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# Life's Essential 8, genetic susceptibility, and risk of degenerative valvular heart disease

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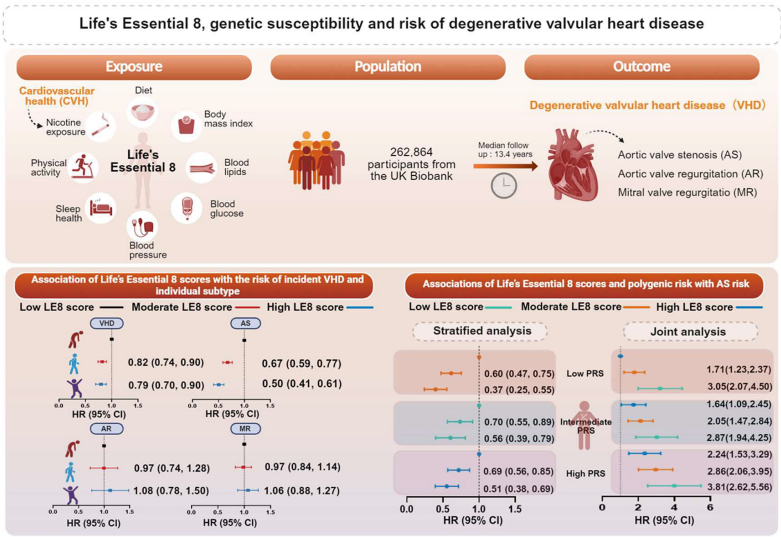
## Graphical abstract




## Abstract

**Background:** Adherence to high cardiovascular health (CVH) is effective for preventing atherosclerotic cardiovascular disease, its impact on degenerative valvular heart disease (VHD) remains poorly understood. We aimed to investigate the associations of CVH status, reflected by Life's Essential 8 (LE8), with incident VHD, and the potential modification of genetic susceptibility.

**Methods:** A total of 262,864 participants without VHD at baseline were included from the UK Biobank. CVH status was categorized into 3 groups according to LE8 scores: low (0–49), moderate (50–79), and high (80–100). Genetic susceptibility to aortic valve stenosis (AS) was assessed using a polygenic risk score (PRS) and categorized into tertiles. Fine–Gray competing risk models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), and multiplicative and additive interactions between CVH and PRS were evaluated.

**Results:** The mean (SD) age was 56.0 (8.1) years, and 51.1% of participants were female. During a mean follow-up of 13.4 years, 6371 incident VHD cases were recorded, including 2754 AS, 1013 aortic valve regurgitation, and 3089 mitral valve regurgitation. Compared with individuals with low LE8 scores, the multivariable-adjusted HRs of incident VHD risk for those with moderate and high LE8 scores were 0.82 (95% CI: 0.74–0.90) and 0.79 (95% CI: 0.70–0.90), respectively. Notably, optimal CVH status was significantly associated with a reduced risk of incident AS, but not with mitral valve regurgitation or aortic valve regurgitation. Compared with low CVH status, AS risk was decreased by 33% and 50% in the moderate (HR: 0.67, 95% CI: 0.59–0.77) and high CVH groups (HR: 0.50, 95% CI: 0.41–0.61), respectively. The PRS of AS did not modify these associations. Nonetheless, adults with both low CVH status and high genetic susceptibility had the highest risk of AS, with a nearly 4-fold increase compared with those with high CVH condition and low genetic predisposition. Both lifestyle behaviors and biological features of CVH were significantly associated with AS incidence. Among the individual LE8 components, body mass index, sleep duration, and nicotine exposure had the strongest effects on valvular outcomes.

**Conclusion:** Higher LE8 scores were significantly associated with a lower incidence of AS, irrespective of genetic susceptibility. These findings indicate that optimal CVH is associated with a lower risk of AS across genetic backgrounds.

**Keywords:** aortic valve regurgitation, aortic valve stenosis, cardiovascular health, genetic predisposition, Life's Essential 8, mitral valve regurgitation, UK Biobank

**Nonstandard Abbreviations and Acronyms**

| | |
|---|---|
| **AHA** | American Heart Association |
| **AR** | aortic valve regurgitation |
| **AS** | aortic valve stenosis |
| **ARIC** | Atherosclerosis Risk in Communities |
| **BMI** | body mass index |
| **CVD** | cardiovascular disease |
| **CVH** | cardiovascular health |
| **CI** | confidence interval |
| **GWAS** | Genome-Wide Association Study |
| **HR** | hazard ratio |
| **ICD-10** | International Classification of Diseases, Tenth Revision |
| **LE8** | Life's Essential 8 |
| **MR** | mitral valve regurgitation |
| **PRS** | polygenic risk score |
| **SNP** | single-nucleotide polymorphism |

**HIGHLIGHTS**

- High cardiovascular health (CVH) scores are strongly associated with a lower risk of degenerative VHD, particularly aortic valve stenosis (AS).
- This is the first study to show that the protective association between high CVH and AS remains robust across genetic risk strata, with substantial benefits even among individuals with high genetic susceptibility or low socioeconomic status.
- Our findings highlight that higher cardiovascular health is associated with a lower risk of degenerative VHD, particularly AS, among individuals with high genetic susceptibility or low socioeconomic status.

## 1. Introduction

As a major health burden, degenerative valvular heart disease (VHD) adversely affects physical ability, undermines overall well-being, and limits lifespan.[1] The global epidemiological features of VHD exhibit marked geographic heterogeneity, with rheumatic heart disease predominating in countries with low to moderate income levels, whereas functional and degenerative changes remain the leading etiology in high-income settings.[2,3] As populations worldwide grow older, both the incidence and prevalence of VHD are expected to increase further. The incidence of aortic valve stenosis (AS), the most prevalent degenerative valve disorder in Europe and North America, has increased nearly 7-fold over the past 3 decades.[2,4–6] However, VHD remains underrecognized by the public and policymakers.[4] Moreover, no validated pharmacological therapies currently exist to halt its progression. Despite the mature clinical implementation of surgical and transcatheter aortic valve replacements, challenges remain, and associated healthcare expenditures remain prohibitive for lower-to-middle-income households.[7] Optimizing cardiovascular health (CVH) is associated with a lower risk of VHD and may represent a cost-effective and feasible approach to mitigating its overall burden.

