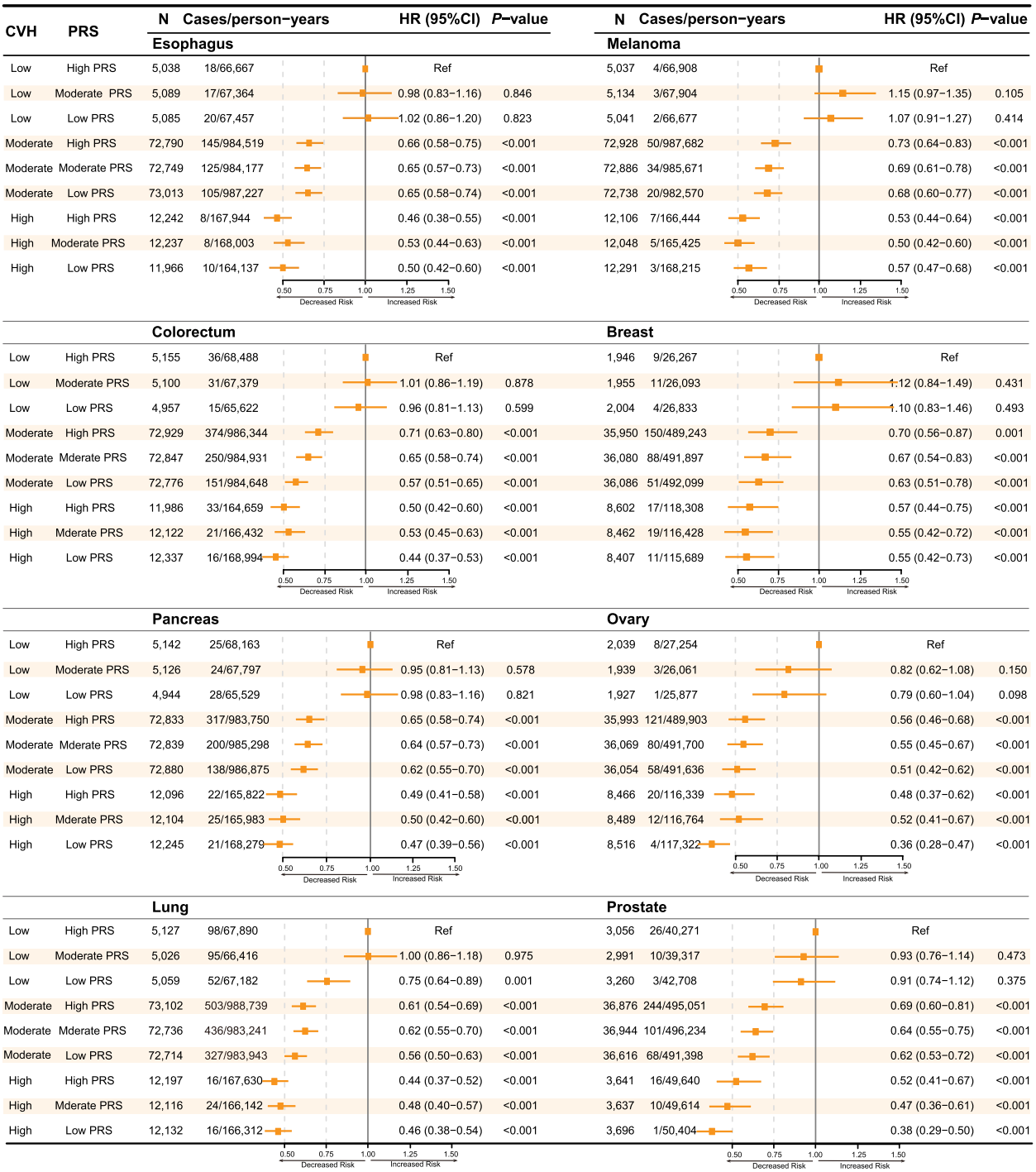


**Fig. 3** Associations of joint categories of CVH score and each cancer genetic risk with cancer subtypes mortality in the UK Biobank cohort. The model was adjusted for age, sex, ethnicity, assessment center, Townsend deprivation index, CCI, and education levels, hormone replacement therapy, C-reactive protein, and the first 10 principal components of ancestry. CVH, cardiovascular health; HR, hazard ratio; CI, confidence interval; PRS, polygenic genetic risk; CCI, Charlson comorbidity index

consistently supported the primary results (Additional file 1: Table S14). In the first sensitivity analysis, we utilized the more accurate 24-h recall questionnaire data to calculate the original DASH diet score. Encouragingly, the findings aligned closely with the main results, confirming the stability of our conclusions. Second, we

explored the temporal aspect by restricting the analysis to participants with an overall cancer death occurring more than two years from baseline. Notably, the results remained in harmony with the primary analysis, suggesting the durability of the observed associations over time. Moreover, ensuring the completeness of covariate data is crucial. When restricting the analysis to participants with complete covariate information, the results exhibited no substantial changes, further reinforcing the robustness of our findings. In addition, to assess the impact of baseline comorbidities, participants with a baseline CCI score greater than one score were excluded. Gratifyingly, the inverse association of CVH with cancer deaths persisted, mirroring the results of the main analysis. In our final sensitivity analysis, we introduced adjustments for hormone replacement therapy and C-reactive protein. Impressively, the results showed no significant deviations from the main analysis, providing additional confidence in the stability of our findings.

