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Associations of genetic and non-genetic cardiovascular health metrics with coronary artery disease incidence in cancer survivors

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Associations of Genetic and Non-Genetic Cardiovascular Health Metrics with Coronary Artery Disease Incidence in Cancer Survivors

Running title: Coronary Artery Disease Risk among Cancer Survivors

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Abstract

Background Cardiovascular disease (CVD) is a leading threat to long-term health in cancer survivors. This study aimed to evaluate whether integrating genetic risk with the composite cardiovascular health metric, the Life Essential 8 (LE8) score, can improve primary prevention and guide personalized survivorship care in this population.

Methods We conducted a retrospective cohort study including 21,715 cancer survivors and 87,004 matched non-cancer controls from the UK Biobank. For each participant, a LE8 score, encompassing eight CVD-related factors (diet, physical activity, nicotine exposure, sleep, body mass index, blood pressure, blood glucose, and non-high-density lipoprotein cholesterol), and a polygenic risk score (PRS) for coronary artery disease (CAD) were calculated. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident risk of CAD across LE8 (or individual LE8 components) and PRS levels and to examine their potential interactions.

Results A higher LE8 score and a lower PRS were independently associated with reduced CAD risk in cancer survivors. Participants with a high LE8 score and low PRS had the lowest CAD risk (HR 0.22; 95% CI, 0.09 0.53) when compared with those with a low LE8 score and high PRS. Similar patterns were observed in matched controls who had a lower CAD incidence rate. Associations between optimal blood lipid levels (as defined in the LE8 score) seemed to be more pronounced in individuals with high PRS, although it did not reach statistical significance among cancer survivors (p for interaction with PRS = 0.14 and 0.011, respectively, in cancer survivors and matched controls). Subgroup analyses showed consistent associations between LE8 score and CAD risk in breast, prostate, colorectal, and malignant skin cancer survivors, but not in those with lymphoma or hematologic malignancies. Furthermore, the association between LE8 score and CAD risk was stronger 5–10 years after cancer diagnosis and among younger cancer survivors aged under 55 years.

Conclusions Both a higher LE8 score and lower PRS for CAD were independently associated with substantially reduced risk of incident CAD.

Keywords cancer survivors, coronary artery disease, Life's Essential 8 score, polygenic risk score

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Contributions to the literature

- Demonstrates that combining Life's Essential 8 (LE8) and polygenic risk score (PRS) identifies cancer survivors at highest risk of coronary artery disease (CAD) .
- Highlights opportunities for targeted CAD prevention in cancer survivors, as the impact of LE8 on heart disease risk differs by cancer type, age, and time since diagnosis.
- Suggests blood lipid management may be important for those with high genetic risk, supporting precision survivorship care.

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Background

Cancer is a major public health burden worldwide with an estimated 20 million new cases in 2022 [1]. Compared to the general population, cancer patients are more likely to develop and die of cardiovascular disease (CVD) due to exposure to cardiotoxic therapies, well-established CVD risk factors, and the significant psychological distress associated with a cancer diagnosis [2–7], and mortality from CVD might overtake mortality due to primary cancer among the long-term cancer survivors [6].

Like many other complex diseases, CVD is multifactorial and involves both genetic and non-genetic factors. Previous studies [8,9] have identified multiple non-genetic risk factors that can increase the likelihood of developing CVD. The American Heart Association's (AHA) Life's Essential 8 (LE8) score [10] considers the overall impact of multiple factors [diet, physical activity, smoking, sleep, blood lipids, body mass index (BMI), blood sugar, and blood pressure] on cardiovascular health (CVH), which is also related to a range of other health outcomes [11–14]. All factors incorporated in LE8 score are modifiable, such as BMI, blood pressure, non-high-density lipoprotein (non-HDL) cholesterol, current smoking, and diabetes, which makes early prevention possible. A recent study has shown that over 50% of incident CVD cases are attributable to these five risk factors mentioned above [15]. Studies also highlight the potential of polygenic risk scores (PRSs) that aggregate information from genetic variants associated with susceptibility to CVD, in improving CVD risk stratification in the general population for targeted prevention [11,16,17]. However, evidence on the relationship between these two kinds of factors among cancer survivors is limited [18,19], and whether the association varies according to cancer types is unclear.

Therefore, this study aimed to evaluate the individual and combined associations of PRS for coronary artery disease (CAD) and the composite LE8 score (or its individual components) with cardiovascular outcomes, as well as their potential interactions in cancer survivors and in subpopulations by main cancer types. Such insights may help identify survivors at high risk of developing CVD, thereby facilitating targeted prevention strategies and addressing the challenge of low adherence to preventive measures in this population [20,21].

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Methods

Study population

Data for analysis were extracted from the UK Biobank study, a population-based cohort study that recruited more than half a million adults (40-69 years) between 2006 and 2010 throughout the UK (England, Scotland, and Wales). Health, demographic, and anthropometric data were collected at baseline assessment. Moreover, biological samples (blood, saliva, and urine) were taken and stored. Follow-up of health-related outcomes was conducted through linkage to electronic health records. Further details of the UK Biobank study have been published elsewhere [22].

Flowchart of participants' inclusion and cancer-control matching

Among the participants with imputed genetic data (N = 487,197), we excluded those who had their consent withdrawn (N = 449), who were not white (N = 78,269) or had a history of CAD (prevalent CAD), stroke, or heart failure (N = 19,204) at baseline. White British participants were identified according to self-reported data (Field ID in UK Biobank: 21000) and results of principal component analysis of ancestry (Field ID in UK Biobank: 22006), and were exclusively included in the current study given that participants in the UK Biobank cohort are predominantly White British, and variants used for building the PRS here were identified in a genome-wide association study (GWAS) of individuals of European descent. History of CAD, stroke, or heart failure was identified using International Classification of Diseases (ICD) codes (CAD: ICD-10 I20-I25; ICD-9 410-414; stroke: ICD-10 I60, I61, I63 or I64; ICD-9 430, 431, 434, 436 and 437; heart failure ICD-10 I50; ICD-9 428). Missing values were then imputed using either replacement with the median values, replacement with the majority category for the variables with low missingness, or multiple imputations with chained equations for the non-genetic exposure and covariate variables that had relatively high missingness and were predictable (**Table S1**). One of the five imputed datasets was selected for the propensity score matching analysis below. As shown in **Table S2**, the distributions of imputed characteristics were highly consistent across all five imputed datasets, supporting the robustness of this approach.