Life's Essential 8 (LE8), issued by the American Heart Association (AHA) in 2022, represents an expanded CVH framework comprising 8 essential domains: diet, physical activity, nicotine exposure, sleep health, body mass index (BMI), blood lipids, blood glucose, and blood pressure.[8,9] Evidence from cohort studies indicates that achieving high CVH (as defined by LE8) significantly reduces the incidence of atherosclerotic cardiovascular disease (CVD). Improved LE8 scores contribute to reduced atherosclerotic CVD rates and a diminished occurrence of major adverse cardiovascular events.[10,11] Recent studies have extended the application of LE8 beyond static risk stratification to dynamic, longitudinal frameworks. In the Atherosclerosis Risk in Communities (ARIC) cohort, LE8 demonstrated robust short- and long-term predictive performance for incident CVD among individuals free of baseline CVD using time-dependent discrimination analyses.[12] The Coronary Artery Risk Development in Young Adults study applied LE8 within a life-course framework, integrating cumulative exposure, midlife levels, and longitudinal trajectories to characterize CVH from young adulthood to midlife.[13] In addition, a UK Biobank study applied LE8 in multistate models to examine transitions across sequential stages of CVD progression, highlighting its utility in modeling dynamic disease pathways.[14] Although the aforementioned studies highlight the potential of LE8 in predicting atherosclerotic CVD, research based on LE8 remains extremely scarce in the context of degenerative VHD.[15] Notably, few existing studies have simultaneously examined the interaction between composite lifestyle

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indices and genetic susceptibility—an aspect of critical importance for understanding the integrated risk architecture of AS and for informing primary prevention strategies.

Research has demonstrated VHD risk reduction through CVH optimization, particularly by smoking cessation, alcohol moderation, blood pressure control, and healthy sleep habits.[16,17] However, existing research has focused primarily on isolated factors, limited cohorts, or particular patient groups, such as hypertensive populations.[18–20] Additionally, research investigating the relationship between comprehensive CVH status and degenerative VHD progression remains scarce. The ARIC Study recently assessed the cross-sectional association between high CVH defined by 6 metrics and lower odds of aortic sclerosis and stenosis among 6034 participants.[21] Diet quality and sleep health were not included, and the conclusions might be somewhat limited by the study's cross-sectional design and relatively small sample size.

Thus, the present cohort study prospectively evaluated LE8-defined CVH in relation to the incidence of degenerative VHD, including AS, aortic valve regurgitation (AR), and mitral valve regurgitation (MR), among 262,864 participants from the UK Biobank. Given that lifestyle and genetic predispositions appear to interactively influence health conditions,[22–24] we further assessed whether the associations were modified by genetic susceptibility.

## 2. Methods

### 2.1. Study design and participants

The United Kingdom Biobank (UKB) is a large prospective cohort study with a population-based design. From 2006 to 2010, this study recruited more than 500,000 participants aged 37–73 years across England, Scotland, and Wales.[25] Data were collected via self-administered touchscreen questionnaires, physical and functional assessments, and baseline biochemical tests. Follow-up was linked to national datasets captured disease and mortality outcomes, initially ascertained electronically and validated through medical records, imaging, or archived tissue samples.[26] This research was conducted with approval from the North West Multicenter Research Ethics Committee and in accordance with the STROBE guidelines.

The present study excluded participants at baseline with self-reported pregnancy ($n$ = 150), a history of VHD on the basis of self-reports or hospital records ($n$ = 1998), incomplete LE8 data ($n$ = 200,375), or missing information on covariates ($n$ = 36,719). Following these criteria, the final analysis included 262,864 participants. The complete inclusion and exclusion criteria are presented in Figure S1, Supplemental Digital Content, https://links.lww.com/CARES/A4.

### 2.2. Assessment of updated CVH metrics as defined by LE8

CVH was assessed via the updated LE8 metrics according to the latest AHA criteria. LE8 comprises 8 components: 4 health behaviors (diet, physical activity, tobacco use, and sleep) and 4 health factors (BMI, blood lipids, blood glucose, and blood pressure).[9,27] Diet quality was assessed using a modified version of the original Dietary Approaches to Stop Hypertension (DASH) diet score based on the AHA eating pattern and adapted for the UK Biobank dietary data. Dietary intake frequencies were converted to weekly values using midpoint estimates for categorical responses, and individual dietary components were dichotomized at the population median and summed to generate an overall DASH-style diet score, consistent with established approaches in large cohort studies (Table S1, Supplemental Digital Content, https://links.lww.com/CARES/A4).[9,28] Baseline information on physical activity, smoking, sleep, and medication use was obtained through touchscreen questionnaires. BMI was computed on the basis of anthropometric measurements of height and body weight. Laboratory tests were used to measure total cholesterol (cholesterol oxidase-peroxidase enzymatic analysis), non–high-density lipoprotein cholesterol (high-density lipoprotein cholesterol, enzyme immunoinhibition, Beckman Coulter AU5800), and HbA1c (high-performance liquid chromatography, Bio-Rad VARIANT II Turbo) levels. Blood pressure assessments were conducted with an Omron automated device, employing averaged systolic/diastolic readings in subsequent analyses. Sleep duration was quantified based on self-reported average hours of sleep per day at baseline. Each of the 8 LE8 components was scored according to AHA guidelines, and the overall LE8 score was calculated as the mean of all component scores, yielding a continuous score ranging from 0 to 100, with higher scores indicating more favorable CVH. CVH scoring followed the LE8 algorithms detailed in Table S2, Supplemental Digital Content, https://links.lww.com/CARES/A4, with each component scoring 0 to 100; CVH was stratified by LE8 scores into low (< 50), moderate (50–80), and high (≥ 80) groups, with ascending scores reflecting progressively better CVH.