## Discussion

Overall, the findings from two prospective cohort studies conducted in the UK Biobank and US NHANES underscore a compelling association between a higher LE8 score and a reduced risk of overall cancer mortality. This consistency across diverse populations adds robustness to the observed relationship, emphasizing the potential universality of the impact of a healthful lifestyle on cancer outcomes. Expanding our inquiry within the UK Biobank, our analysis delves into the site-specific nuances of cancer mortality. The results reveal a linear association between a higher LE8 score and reduced mortality across nine specific cancer types. This granularity provides valuable insights into the diverse ways in which a comprehensive healthy lifestyle may influence cancer outcomes. Importantly, our exploration of the interplay between genetic risk and CVH unveils a significant finding—irrespective of high or low genetic risk, a high CVH score is linked to reduced mortality across eight distinct cancers. This suggests that fostering CVH may notably reduce cancer mortality, regardless of genetic predisposition. Further stratification demonstrates a more pronounced protective association among younger participants and those with low SES. This age and SES add depth to our understanding, suggesting that the benefits of a healthy lifestyle, as measured by the LE8 score, may be especially impactful in these demographic subgroups.

To the best of our knowledge, this study stands as the inaugural exploration of correlation between the new CVH metrics, as characterized by the LE8 score, and the risk of cancer outcomes in two prospective cohort studies. The observed association between better CVH at baseline and a diminished risk of cancer mortality in both the US and UK cohorts complements the findings of three prior US-based studies. Notably, the Multi-Ethnic Study of Atherosclerosis (MESA) [21] and the Women's Health Initiative study reported significant protective associations for cancer-related mortality [22]. In contrast, the Aerobics Center longitudinal study yielded nonsignificant results [24]. However, it is worth noting that prior studies predominantly focused on the old CVH score (defined by LS7), targeted specific populations, or produced inconsistent results. In contrast, our study extends the scope by utilizing two extensive cohort analyses encompassing US adults aged 30–80 and UK adults aged 37–73. This robust approach not only confirms the consistent protective association of newly defined high CVH scores and cancer mortality but also ensures more accurate and stable results. This broader perspective enhances the generalizability of our findings, emphasizing the reliability of the observed relationship between high CVH and reduced cancer mortality risk.

Taking into account the heterogeneous etiology of various cancer subtypes [37] and recent evidence suggesting a significant association between CVDs and specific cancer subtypes [38], it becomes imperative to investigate the correlations between CVH and cancer subtypes. Our findings reveal that a higher CVH score was linked to 42–80% lower risks of mortality in lung, bladder, kidney, esophagus, breast, colorectal, and pancreatic cancers. Notably, the Women's Health Initiative findings support our results, demonstrating that elevated CVH is associated with reduced mortality in lung and colorectal cancer, and while the association with breast cancer mortality trends is expected, it does not reach statistical significance [22]. In the GAZEL (GAZ et ELECTRICITE de France) study in France, an observable trend suggested a potential link between CVH and a decreased risk of prostate cancer, although the results did not attain statistical significance [23]. Contrastingly, our study found that each SD increase in the CVH score approached statistical significance in reducing the risk of prostate cancer mortality ($P=0.085$). This underscores the need for further prospective cohort studies to delve deeper into the relationship between CVH and the risk of prostate cancer.

Other studies have delved into the subscale of CVH regarding the risk of cancer subtypes. For instance, a diminished adherence to lifestyle recommendations has been correlated with an elevated risk of overall cancer and cancer subtypes [26]. Adopting the healthiest lifestyle has been found to reduce the risk of bladder, breast, colon, endometrial, esophagus, kidney, liver, lung, rectum, and stomach cancers by 17 to 58% [2], which were comparable to our results. Furthermore, we demonstrated a linear relationship between CVH and the risk

of mortality for eight cancer subtypes. This finding is particularly encouraging for individuals with low CVH scores, suggesting that, regardless of their current score, it is never too late to enhance their CVH.