Then we divided participants into two groups according to cancer history (ICD 10: C00-C97; ICD 9:140-208). We focused on adult cancer survivors who were aged > 18 years at the date of diagnosis and had a

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history of cancer diagnosed over one year (from the date at diagnosis to the date at enrollment). Four non-cancer controls were selected and matched to each cancer survivor using propensity score matching with a caliper width of 0.2 [23] based on the following predefined covariates: age, sex, education, Index of Multiple Deprivation, family history of heart disease or stroke, diet, physical activity, nicotine exposure, sleep, BMI, systolic blood pressure, history of diabetes, glycated hemoglobin, non-HDL cholesterol, and weighted PRS for CAD. Standardized mean differences of variables in the unmatched and matched populations are shown in **Figure S1**. One cancer survivor was not matched and thus was excluded from the study. The flowchart for inclusion of study participants is presented in **Figure 1**.

Derivation of the polygenic risk score for CAD

DNA was extracted from blood samples and genotyped using the UK BiLEVE Axiom (~50,000 participants) and the UK Biobank Axiom (~450,000 participants) arrays. These two arrays share over 95% content. Phasing was conducted using SHAPEIT3, and imputation was done using IMPUTE2 with merged UK10K and 1000 Genomes Phase 3 reference panels or Haplotype Reference Consortium (HRC) panel as reference, which supplies missing information about genetic variants that could not be directly genotyped with DNA microarrays. Details for genome sequencing, quality control, and imputation are provided elsewhere [22].

The PRS in the current analysis integrated information from 240 of 241 genetic variants (**Table S3;** rs582384 was triallelic and thus excluded) that were related to CAD risk and identified in a recent GWAS.[24] The PRS was calculated by summing the product of the number of risk alleles and their effect sizes (log odds ratio of each risk variant) that were obtained from the GWAS, and was categorized into three groups (low, medium, and high) according to tertiles of PRS in the whole study population.

Assessment of the LE8 score

The LE8 score was built based on eight metrics: diet, physical activity, nicotine exposure, sleep, BMI, blood pressure, blood glucose, and non-HDL cholesterol [10]. Following the AHA scoring algorithm, each metric is rated on a scale from 0 to 100 points. The composite LE8 score, ranging from 0 to 100, was calculated as the average of all eight metrics. In the UK Biobank, the diet metric was modified following the approach outlined in a previously published paper [25] (**Table S4**). Based on AHA guidelines, LE8 scores were classified as follows: 80–100 for high cardiovascular health (CVH), 50–79 for moderate CVH, and 0–49 for low CVH. Additional details on the coding procedures and the definitions of LE8 components

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can be found in **Table S5**. We also categorized each component of the LE8 score into binary variables (100 points vs. other points). For example, for blood lipids, we created a binary variable named "optimal blood lipids", which was defined as "non-HDL<130 mg/dL and without blood lipids lowering medications" and scored 100 points according to LE8 score's scoring strategies. Detailed categories of other LE8 factors are presented in **Table 1**.

Follow-up and outcome ascertainment

The outcome of this study was incident CAD events, a well-validated outcome associated with the PRS for CAD. The outcome was obtained through linkage to hospital admission using the ICD-10 codes: CAD (ICD10: I20-25). Participants were followed until the first episode of outcome of interest, death, or the end of follow-up. The censoring date was 30 September 2021 for England and Wales and 31 October 2021 for Scotland.

Statistical analysis

In the complete dataset, baseline characteristics of the participants were summarized as frequencies and percentages for categorical variables and as median values with interquartile range (IQR) for skewed continuous variables. Difference between cancer survivors and non-cancer controls were tested by using Chi-square tests for categorical variables and Wilcoxon rank-sum test for not-normally distributed variables.

We applied Cox proportional hazard models to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs) of the associations of PRS and LE8 score with CAD risk for cancer survivors and their matched controls. The basic models were adjusted for age at baseline and sex. Then we additionally included education, Index of Multiple Deprivation, family history of heart disease or stroke, and history of chemoradiotherapy (only for cancer survivors) in models. Detailed categories of each covariate are shown in **Table 1.** The proportional hazards assumption was evaluated using Schoenfeld residual plots for each covariate, and no significant violations were observed.

Interactions between categorical PRS and the LE8 metric were assessed by including their multiplicative interaction terms in the models along with the main effects. We additionally fitted a Cox model including a three-way interaction term among PRS, LE8, and cancer status in the combined dataset to assess whether the PRS–LE8 association differed by cancer status. Joint associations of LE8 score and PRS were also assessed using the combination of low CVH and high PRS or moderate CVH and medium PRS as the

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reference group. We utilized two reference groups to serve complementary purposes: the lowest-risk group to quantify excess CAD risk relative to the optimal profile, and the intermediate PRS–LE8 category to better illustrate the risk gradient across the full spectrum of combinations and to provide more stable statistical estimates, given the larger sample size in the middle category. Similar analyses were conducted to assess the relationship between individual components of the LE8 score, PRS levels, and CAD risk. Stratified analyses by PRS levels were done if the interaction between LE8 score or any components of LE8 score and PRS was statistically significant.

To test the robustness and potential variations of the main results among cancer survivors, we also examined the patterns of hazard ratios by main cancer types (breast cancer, colorectal cancer, malignant skin cancer, prostate cancer, and lymphatic or hematopoietic cancer) and by latency (time since cancer diagnosis to enrollment: 1 to <5 years/5 to <10 years/≥10 years, and age at cancer diagnosis: <55 years/ ≥55 years). Additionally, we examined interactions by introducing multiplicative terms of CVH and sex into the model. In sensitivity analysis, we conducted the primary analysis in cancer survivors based on the complete cases to evaluate the potential impact of missing data on the results.