### 2.3. Incident degenerative valvular heart disease

The follow-up period spanned from baseline to the first incident of VHD, death, loss to follow-up, or December 2022. The study outcome was incident degenerative VHDs. These include 3 subtypes: AS, AR, and MR. For case identification, the following International Classification of Diseases, Tenth Revision (ICD-10) codes were used: I35.0/I35.2 for AS, I35.1 for AR, and I34.0 for MR. Incident VHD events were ascertained through continuous linkage to national hospital admission records and death registry data using ICD-10 codes. Self-reported VHD information was used only at baseline to exclude prevalent disease and was not used to define incident outcomes. The data sources included hospital records, self-reported diagnoses, and death registry information. The corresponding diagnostic and procedural codes used to ascertain degenerative VHDs are provided in Table

S3, Supplemental Digital Content, https://links.lww.com/CARES/A4.

### 2.4. Genetic susceptibility of AS

Genetic instruments were derived from publicly available Genome-Wide Association Study (GWAS) summary statistics in individuals of European ancestry (GWAS Catalog ID: GCST90310293). Single-nucleotide polymorphisms (SNPs) were selected on the basis of (1) genome-wide significance for AS ($P \leq 5 \times 10^{-8}$), (2) minor allele frequency > 0.01, and (3) exclusion of insertion/deletion variants and ambiguous SNPs. Linkage disequilibrium pruning was performed via a clumping method with a 250 kb window and $R^2 < 0.001$. These linkage disequilibrium clumping parameters were chosen to retain largely independent variants and reduce redundancy from correlated SNPs, consistent with commonly used polygenic risk score (PRS) construction practices in cardiovascular genetics.[18,29] A total of 38 SNPs met these criteria (Table S4, Supplemental Digital Content, https://links.lww.com/CARES/A4). Each SNP was coded as 0, 1, or 2 according to the number of AS risk alleles carried by each individual. The PRS was calculated via PRSice as the weighted sum of risk alleles, with weights from the primary GWAS effect sizes, and was standardized to a $z$-score (PRS-$z$) on the basis of the sample mean and standard deviation. Specifically, the PRS was constructed using a standard weighted approach as follows: $\text{PRS} = \beta_1\text{SNP}_1 + \beta_2\text{SNP}_2 + \ldots + \beta_{38}\text{SNP}_{38}$. The PRS was further normalized by multiplying by $N$ divided by the sum of the $\beta$ coefficients, and subsequently standardized to a PRS-$z$ based on the sample mean and standard deviation. Higher PRS-$z$ values indicate greater genetic risk of AS. We validated the PRS-$z$ by examining its association with incident AS. This was done via PRS-$z$ both as a continuous variable and categorized into quartiles, with the lowest quartile serving as the reference group (Figure S2, Supplemental Digital Content, https://links.lww.com/CARES/A4).

### 2.5. Assessment of covariates

Age, sex, race/ethnicity, Townsend scores, education, income, and alcohol use data were obtained through touchscreen questionnaires. Race/ethnicity was classified as White or Nonwhite. This deprivation index (Townsend) evaluates socioeconomic status through four indicators: unemployment, car ownership, home ownership, and household crowding. The scoring system is designed so that increasing values denote worsening deprivation. Educational attainment was categorized into 6 levels: (1) no qualification, (2) secondary education/GCSE or equivalent, (3) advanced degree/minor degree or equivalent, (4) other professional qualifications, (5) national vocational qualification/advanced national certificate or equivalent, and (6) college or university degree. Annual household income before tax was grouped into (1) < £18,000, (2) £18,000–£29,999, (3) £31,000–£51,999, (4) £52,000–£100,000, and (5) > £100,000. Clinical comorbidities, including hypertension, diabetes and CVD, were identified using a combination of baseline self-reports, medication records, clinical measurements, and linked primary care or hospital admission data, with detailed definitions provided (Table S5, Supplemental Digital Content, https://links.lww.com/CARES/A4). CVD included coronary artery disease, stroke, heart failure, and atrial fibrillation. Further details are available via the UK Biobank's online platform (biobank.ctsu.ox.ac.uk/showcase).

In the main analyses, individuals with missing covariate data were excluded. To assess the robustness of our findings, sensitivity analyses were conducted in which missing covariates were imputed using multiple imputation by chained equations, and results were compared between analyses with and without exclusion of missing covariates.

### 2.6. Statistical analysis

Continuous variables are expressed either as the means with standard errors (Student's $t$ test for normally distributed data) or medians accompanied by interquartile ranges (Mann–Whitney $U$ test for nonnormally distributed data). For categorical variables, numerical counts with corresponding percentages were calculated and statistically analyzed via chi-square tests.

To assess the temporal progression of VHD according to CVH stratification (low/moderate/high), we employed Kaplan–Meier survival analysis with log-rank tests for group comparisons. The continuous relationship between LE8 scores and VHD risk was examined via restricted cubic splines, with likelihood ratio tests used to evaluate potential nonlinear associations. The restricted cubic spline models were specified with four knots placed at the 5$^{th}$, 35$^{th}$, 65$^{th}$, and 95$^{th}$ percentiles of the LE8 distribution, following established methodological recommendations to balance model flexibility and numerical stability. The lowest LE8 score was used as the reference value to facilitate clinical interpretation of the spline curves. A multivariate Fine–Gray competing risk regression analysis was conducted to estimate the multivariable-adjusted hazard ratio (HR) (95% confidence interval [CI]) of incident VHD and individual types across CVH groups. In degenerative VHD, death precludes the subsequent diagnosis of VHD and therefore functions as a competing event. Conventional Cox models handle death as noninformative censoring, which may introduce bias—particularly over long follow-up. To address this, we applied Fine–Gray subdistribution hazard models, which allow for a more accurate estimation of cumulative incidence in the presence of competing mortality. Non-VHD death was handled as a competing risk for potential informative censoring. The proportional hazards assumption for the Fine–Gray competing risk models was evaluated using Schoenfeld residuals, and no violations were observed. Additionally, LE8 was modeled as a continuous variable