In the stratified analyses, a noteworthy finding deserving of mention is that the associations between CVH and mortality from any cancer consistently strengthened among relatively young participants (< 65 vs. ≥ 65 years). Previous research has also suggested that the impact of traditional cardiovascular risk factors tends to diminish with age [39]. Hence, we hypothesize that maintaining high CVH scores in younger individuals may yield greater benefits compared to preserving scores in older individuals. Our stratified analyses further revealed that the protective associations of high CVH on mortality from any cancer were significant in both men and women. While sex appears to play a crucial role in cancer-specific survival, with female patients outperforming male patients in most cancers [40], our study indicates that for men, maintaining a healthier CVH score can effectively reduce the risk of cancer death and appears to be more significant than in women. The sex disparities influencing the connection between CVH and cancer death are reflected in various aspects of life, such as hormonal levels, behavioral psychology, economic preferences, emotional traits, and the immune system [41, 42]. Given the intricate relationship between sex and cancer, additional prospective studies are warranted to explore the gender-specific effects of CVH on cancer mortality.

Additionally, acknowledging the substantial impact of SES on optimizing and maintaining CVH [10], we conducted a stratified analysis of SES and CVH in relation to cancer mortality. Our results revealed that each SD increase of CVH score was associated with total cancer mortality in both high and low SES groups, with a particularly notable effect in the low SES population. Previous literature has indicated that cancer mortality in Europe is predominantly influenced by the levels and trends of cancer mortality rates in lower-education groups [43]. Consequently, for individuals in low SES populations, maintaining a high CVH score can significantly reduce cancer risk. This finding suggests that by improving CVH, it may be possible to reduce the gap in cancer mortality between low SES and high SES, thereby contributing to an improvement in the prognosis of cancer.

Cancer ranks among the leading causes of death, and our findings reveal significant associations between CVH and reduced risks of cancer mortality. Several potential mechanisms may explain the impact of poor CVH on increased cancer mortality risk. Unhealthy behaviors can induce cancer risk by influence immune function and inflammatory response, contributing to DNA damage [44], the generation of reactive oxygen species [45], and disruption of circadian rhythm [46, 47]. Moreover, unfavorable health factors may increase cancer risk through metabolic disruption. For instance, dysregulation of cholesterol homeostasis can promote cancer cells' resistance to iron-induced cell death, thereby enhancing tumorigenicity and metastatic capabilities [48]. Hyperinsulinemia, chronic inflammation, and certain medication are potential mechanisms underlying the association between diabetes, obesity, and cancer risk [49, 50]. While hypertension's specific mechanisms in relation to cancer risk remain unclear, existing research suggests a significant association between hypertension and malignant tumors [51]. Additionally, certain targeted drugs may lead to adverse reactions, including hypertension, potentially exacerbating the risk of cancer-related mortality [52].

In summary, achieving an optimal LE8 score encompasses maintaining robust immune function, minimizing inflammation, and promoting a healthy metabolic state, all of which contribute to reducing the risk of cancer-related mortality.

Our study is the first to investigate the correlation between CVH, genetic predisposition, and the mortality risk of eight cancer subtypes. The current analyses reveal that CVH demonstrates no interactions with PRS, and optimal CVH is associated with reduced mortality for eight specific cancers compared to poor CVH within the same PRS group. A previous study reported an additive interaction between genetic and lifestyle factors on overall cancer risk, observed in women but not in men [53]. The inconsistent findings might stem from variations in the definition and quantification of genetic predisposition and CVH. These results underscore the substantial potential benefits of adhering to optimal CVH, irrespective of PRS. Consequently, preventive policies should advocate for stricter adherence to optimal CVH.

#### Strengths and limitations

We believe our study possesses several strengths, which include, but are not limited to, the following aspects: firstly, we employed a large sample size and implemented a long-term tracking design within two well-established nationwide cohorts. This approach effectively mitigated selection bias and recall bias, thereby enhancing the reliability and consistency of our research findings. Secondly, the ample sample size enabled us to conduct joint and stratified analyses with sufficient statistical power. This allowed for a more comprehensive examination of the data. Furthermore, the incorporation of the new LE8 score to assess CVH, along with the genetic risk score for cancer, facilitated further exploration of the interaction and combined effects of CVH and genetic susceptibility

on cancer mortality. Finally, we employed rigorous statistical analysis methods and supplemented them with various sensitivity analyses to ensure the robustness and coherence of our results. However, it is important to acknowledge the existence of limitations within our study. First, these two cohort studies specifically represent adult populations in the US and the UK, respectively, which raises concerns about generalizing summary statistics to a broader global population. Second, these prospective cohort studies investigating the relationship between CVH and cancer mortality face the challenge of reverse causation, prompting the exclusion of individuals who died from cancer within the initial 2 years of the follow-up period. Despite the implementation of a robust correction scheme, the possibility of residual confounding remains, which could impact the accuracy of the study's findings. Furthermore, the absence of detailed cancer subtype and genetic data in NHANES limited our ability to assess the correlation between CVH scores and deaths from specific cancer subtypes in the US population. Lastly, utilizing data from hospital admissions and death registrations in the UK introduces the possibility of misclassification for cancer subtypes or less prevalent forms of cancer. Despite its substantial observational nature, the UK Biobank faces limitations in terms of the occurrence frequency for certain malignancies, thereby constraining the study's ability to uncover relationships with CVH scores.