All the analyses were performed using R software (version 4.2.1). Statistical tests were two-sided, and the significance threshold was set at 0.05 for p values.

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Results

Baseline Characteristics of Participants

This study included a total of 21,751 cancer survivors and 87,004 matched non-cancer controls from the UK Biobank cohort. The median age at recruitment was approximately 62 years (IQR 57–66), and the proportion of male participants was 38.7% in cancer survivors. Most baseline characteristics, including the distribution of LE8 score, were comparable between the two groups (**Table 1**). Among cancer survivors, the median LE8 score was 62.6 (IQR 55.8, 68.9). The prevalence of low, moderate, and high CVH was 10.8%, 86.9%, and 2.3%. Cancer survivors had a lower prevalence of optimal sleep duration (67.5% vs. 69.3%, p value <0.0001) compared to non-cancer controls. The prevalence of optimal LE8 components was lowest for blood lipids (10.6%), followed by BMI <25 kg/m^2 (34.2%) and blood pressure (38.0%) in cancer survivors.

Associations of LE8 Score and PRS with CAD Risk

Both higher LE8 scores and lower PRS levels were associated with reduced risk of CAD in cancer survivors and matched controls (**Table 2**). Among cancer survivors, the incidence rates (IRs) of CAD per 10,000 person-years were 125.9, 80.9, and 37.2 for those with low, moderate, and high CVH, respectively. Compared to individuals with low CVH, those with moderate and high CVH had reduced CAD risks with HRs (95% CIs) of 0.67 (0.59, 0.76) and 0.43 (0.28, 0.67), respectively.

Similarly, incidence rates of CAD increased as PRS levels increased. Adjusted HRs (95% CIs) for medium and low PRS compared to high PRS were 0.72 (0.65, 0.80) and 0.60 (0.54, 0.67), respectively. A similar pattern of reduced CAD risk across CVH and PRS categories was observed in the control group, though the incidence rate of CAD was generally lower than that in cancer survivors. There was no statistically significant interaction between PRS and LE8 scores with respect to CAD risk in both groups (all p values for interaction > 0.05). The three-way interaction was also not statistically significant (p value = 0.79), suggesting that the association pattern was generally consistent between the cancer survivor group and the non-cancer control group. Similar results were obtained based on the complete dataset for cancer survivors (**Table S6).**

Joint Associations of LE8 score and PRS with CAD Risk

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Among cancer survivors, the highest CAD risk was observed in those with high PRS and low CVH (HR 2.00, 95% CI 1.65 2.42), and the lowest risk was seen in those with low PRS and high CVH (HR 0.43, 95% CI 0.18 1.04), when compared to the uniform group with medium PRS and moderate CVH (**Table S7**). Similar patterns were observed in the control group. Using participants with high PRS and low CVH as the reference, we observed a strong CAD risk reduction by joint consideration of PRS and LE8 score (Low PRS-high CVH vs. reference: HR 0.22, 95% CI 0.09 0.53; **Figure 2**).

In subgroup analyses by main cancer types, we observed a strong association between LE8 score and cardiovascular outcomes among cancer survivors except those with lymphoma or other hematologic malignancies (**Table 3**). A higher PRS was associated with an increased risk of CAD regardless of cancer types. A higher LE8 score and a lower PRS was consistently associated with reduced CAD risk across various time intervals from diagnosis to enrollment (**Table 4**), while the associations of LE8 with CAD risk were more pronounced in 5-10 years after cancer diagnosis. Notably, the risk reduction seemed to be more pronounced in younger survivors, where high CVH was strongly associated with reduced CAD risk with an HR (95% CI) of 0.27 (0.19, 0.38) (**Table 5**), and little variation of PRS-related associations by age at cancer diagnosis was observed.

Associations of Individual Components of LE8 score with CAD Risk

Among cancer survivors, adherence to all individual components of the LE8 score (except for high diet score and optimal blood pressure) was associated with lower CAD risk (**Figure 3** and **Table S8**). PRS was independently associated with CAD risk, with no evidence of significant interactions between genetic risk and lifestyle factors. A similar trend was observed among non-cancer controls, but we noticed that the association between optimal blood lipid levels and CAD risk varied significantly across PRS levels (p for interaction with PRS = 0.011). The association between optimal blood lipid levels and CAD risk also seemed to be more pronounced among cancer survivors with high PRS, although the interaction between PRS and optimal blood lipid levels did not reach statistical significance (p for interaction with PRS = 0.14). Among participants with high PRS, optimal blood lipid levels were strongly associated with reduced CAD risk by 39% (HR 0.61, 95% CI 0.44 0.86) in cancer survivors and 29% (HR 0.71, 95% CI 0.60 0.84) in controls (**Table S9**).

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Discussion

Using data from the large UK cohort, we observed that LE8 score and PRS for CAD, major risk factors of CVD, were independently associated with new-onset CAD among cancer patients and their matched controls. The absence of a statistically significant multiplicative interaction between PRS and LE8 suggests that the protective association of higher LE8 with CAD risk is consistent across levels of genetic predisposition. These findings also highlight the complementary value of considering both genetic and non-genetic cardiovascular health factors when evaluating CAD risk in cancer survivors. Overweight/obesity, blood lipids, and blood pressure are the major metrics that resulted in poor CVH for cancer survivors in the UK Biobank. Moreover, the association of CAD risk associated with blood lipids in the high PRS group seemed to be stronger than in the low and medium PRS groups, although it was not statistically significant in the cancer survivor group. These findings may help target precision strategies for the prevention and management of CAD among cancer survivors.