(per standard deviation increase) in Fine–Gray competing risk regression to assess its association with VHD risk. The multivariable-adjusted models were included sequentially: Model 1 was adjusted for age, sex, and race; Model 2 was additionally adjusted for household income, education, the Townsend deprivation index, alcohol use, baseline diabetes, hypertension, and CVD. Additionally, mutually adjusted models were used to analyze health behavior and health factor subscales separately. Finally, all 8 components of LE8 were included simultaneously in one model to assess their independent effects.

The genetic risk of AS was categorized into tertiles to define low, intermediate, and high genetic risk. We assessed the associations between CVH and VHD outcomes stratified by PRS-AS tertiles. Furthermore, we conducted a cross-tabulation analysis of CVH categories and PRS-AS tertiles for the hazard of AS onset, taking optimal CVH and low genetic predisposition as the reference category. Multiplicative interactions were evaluated through likelihood ratio testing, whereas additive interaction effects were quantified via 3 metrics: (1) relative excess risk due to interaction, (2) attributable proportion, and (3) synergy index.[30]

To ensure robustness, several robustness checks were performed. First, baseline characteristics were compared between participants with complete versus missing LE8 data to assess selection bias. Second, individuals with AS onset or death within the first follow-up year were excluded to reduce reverse causality. Additional analyses stratified by PRS were also conducted. Third, to address heterogeneity in the moderate CVH group, it was subdivided into 5 finer categories to better assess dose-response relationships. Fourth, missing data in both LE8 components and covariates were addressed via multiple imputation via chained equations. Fifth, analyses stratified by sex, age (< 60, ≥ 60), and household income (< £31,000, ≥ £31,000) were performed to assess the consistency of the CVH–VHD associations. All analyses were conducted using Stata 17 and R version 4.4.2, with 2-tailed tests and a significance level of 0.05.

## 3. Results

### 3.1. Participant characteristics

The study included 262,864 participants with complete data who were free of VHD at the time of enrollment (Table 1). The mean age was 56.01 ± 8.1 years, and 51.1% of them were female. The LE8 scores categorized individuals into 3 groups: low (< 50 points), moderate (50–79 points), and high CVH (≥ 80 points). The distribution of LE8 scores among the included participants is presented in Figure S3, Supplemental Digital Content, https://links.lww.com/CARES/A4. Overall, 13,332 (5.1%) of the participants had low CVH, 211,911 (80.6%) had moderate CVH, and 37,621 (14.3%) had high CVH. Compared with participants with low CVH, those with higher CVH were more often females, younger, had higher education and income levels, and were less likely to have diabetes, hypertension, or CVD at baseline. A range of significant differences in all the components of LE8 were identified across the CVH categories (Table 1). Baseline characteristics were similar across LE8 data completeness and inclusion status (Table S6, Supplemental Digital Content, https://links.lww.com/CARES/A4).

### 3.2. Associations between LE8 and incident VHD and its subtypes

During a median follow-up period of 13.4 years, a total of 6371 incident cases of VHD were documented, including 2754 cases of AS, 1013 cases of AR, and 3089 cases of MR. According to the Kaplan–Meier curves (Fig. 1), higher CVH scores were significantly associated with a lower cumulative incidence of overall VHD and its subtypes over the follow-up period (log-rank $p \leq 0.017$). LE8 scores showed an L-shaped association with the risk of VHD and AS, which was especially pronounced for AS, whereas the associations with MR and AR were weak or insignificant (Fig. 2). LE8 scores ≥ 77 were associated with maximal AS risk reduction ($p = 0.042$). Over long-term follow-up, the absolute burden of VHD was quantified using incidence rates, with an estimated rate of 242.4 cases per 10,000 person-years. In population-level analyses, suboptimal CVH was associated with a substantial population-attributable fraction for AS (Fig. 2).

We next investigated the long-term risk of incident VHD across VHD categories via a competing risk model. Overall, the risk of VHD significantly decreased as the LE8 score increased ($p$ for trend < 0.001). In the fully adjusted model, compared with participants with low LE8 scores, the HRs for VHD in the intermediate LE8 group and the high LE8 group were 0.82 (95% CI: 0.74–0.90) and 0.79 (95% CI: 0.70–0.90), respectively (Table 2). A higher LE8 score had a stronger negative association with the risk of AS. Compared with those in the low LE8 group, the HRs for AS in the intermediate LE8 group and the high LE8 group were 0.67 (95% CI: 0.59–0.77) and 0.50 (95% CI: 0.41–0.61), respectively. However, no significant differences were found in the AR or MR outcomes across the LE8 categories.

When the LE8 score was analyzed as a continuous variable, each 10-point increase in the LE8 score was associated with a lower risk of VHD (HR: 0.91, 95% CI: 0.88–0.93), and a substantially lower risk of AS (HR: 0.78, 95% CI: 0.75–0.81). The associations between the LE8 score and incident VHD remained robust in multiple sensitivity analyses, including the exclusion of participants diagnosed with or dying from AS within the first 1 and 3 years of follow-up (Tables S7 and S8, Supplemental Digital Content, https://links.lww.com/CARES/A4), finer LE8 categorizations (10-point increments, quartiles, and quintiles; Tables S9–S11, Supplemental Digital Content, https://links.lww.com/CARES/A4), models without adjustment for hypertension and diabetes, and exclusion of participants with baseline CVD (Tables S12 and S13, Supplemental Digital Content, https://links.lww.com/CARES/A4), imputation of missing covariates (Table S14, Supplemental Digital Content, https://links.lww.com/CARES/A4). Associations between LE8 scores and AS risk were robust across sex,