## Conclusions

Ideal CVH demonstrated an association with reduced overall cancer mortality, particularly noteworthy in younger individuals and those with low SES. Adhering to CVH score exhibited a linear association with mortality for various cancers, including lung, bladder, liver, kidney, esophagus, breast, colorectal, and pancreatic cancer. The promotion of improving CVH based on LE8 guidelines is encouraged, due to its benefit effects demonstrated in individual with either high or low cancer genetic predispositions.

### Abbreviations

| | |
|---|---|
| CVD | Cardiovascular disease |
| CVH | Cardiovascular health |
| AHA | American Heart Association |
| LS7 | Life's Simple 7 |
| LE8 | Life's Essential 8 |
| US NHANES | United States National Health and Nutrition Examination Survey |
| UK | United Kingdom |
| NCHS | National Center for Health Statistics |
| BMI | Body mass index |
| HDL-C | High-density lipoprotein cholesterol |
| DASH | Dietary approaches to stop hypertension |
| HbA1c | Hemoglobin A1c |
| ICD-10 | International classification of disease, 10th revision |
| NHS | National Health Service |
| CCI | Charlson comorbidity index |
| SES | Socioeconomic status |
| PRS | Polygenic genetic risk score |
| SNP | Single nucleotide polymorphism |
| SD | Standard deviation |
| IQR | Interquartile range |
| HR | Hazard ratio |
| CI | Confidence interval |
| FDR | False discovery rate |
| MESA | Multi-Ethnic Study of Atherosclerosis |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03553-2.

Additional file 1: Table S1. Scoring criteria of diet in two cohorts according to the DASH-style diet score. Table S2. Definition of CVH metrics and scoring algorithm in two cohorts. Table S3. Cancer classification according to the ICD-10 in the UK Biobank. Table S4. Disease definitions used in two cohorts. Table S5. Diagnosis codes used for the Charlson comorbidities identification in the UK Biobank. Table S6. Sources and components of the polygenic risk score scores for the eight cancer types in the UK Biobank. Table S7. The percentages of participants with missing covariates involved in two cohorts. Table S8. Baseline characteristics of study population in two cohorts. Table S9. Baseline Characteristics of all participants with Life's Essential 8 data and those with and without prevalent cancer in two cohorts. Table S10. Baseline Characteristics According to cancer death in two cohorts. Table S11. Associations of individual CVH score with all cancer mortality in two cohorts. Table S12. Death risk of 8 cancer subtypes according to their respective PRS in the UK Biobank. Table S13. The joint association of PRS and CVH score with cancer subtype mortally in the UK Biobank. Table S14. Sensitivity analysis of the association of per SD increase in CVH score with all cancer deaths and 18 cancer deaths in the UK Biobank. Fig. S1. Association of CVH score with mortality from various cancers in the UK Biobank. Fig. S2. Associations of CVH score with overall and subtype cancer mortality by sex in the UK Biobank. Fig. S3. Associations of CVH score with overall and subtype cancer mortality by age in the UK Biobank. Fig. S4. Associations of CVH score with overall and subtype cancer mortality by socioeconomic status in the UK Biobank

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### Authors' contributions

LL and YH designed the study, collected and analyzed data, and wrote the manuscript. FL, XH, XZ, TS, TS, WL, and RL collected and reviewed data and contributed to data analysis. X-JZ and JC revised the manuscript and provided valuable suggestions for study design and data analysis. Z-GS, GW, and HL contributed equally, designed the project, edited the manuscript, and supervised the study. All authors read and approved the final manuscript.

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### Availability of data and materials

For the US NHANES study, the datasets generated and analyzed are publicly available at NHANES website: https://www.cdc.gov/nchs/nhanes/index.htm. For the UK Biobank study, the data are available at UK Biobank website: https://www.ukbiobank.ac.uk/, but restrictions apply to the availability of these data, which were used under license for the current study, and so are

not publicly available. Data are however available from the authors upon reasonable request and with permission of UK Biobank.

## Declarations

### Ethics approval and consent to participate

The US NHANES study received ethical approval from the NCHS' Research Ethics Review Board, and all participants provided written informed consent. Similarly, ethical approval for the UK Biobank research was granted by the North West Multicenter Research Ethical Committee, and written informed consent was obtained from all the participants during the baseline recruitment to the UK Biobank. This current study was specifically approved by the UK Biobank under application number 77195.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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