The study by Peng et al. [19] employed PRS for CVD with a healthy lifestyle score (built based on BMI < 25 kg/m^2, non-smoking, non-excessive alcohol intake, being physically active, and having healthy dietary habits) for risk stratification of CVD among breast cancer survivors. Only BMI and smoking were associated with CAD risk in their study. With increased lifestyle scores, the risk of CVD and other subtypes of CVD including CAD changed a little, which indicated that modification of lifestyle factors except for smoking and obesity might have slight improvement on cardiovascular health among persons with past cancer in their study. Other cardiometaolic factors like high blood lipids that were prevalent and well associated with CVD risk might also be the main targets for CAD prevention and should be incorporated into a composite metric for cardiovascular health assessment among cancer survivors.

A higher LE8 score, as a measure of cardiovascular health aggregating major CVD risk factors, was independently linked to a lower all-cause and cardiovascular mortality in US cancer survivors [26,27]. Consistent with their results, a high CVH defined by a high LE8 score was associated with a lower risk of CAD in our study. The difference is that we also incorporated the genetic factors in the analysis, which were independently and strongly associated with CAD risk. However, it should be noted that the consistent relative risk of CVH categories defined LE8 score across different PRS levels on a multiplicative

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316 scale can be translated into a greater absolute risk reduction for individuals with higher PRS levels, given
317 their higher baseline risk. Therefore, individuals with high PRS levels for CAD may benefit most from
318 maintaining optimal cardiovascular health as defined by the LE8 criteria. Our results offer valuable insights
319 for enhancing CAD risk prediction through the joint assessment of PRS and LE8 scores among cancer
320 survivors.

321 The incidence of cardiovascular disease was highest among cancer survivors 5–10 years after diagnosis,
322 likely due to declining cancer-related mortality and delayed cardiotoxic effects of treatment. During this
323 period, the association between LE8 score and CAD risk was strongest, indicating a critical window for
324 cardiovascular risk assessment and intervention. A similar pattern was observed in a recent study that
325 characterized heart disease mortality within 10 years after cancer diagnosis [28]. In the subgroup analysis
326 by age at diagnosis, the magnitude of associations between LE8 score and CAD risk seemed to be greater
327 among cancer survivors diagnosed < 55 years. Similar results were also observed in studies based on the
328 general population [11,14]. The other differences between our study and the study by Lin et al [14] lie in
329 the outcomes and the PRS used, which in their study were cancer mortality and cancer risk-related PRS.
330 The age-specific associations observed in the current study could be due to the age-dependent associations
331 of risk factors with CVD risk, which have been seen in the general population. For example, the HRs of
332 obesity, hypertension, and diabetes with CVD events decreased with age category [9]. Integrating the age-
333 and PRS-specific risk profiles shown in this study might contribute to more targeted CAD prevention;
334 however, this needs to be explored in future studies on a larger-scale population.

335 Evidence regarding the interplay between individual components of LE8 score and PRS was limited. A
336 recent study explored the potential of PRS for CAD to predict CAD events among breast cancer survivors
337 [18]. They did not incorporate dyslipidemia, high blood pressure, lipid-lowering medications, diabetes, and
338 family history of CVD in the model due to the unavailability of data. Consistent with their findings, we did
339 not find an interaction of PRS with BMI and smoking in survivors with any cancer. We observed a stronger
340 association of blood lipids with CVD risk among noncancer participants with high PRS, but it did not reach
341 statistical significance among cancer survivors. Our results support and extend their findings in well-
342 adjusted models, which provides evidence that both PRS and modifiable CVD risk factors incorporated in
343 the LE8 score could be helpful for risk stratification among cancer survivors.

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The observed interaction between PRS for CAD and optimal blood lipids on CAD risk in non-cancer controls suggests that variants incorporated in PRS, individually or combined, might influence CVD risk via perturbations of lipid metabolism. This is well supported by the genetic functional analysis, for example, several variants associated with CAD risk were located in the gene LPA, which is involved in processes like plasma lipoprotein assembly, remodeling, clearance, and cholesterol metabolism [29]. Besides variants in autosomes, a recent study also identified a locus located in the X chromosome reduced CAD risk through strong lipid-lowering effects among 65,322 multi-ancestry participants, which was well replicated in European participants [30]. The null significant interactions between PRS categories and other factors and robust associations of PRS with CAD risk in multivariable models indicate there might be little overlap in the molecular pathways of CVD development between PRS and risk factors such as smoking and BMI.

The major strength of our study is that it was a large population-based study of cancer survivors with detailed information on both genetic and non-genetic factors that could be incorporated into the models for comprehensive analyses. To our knowledge, we, for the first time, well characterized the relationship between LE8 score, individual components of LE8 score, and PRS for CAD with CAD risk among cancer survivors.

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However, this study also has some limitations that require careful consideration. First, due to the nature of observational study, recall bias, especially for the self-reported factors obtained from the baseline questionnaire, cannot be avoided. Besides, changes in these factors were not accounted for in our study. However, this impact might be relatively small as our analysis was focused on cancer survivors, who were less likely to change their health behaviors than newly diagnosed patients or patients under treatment. Second, although we have considered possible covariates, residual confoundings cannot be removed due to imperfectly measured or unmeasured confounding factors, especially in subgroup analysis where cancer-specific risk factors should have been considered.Third, our analysis used a PRS derived from populations of European ancestry and performed analyses in a White British population, and thus future studies on populations of different ancestries are warranted to explore the associations of interest in our study and yield results based on their distinct PRS and risk factors profiles. Fourth, the lack of detailed treatment data and specific drugs or doses received limit our study for further analyses and could have biased the results since these factors have been shown to be related to CVD risk [31], especially for those short-term cancer

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survivors. Fifth, survival bias may have influenced the findings, leading to an underestimation of the true burden of cardiovascular risk among cancer survivors.