**Table 1**

**Baseline characteristics of participants by CVH category.**

| Variables | Overall | Low CVH (< 50 points) | Moderate CVH (50–79 points) | High CVH (≥ 80 points) | *P* for trend |
|---|---|---|---|---|---|
| No. of participants (%) | 262,864 | 13,332 (5.1) | 211,911 (80.6) | 37,621 (14.3) | |
| Age, mean (SD), year | 56.01 (8.1) | 56.21 (7.5) | 56.48 (8.0) | 53.26 (8.5) | < 0.001 |
| Sex, female (%) | 134,440 (51.1) | 5098 (38.2) | 103,745 (49.0) | 25,597 (68.0) | < 0.001 |
| Race and ethnicity (%) | | | | | |
| White | 252,229 (96.0) | 12,698 (95.2) | 203,518 (96.0) | 36,013 (95.7) | < 0.001 |
| Non-White | 10,635 (4.0) | 634 (4.8) | 8393 (4.0) | 1608 (4.3) | |
| Education level (%) | | | | | |
| No qualification | 33,348 (12.7) | 2406 (18.0) | 28,319 (13.4) | 2623 (7.0) | < 0.001 |
| CSE or ordinary Levels/ GCSE or equivalent | 42,892 (16.3) | 2415 (18.1) | 34,969 (16.5) | 5508 (14.6) | |
| Advanced levels/A Levels or equivalent | 15,028 (5.7) | 825 (6.2) | 12,019 (5.7) | 2184 (5.8) | |
| Other professional qualification | 31,773 (12.1) | 1531 (11.5) | 25,840 (12.2) | 4402 (11.7) | |
| NVQ or HNC or equivalent | 41,918 (15.9) | 2560 (19.2) | 34,354 (16.2) | 5004 (13.3) | |
| College or university degree | 97,905 (37.2) | 3595 (27.0) | 76,410 (36.1) | 17,900 (47.6) | |
| Townsend deprivation Index, mean (SD) | −1.49 (3.0) | −0.58 (3.4) | −1.51 (3.0) | −1.72 (2.8) | < 0.001 |
| Household income, *n* (%) | | | | | |
| <18,000 | 53,359 (20.3) | 3755 (28.2) | 43,775 (20.7) | 5829 (15.5) | < 0.001 |
| 18,000–30,999 | 66,410 (25.3) | 3391 (25.4) | 54,526 (25.7) | 8493 (22.6) | |
| 31,000–51,999 | 70,491 (26.8) | 3348 (25.1) | 56,791 (26.8) | 10,352 (27.5) | |
| 52,000–100,000 | 56,803 (21.6) | 2338 (17.5) | 44,738 (21.1) | 9727 (25.9) | |
| >100,000 | 15,801 (6.0) | 500 (3.8) | 12,081 (5.7) | 3220 (8.6) | |
| Alcohol status | | | | | |
| Never | 8584 (3.3) | 343 (2.6) | 6566 (3.1) | 1675 (4.5) | < 0.001 |
| Past | 7756 (3.0) | 509 (3.8) | 6164 (2.9) | 1083 (2.9) | |
| Current | 246,524 (93.8) | 12,480 (93.6) | 199,181 (94.0) | 34,863 (92.7) | |
| Comorbidities, *n* (%) | | | | | |
| Diabetes (%) | 12,574 (4.8) | 2088 (15.7) | 10,234 (4.8) | 252 (0.7) | < 0.001 |
| Hypertension at baseline (%) | 68,770 (26.2) | 6194 (46.5) | 58,500 (27.6) | 4076 (10.8) | < 0.001 |
| CVD at baseline (%) | 9859 (3.8) | 608 (4.6) | 7973 (3.8) | 1278 (3.4) | < 0.001 |
| AHA Life's Essential 8 score, mean (SD) | | | | | |
| Total CVH score | 67.99 (10.9) | 44.86 (4.3) | 66.52 (7.6) | 84.51 (3.8) | |
| DASH diet score | 26.77 (25.9) | 11.26 (17.5) | 24.38 (24.3) | 45.75 (27.6) | < 0.001 |
| Physical activity score | 70.75 (27.6) | 38.59 (26.1) | 68.96 (26.7) | 92.22 (14.5) | < 0.001 |
| Tobacco exposure score | 86.68 (24.0) | 62.31 (32.6) | 86.59 (23.9) | 95.86 (12.5) | < 0.001 |
| Sleep health score | 55.65 (30.1) | 29.56 (25.9) | 52.94 (29.0) | 80.15 (21.3) | < 0.001 |
| Body mass index score | 71.13 (33.5) | 35.96 (33.8) | 69.69 (33.2) | 91.73 (19.0) | < 0.001 |
| Blood lipid score | 90.09 (17.8) | 76.40 (25.6) | 89.91 (17.7) | 95.95 (10.8) | < 0.001 |
| Blood glucose score | 91.74 (18.9) | 74.60 (27.7) | 91.62 (18.9) | 98.50 (8.2) | < 0.001 |
| Blood pressure score | 51.13 (31.0) | 30.17 (27.3) | 48.05 (29.5) | 75.93 (26.6) | < 0.001 |

Continuous variables are presented as the means (SDs) and were compared via Student *t* test or the Mann–Whitney *U* test, as appropriate; categorical variables are presented as *N* (%) and were compared via the chi-square test.

AHA = American Heart Association; BMI = body mass index; CSE = Certificate of Secondary Education; CVH = cardiovascular health; CVH = cardiovascular health; DASH = dietary approaches to stop hypertension; GCSE = General Certificate of Secondary Education; HNC = Higher National Certificate; LE8 = Life's Essential 8; NVQ = National Vocational Qualification.

age, and TDI subgroups (Table S15, Supplemental Digital Content, https://links.lww.com/CARES/A4).

### 3.3. Associations of LE8 components with VHD

Higher scores on both the behavior and biological subscales of the LE8 were independently associated with a lower risk of VHD and AS. Compared with the lowest group, moderate and high health behavior scores corresponded to 18% and 22% decreased risks of VHD, respectively, whereas moderate and high health factor scores were associated with 17% and 14% lower risks of VHD, respectively. For each increase in the scores of behavior and biological factors, the risk of VHD decreased by 8% and 6%, respectively. Comparable results were observed for AS (Table 3). Consistent results were observed after excluding early AS events, including across genetic risk strata, and the findings remained robust after multiple imputation (Tables S7, S9, and S14, Supplemental Digital Content, https://links.lww.com/CARES/A4).

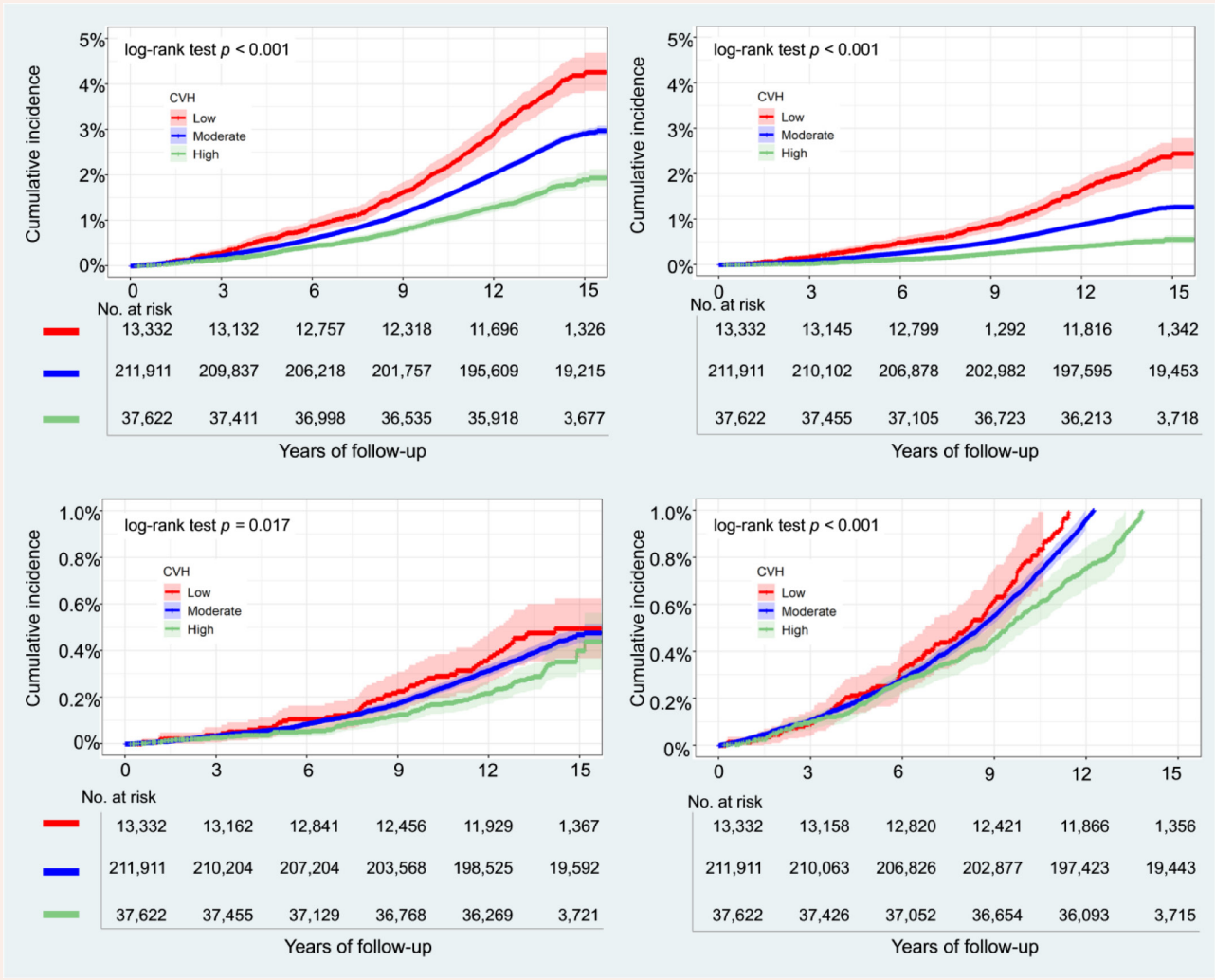


**Figure 1.** Cumulative incidence of degenerative VHD by CVH category. Kaplan–Meier failure estimates are shown for the cumulative incidence of (A) VHD, (B) AS, (C) AR, and (D) MR, stratified by CVH categories. Shaded regions indicate 95% CIs. Log-rank *p* values are shown for between-group comparisons. AR = aortic valve regurgitation; AS = aortic valve stenosis; CVH = cardiovascular health; MR = mitral valve regurgitation; VHD = degenerative valvular heart disease.

Additionally, among the individual LE8 components, higher BMI, nicotine exposure, blood glucose, and sleep duration scores were significantly associated with reductions in VHD and AS risk. In contrast, diet quality, physical activity, and blood pressure score was not significantly associated with VHD or AS risk ($p \geq 0.259$). The multivariable-adjusted HRs (95% CIs) per SD increase in the health scores for AS were as follows: BMI, 0.77 (0.74–0.80); nicotine exposure, 0.87 (0.84–0.91); blood glucose, 0.89 (0.86–0.92); sleep health, 0.95 (0.92–0.98); and blood lipid score, 0.93 (0.90–0.97) (Fig. 3).