Conclusions

In conclusion, this study provides compelling evidence that both the LE8 score and PRS for CAD are independently associated with the risk of incident CAD among cancer survivors and matched controls. These findings underscore the critical role of maintaining optimal cardiovascular health as defined by the LE8 score, regardless of background genetic predisposition to CAD. With no statistically significant interaction observed between LE8 and PRS on a multiplicative scale, individuals with a higher genetic risk may have a greater absolute benefit from adherence to LE8-based cardiovascular health practices. Further studies are warranted to explore the individualized approaches according to genetic risk in subgroups by broad age categories and cancer types for effective prevention of CAD, and in newly diagnosed cancer patients for whom adverse CVD events might be minimized by appropriate modification of CVD-related risk factors.

List of Abbreviations

AHA, American Heart Association; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; CVH, cardiovascular health; GWAS, genome-wide association study; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; LE8, Life's Essential 8; PRS, polygenic risk score.

Declarations

Ethics approval and consent to participate

Data for analysis were extracted from the UK Biobank study that obtained approval as a Research Tissue Bank (RTB) from the North West Multicenter Research Ethics Committee (renewed approval in 2021: 21/NW/0157). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants in the UK Biobank study provided informed consent.

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Consent for publication

Not applicable.

Availability of data and materials

This research was conducted using the UK Biobank resource under access application 66591. Data used for analysis can be obtained by application for the UK Biobank through this website: http://www.ukbiobank.ac.uk/register-apply.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

H.Z.: Formal analysis, Methodology, Writing-review & editing.

X.L.: Formal analysis, Methodology, Writing-review & editing.

Y.T.: Writing-review & editing.

X.H.: Formal analysis, Methodology, Writing-review & editing.

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F.R.: Data curation, Writing-review & editing.

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Figure legends

Figure 1. Flow diagram of including eligible study participants from the UK Biobank.
Abbreviation: CVD, cardiovascular disease.

Figure 2. Joint associations of Life's Essential 8 score and PRS with CAD risk in cancer survivors and non-cancer matched controls
Abbreviations: CAD, coronary artery disease; CVH, cardiovascular health; CI, confidence interval; HR, hazard ratio; PRS, polygenic risk score; Ref., reference.

Figure 3. Associations of individual components of Life's Essential 8 score and PRS with CAD risk in cancer survivors and non-cancer matched controls
Abbreviations: BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; PRS, polygenic risk score.

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Table 1. Characteristics of cancer survivors and their matched controls

Characteristics	**Cancer survivors, N (%)**	**Non-cancer matched controls, N (%)**	**P**
No. of participants	21,751	87,004	
Age at recruitment (years), Median (IQR)	62 (57, 66)	62 (57, 66)	0.52
Sex			0.35
Female	13,339 (61.3)	53,052 (61.0)	
Male	8,412 (38.7)	33,952 (39.0)	
Education[a]			0.86
Low	7,346 (33.8)	29,526 (33.9)	
Intermediate	8,143 (37.4)	32,407 (37.2)	
High	6,262 (28.8)	25,071 (28.8)	
Index of Multiple Deprivation (quintile)[b]			0.95
1 (least deprived)	5,072 (23.3)	20,180 (23.2)	
2	4,335 (19.9)	17,489 (20.1)	
3	4,240 (19.5)	16,998 (19.5)	
4	4,113 (18.9)	16,514 (19.0)	
5 (most deprived)	3,991 (18.3)	15,823 (18.2)	
Family history of heart disease or stroke	13,066 (60.0)	52,495 (60.3)	0.48
High diet score[c]	11,322 (52.1)	45,285 (52.0)	0.99
Physically active[d]	13,806 (63.5)	55,654 (64.0)	0.18
Smoking			0.90
Current	11,649 (53.6)	46,535 (53.5)	
Former	8,746 (40.2)	34,973 (40.2)	
Never	1,356 (6.2)	5,496 (6.3)	
Sleep health			
Sleep duration, Median (IQR)	7 (7-8)	7 (7-8)	0.97
Good sleep (7-<9 h/night)	14,676 (67.5)	60,330 (69.3)	<0.0001
BMI (kg/m^2)			0.16
≥30	4,998 (23.0)	19,742 (22.7)	
25-<30	9,307 (42.8)	37,855 (43.5)	
<25	7,446 (34.2)	29,407 (33.8)	
Blood pressure			
SBP (mm Hg), Median (IQR)	141 (128, 156)	141 (129, 156)	0.32
DBP (mm Hg), Median (IQR)	82 (75, 89)	82 (75, 89)	0.97
Optimal blood pressure[e]	8,276 (38.0)	33,402 (38.4)	0.36
Blood glucose			
HbA1c (%), Median (IQR)	5.4 (5.2, 5.6)	5.4 (5.2, 5.6)	0.20
Optimal blood glucose[f]	17,072 (78.5)	68,534 (78.8)	0.37
Blood lipids			
Non-HDL cholesterol, Median (IQR)	165.3 (137.6, 194.5)	165.4 (138.6, 194.1)	0.41
Optimal blood lipids[g]	2,307 (10.6)	8,340 (9.6)	<0.0001
Life's Essential 8 (LE8) score			
Median (IQR)	62.6 (55.8, 68.9)	62.6 (55.8, 68.9)	0.16
Low CVH (<50)	2,350 (10.8)	9,011 (10.4)	0.15
Moderate CVH (50-<80)	18,896 (86.9)	76,000 (87.4)	
High CVH (80-100)	505 (2.3)	1993 (2.3)	
Polygenic risk score[h]			
Median (IQR)	12.2 (11.9, 12.5)	12.2 (11.9, 12.5)	0.59
High	7,236 (33.3)	29,013 (33.3)	0.18
Medium	7,159 (32.9)	29,095 (33.4)	
Low	7,356 (33.8)	28,896 (33.2)	

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[a]Education was coded into three categories: high (college or university degree), intermediate (A/AS levels or equivalent, O levels/CSEs or equivalent), and low (none of the aforementioned).
[b]IMDs are the property of an area and of the average characteristics of the people living in that area. This index was calculated separately for England, Scotland, and Wales, while the components that make up the index of multiple deprivation are similar. We categorized IMDs according to the area-specific quintile distribution of IMDs. Quintile 1 (Q1) represents the least socioeconomically deprived areas, and Q5 the most.
[c]Originial diet score ≥ 5 points (median of the diet score in the cancer survivors and non-cancer controls).
[d]≥150 minutes of moderate to vigorous physical activity per week.
[e]SBP<120 mmHg/DBP<80mmHg and without bloop pressure lowering medications.
[f]HbA1c<5.7% and without a diabetes diagnosis.
[g]Non-HDL<130 mg/dL and without blood lipids lowering medications.
[h]Polygenic risk score was categorized according to tertiles of polygenic risk score among the whole study population; low: first tertile of PRS; medium: second tertile of PRS, and high: third tertile of PRS.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CVH, cardiovascular health; DBP, diastolic blood pressure; IQR, interquartile range; Non-HDL cholesterol, non-high-density lipoprotein (non-HDL) cholesterol; SBP, systolic blood pressure.