### 3.4. The impact of genetic predisposition on the association of LE8 with incident AS

PRS was validated by examining its association with incident AS both as a continuous measure and across PRS-*z* quartiles, demonstrating a clear graded increase in risk across higher quartiles (Figure S2, Supplemental Digital Content, https://links.lww.com/CARES/A4). Subgroup analyses stratified by sex and age showed broadly consistent associations (Table S16, Supplemental Digital Content, https://links.lww.com/CARES/A4). The discriminative performance of the PRS was further evaluated using the C-statistic, which was 0.80. We assessed the potential impact of genetic risk on the association between CVH conditions and AS risk. In the analyses stratified by genetic risk groups, similar associations between LE8 and the risk of AS were observed, regardless of genetic risk. Compared with participants with low LE8 scores, those with high LE8 scores had significantly lower risks of AS in the low (HR: 0.38, 95% CI: 0.25–0.56), intermediate (HR: 0.58, 95% CI: 0.41–0.82), and high genetic risk subgroups (HR: 0.54, 95% CI: 0.40–0.72). No significant interaction was observed between CVH and genetic risk ($p$ for interaction = 0.174). Thus, the protective effect of high CVH may exist independently of genetic susceptibility (Fig. 4A).

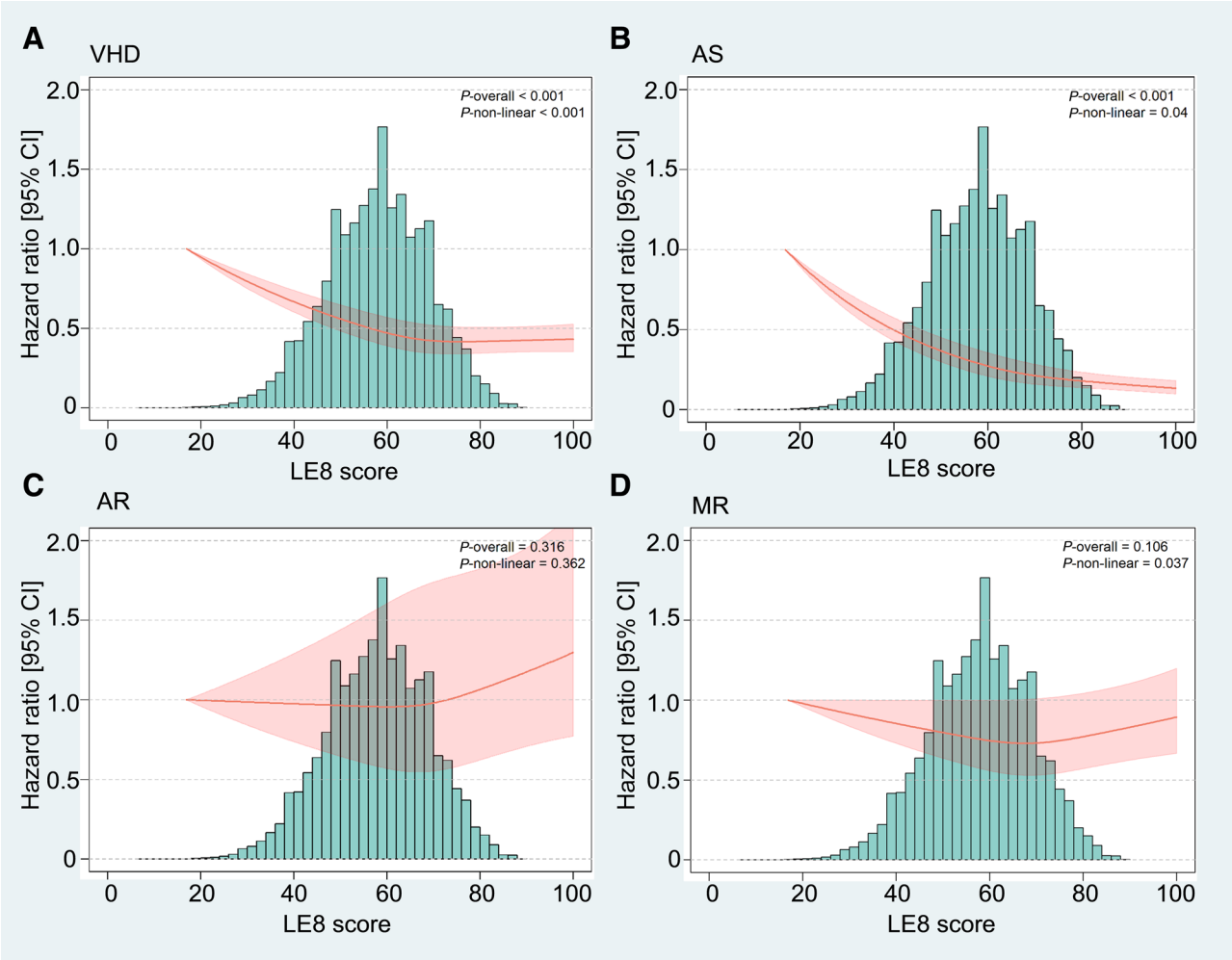


**Figure 2.** Dose-response relationships between CVH and the risk of degenerative VHD. HRs and 95% CIs for (A) VHD, (B) AS, (C) AR, and (D) MR were estimated using Cox proportional hazards models adjusted for age, sex, race, household income, education level, Townsend deprivation index, alcohol use, and baseline diabetes, hypertension, and cardiovascular disease. AR = aortic valve regurgitation; AS = aortic valve stenosis; CI = confidence interval; CVH = cardiovascular health; HR = hazard ratio; LE8 = Life's Essential 8; MR = mitral valve regurgitation; VHD = degenerative valvular heart disease.