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Table 2. Associations of Life's Essential 8 (LE8) score and PRS with CAD risk among cancer survivors and their matched controls

Factors	**Levels**	**IR (per 10,000 person-years)**	**HR (95% CI)[a]**	**HR (95% CI)[b]**
Cancer survivors (N = 21,751)				
LE8 Score	Low CVH	125.9	Ref. (1.00)	Ref. (1.00)
	Moderate CVH	80.9	0.62 (0.55, 0.70)	0.67 (0.59, 0.76)
	High CVH	37.2	0.37 (0.24, 0.57)	0.43 (0.28, 0.67)
PRS	High	107.6	Ref. (1.00)	Ref. (1.00)
	Medium	79.9	0.71 (0.64, 0.79)	0.72 (0.65, 0.80)
	Low	66.8	0.59 (0.53, 0.66)	0.60 (0.54, 0.67)
P value for interaction[c] between LE8 score and PRS = 0.68				
Non-cancer matched controls (N = 87,004)				
LE8 Score	Low CVH	116.9	Ref. (1.00)	Ref. (1.00)
	Moderate CVH	72.0	0.62 (0.58, 0.66)	0.65 (0.61, 0.69)
	High CVH	29.1	0.32 (0.25, 0.41)	0.37 (0.29, 0.47)
PRS	High	98.2	Ref. (1.00)	Ref. (1.00)
	Medium	73.0	0.73 (0.69, 0.77)	0.74 (0.70, 0.78)
	Low	55.8	0.55 (0.52, 0.58)	0.56 (0.53, 0.59)
P value for interaction[c] between LE8 score and PRS = 0.86				
P value for the three-way interaction[c] among PRS, LE8, and cancer status = 0.79				

[a]Adjusted for age and sex.

[b]Additionally adjusted for education, index of multiple deprivation, family history of heart disease or stroke, history of chemoradiotherapy (for cancer survivors), and mutual adjustment for the other factors listed in the Table.

[c]Interaction was tested by adding multiplicative terms of LE8 score and PRS (categorical) in the models with all covariates in subgroup by cancer status, or was tested by adding multiplicative terms of LE8 score , PRS (categorical) and cancer status in the combined dataset.

Abbreviations: CAD, coronary artery disease; CVH, cardiovascular health; CI, confidence interval; HR, hazard ratio; IR, incidence rate; PRS, polygenic risk score; Ref., reference.

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Table 3. Associations of Life's Essential 8 score (LE8) and PRS with CAD risk among specific cancer survivors

Factor	Categories	HR (95% CI)[a]	HR (95% CI)[a]
		Breast cancer (N = 6,306)	**Matched controls (N =24,784)**
LE8	Low CVH	1.00 (Ref)	1.00 (Ref)
	Moderate	0.55 (0.37, 0.84)	0.53 (0.43, 0.65)
	High CVH	0.29 (0.18, 0.47)	0.29 (0.23, 0.36)
PRS	High	1.00 (Ref)	1.00 (Ref)
	Medium	0.95 (0.76, 1.20)	0.74 (0.67, 0.81)
	Low	0.70 (0.54, 0.89)	0.58 (0.53, 0.65)
		Prostate cancer (N = 1,924)	**Matched controls (N = 7,696)**
LE8	Low CVH	1.00 (Ref)	1.00 (Ref)
	Moderate	0.38 (0.21, 0.69)	0.54 (0.39, 0.75)
	High CVH	0.28 (0.14, 0.54)	0.34 (0.23, 0.50)
PRS	High	1.00 (Ref)	1.00 (Ref)
	Medium	0.72 (0.54, 0.96)	0.73 (0.62, 0.87)
	Low	0.73 (0.55, 0.97)	0.58 (0.48, 0.69)
		Colorectal cancer (N = 1,570)	**Matched controls (N = 6,270)**
LE8	Low CVH	1.00 (Ref)	1.00 (Ref)
	Moderate	0.74 (0.38, 1.46)	0.77 (0.49, 1.20)
	High CVH	0.19 (0.075, 0.48)	0.51 (0.31, 0.83)
PRS	High	1.00 (Ref)	1.00 (Ref)
	Medium	0.63 (0.44, 0.89)	0.76 (0.62, 0.91)
	Low	0.61 (0.43, 0.87)	0.60 (0.49, 0.74)
		Malignant skin cancer (N = 1,476)	**Matched controls (N = 5,884)**
LE8	Low CVH	1.00 (Ref)	1.00 (Ref)
	Moderate	0.31 (0.16, 0.61)	0.46 (0.32, 0.68)
	High CVH	0.16 (0.07, 0.37)	0.28 (0.18, 0.44)
PRS	High	1.00 (Ref)	1.00 (Ref)
	Medium	0.53 (0.35, 0.82)	0.74 (0.60, 0.91)
	Low	0.56 (0.36, 0.86)	0.47 (0.37, 0.60)
		Lymphoma or other hematologic malignancies (N = 1,170)	**Matched controls (N = 4,650)**
LE8	Low CVH	1.00 (Ref)	1.00 (Ref)
	Moderate	0.71 (0.37, 1.37)	0.62 (0.38, 1.01)
	High CVH	0.62 (0.30, 1.29)	0.32 (0.18, 0.57)
PRS	High	1.00 (Ref)	1.00 (Ref)
	Medium	0.60 (0.43, 0.85)	0.64 (0.51, 0.81)
	Low	0.41 (0.28, 0.60)	0.51 (0.40, 0.66)

[a]Adjusted for age, sex (for colorectal cancer and skin cancer survivors), education, index of multiple deprivation, family history of heart disease or stroke, history of chemoradiotherapy (for cancer survivors).

Abbreviations: CAD, coronary artery disease; CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio; PRS, polygenic risk score; Ref., reference.

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Table 4. Associations of Life's Essential 8 (LE8) score and PRS with CAD risk among cancer survivors according to time since diagnosis to baseline

Factors	Levels	IR (per 10,000 person-years)	HR (95% CI)[a]
≤5 years			
LE8 Score	Low CVH	148.8	1.00 (Ref.)
	Moderate CVH	94.6	0.62 (0.45, 0.85)
	High CVH	46.6	0.40 (0.28, 0.57)
PRS	High	105.5	1.00 (Ref.)
	Medium	76.3	0.70 (0.59, 0.82)
	Low	74.6	0.68 (0.58, 0.80)
>5-10 years			
LE8 Score	Low CVH	176.9	1.00 (Ref.)
	Moderate CVH	89.0	0.49 (0.45, 0.70)
	High CVH	40.6	0.28 (0.19, 0.42)
PRS	High	105.7	1.00 (Ref.)
	Medium	78.4	0.72 (0.60, 0.86)
	Low	57.1	0.52 (0.43, 0.63)
>10 years			
LE8 Score	Low CVH	156.9	1.00 (Ref.)
	Moderate CVH	99.8	0.62 (0.41, 0.95)
	High CVH	48.0	0.35 (0.22, 0.57)
PRS	High	113.4	1.00 (Ref.)
	Medium	87.8	0.76 (0.62, 0.92)
	Low	67.1	0.60 (0.49, 0.74)

[a]Adjusted for age, sex, education, index of multiple deprivation, family history of heart disease or stroke, history of chemoradiotherapy, and mutual adjustment for the other factors listed in the Table.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio; IR, incidence rate; PRS, polygenic risk score; Ref., reference.

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Table 5. Associations of Life's Essential 8 (LE8) score and PRS with CAD risk among cancer survivors by age at diagnosis

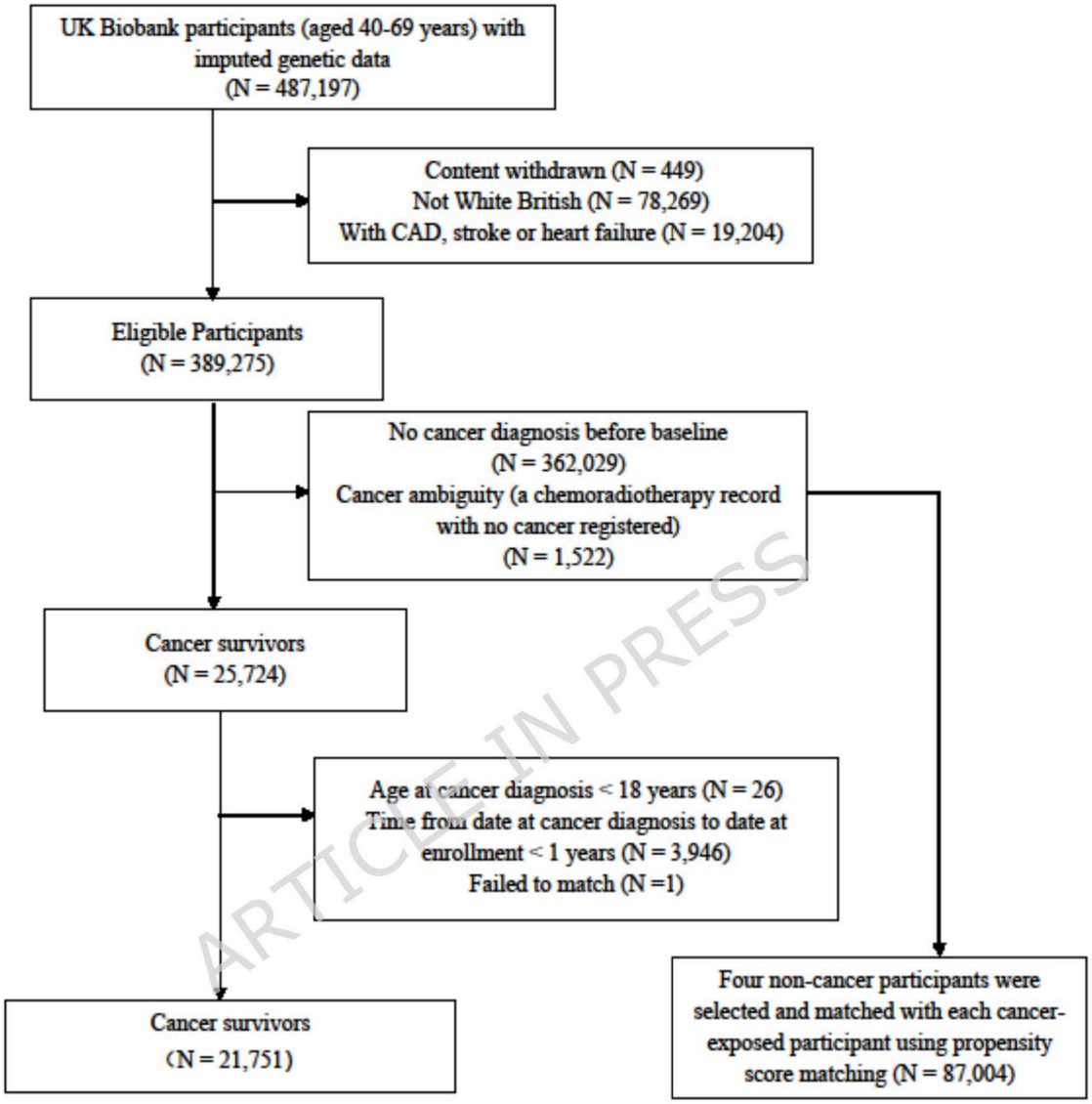
Factors	Levels	IR (per 10,000 person-years)	HR (95% CI)[a]
Age at cancer diagnosis: <55 years			
LE8 Score	Low CVH	145.1	1.00 (Ref.)
	Moderate CVH	71.7	0.51 (0.39, 0.68)
	High CVH	28.7	0.27 (0.19, 0.38)
PRS	High	82.6	1.00 (Ref.)
	Medium	59.0	0.70 (0.60, 0.82)
	Low	46.2	0.56 (0.47, 0.66)
Age at cancer diagnosis: ≥55 years			
LE8 Score	Low CVH	178.1	1.00 (Ref.)
	Moderate CVH	118.6	0.65 (0.49, 0.87)
	High CVH	70.8	0.43 (0.31, 0.60)
PRS	High	139.0	1.00 (Ref.)
	Medium	104.0	0.74 (0.64, 0.84)
	Low	91.1	0.64 (0.56, 0.74)

[a]Adjusted for age, sex, education, index of multiple deprivation, family history of heart disease or stroke, history of chemoradiotherapy, and mutual adjustment for the other factors listed in the Table.

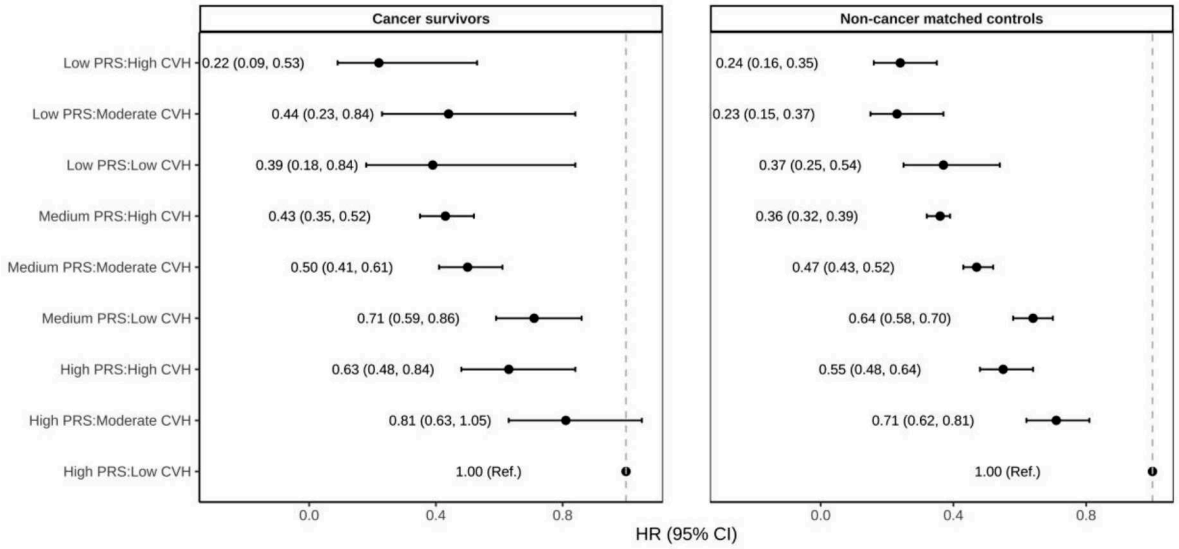
Abbreviations: CAD, coronary artery disease; CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio; IR, incidence rate; PRS, polygenic risk score; Ref., reference.

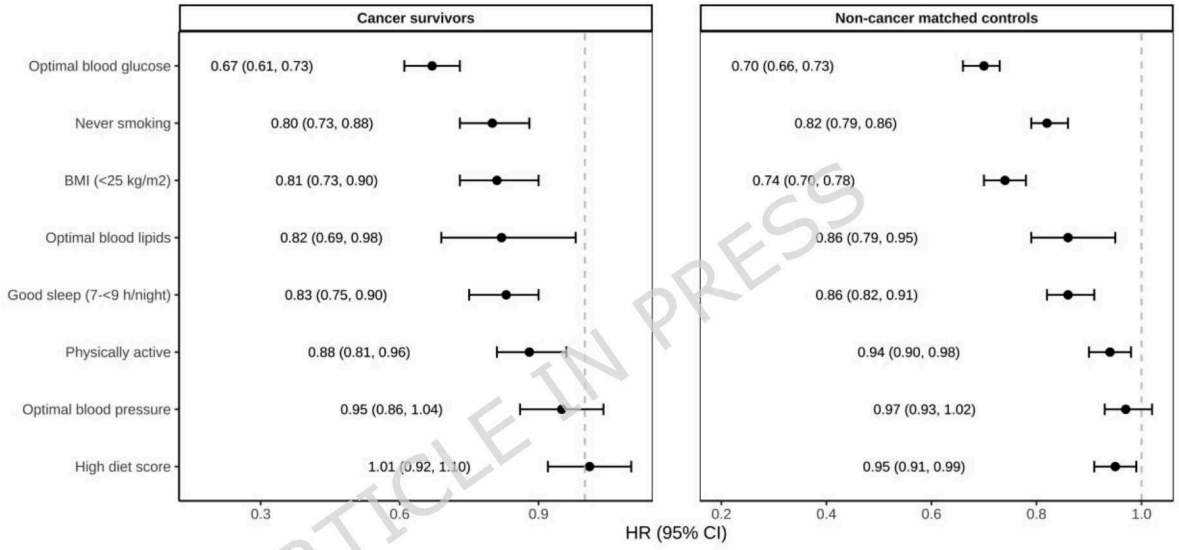
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