Furthermore, we conducted a cross-tabulation analysis of CVH categories and PRS-AS tertiles for the combined associations with incident AS. Compared with individuals with low genetic risk and high LE8 scores, those with high genetic risk and low LE8 scores presented a nearly 4-fold increased risk of AS (HR: 3.81, 95% CI: 2.62–5.56) (Fig. 4B). Similar results were observed across quintiles of PRS (Table S17, Supplemental Digital Content, https://links.lww.com/CARES/A4), among White participants stratified by PRS (Table S18, Supplemental Digital Content, https://links.lww.com/CARES/A4), and after excluding early AS events in PRS-stratified analyses (Table S19, Supplemental Digital Content, https://links.lww.com/CARES/A4). Additive interaction analyses showed no significant interactions for relative excess risk due to interaction, attributable proportion, or synergy index (Table S20, Supplemental Digital Content, https://links.lww.com/CARES/A4).

## 4. Discussion

Among 262,864 participants in this prospective UK Biobank cohort, higher LE8-defined CVH was significantly associated with reduced VHD incidence. This is especially true for AS, regardless of genetic risk background. Individuals at high genetic risk who met the high LE8 score criteria still had a reduced risk of AS. Nonetheless, adults with both low CVH status and high genetic susceptibility had an elevated risk of AS, with a nearly 4-fold increase in contrast to participants who achieved high CVH status and low genetic predisposition. Both lifestyle behaviors and the biological features of CVH were significantly associated with the incidence of AS. Among the individual LE8 components, body mass index, sleep duration, and nicotine exposure had the strongest effects on valvular outcomes. The results demonstrated stability and reliability throughout all subgroup examinations and sensitivity assessments. At the

**Table 2**

**Association of Life's Essential 8 score with the risk of incident VHD and individual subtype.**

| | | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|
| **Outcome** | **LE8 score** | **Case/*N*** | **HR (95% CI)** | ***p* value** | **HR (95% CI)** | ***p* value** |
| VHD | Per 10-point increase | 6371/262,864 | 0.86 (0.84, 0.88) | < 0.001 | 0.91 (0.88, 0.93) | < 0.001 |
| | Low (< 50) | 473/13,332 | Ref. | | Ref. | |
| | Moderate (50–79) | 5289/211,911 | 0.70 (0.63, 0.77) | | 0.82 (0.74, 0.90) | |
| | High (≥ 80) | 609/3,7621 | 0.62 (0.55, 0.70) | < 0.001* | 0.79 (0.70, 0.90) | < 0.001* |
| AS | Per 10-point increase | 2754/262,864 | 0.72 (0.70, 0.75) | < 0.001 | 0.78 (0.75, 0.81) | < 0.001 |
| | Low (< 50) | 266/13,332 | Ref. | | Ref. | |
| | Moderate (50–79) | 2305/211,911 | 0.53 (0.47, 0.61) | | 0.67 (0.59, 0.77) | |
| | High (≥ 80) | 183/37,621 | 0.35 (0.29, 0.42) | < 0.001* | 0.50 (0.41, 0.61) | < 0.001* |
| AR | Per 10-point increase | 1013/262,864 | 0.99 (0.94, 1.05) | 0.718 | 1.02 (0.96, 1.08) | 0.600 |
| | Low (< 50) | 59/13,332 | Ref. | | Ref. | |
| | Moderate (50–79) | 837/211,911 | 0.90 (0.69, 1.17) | | 0.97 (0.74, 1.28) | |
| | High (≥ 80) | 117/37,621 | 0.95 (0.70, 1.31) | 0.997* | 1.08 (0.78, 1.50) | 0.467* |
| MR | Per 10-point increase | 3089/262,864 | 0.96 (0.93, 0.99) | 0.016 | 0.99 (0.96, 1.03) | 0.766 |
| | Low (< 50) | 183/13,332 | Ref. | | Ref. | |
| | Moderate (50–79) | 2552/211,911 | 0.87 (0.75, 1.01) | | 0.97 (0.84, 1.14) | |
| | High (≥ 80) | 354/37,621 | 0.91 (0.76, 1.09) | 0.664* | 1.06 (0.88, 1.27) | 0.368* |

Model 1: adjusted for age, sex, and race. Model 2: additionally adjusted for household income, education, the Townsend deprivation index, alcohol use, baseline diabetes, hypertension, and cardiovascular disease. HRs, 95% CIs, *P* values, and *P* values for trends were estimated via Fine–Gray competing risk models. The population-attributable fraction (PAF) for AS associated with suboptimal CVH (low and moderate LE8 combined) was 53.9% (95% CI: 47.0%–60.0%). Ref. refers to the group with low LE8 score, which was used as the reference category for comparison.
AR = aortic valve regurgitation; AS = aortic valve stenosis; CI = confidence interval; CVH = cardiovascular health; HR = hazard ratio; LE8 = life essential 8; MR = mitral valve regurgitation; Ref = refers to the group with low LE8 score; SD = standard deviation; VHD = degenerative valvular heart disease.
**p* for trend.

population level, our findings suggest that a substantial proportion of AS events could theoretically be avoided under a scenario of optimal CVH. Our findings demonstrate a significant association between CVH status, genetic predisposition, and the long-term risk of incident AS using LE8 scores, underscoring the potential clinical relevance of CVH in relation to AS risk.

Previous research has indicated that inherent characteristics, such as sex and chronological age, are related to VHD burden.[31,32] Recently, research interest has increasingly centered on modifiable factors that could impact its development. A study by Wei et al.[33] revealed that a 5-factor lifestyle score (smoking, obesity, physical activity, diet, and sleep) was associated with a lower VHD incidence and improved life expectancy among older adults, especially in socioeconomically disadvantaged groups. In the ARIC study, individuals with superior midlife CVH profiles demonstrated a significantly lower prevalence and severity of AS later in life,[21] suggesting a protective effect that has accumulated over decades. Similarly, data from the EPIC-Norfolk cohort demonstrated a 55% decrease in the incidence of calcific AS among participants with the highest Life's Simple 7 scores.[34] However, the statistical power and generalizability of these findings may be constrained

**Table 3**

**Associations between health behaviors, health factors and incident VHD.**

| | VHD | | | | AS | |
|---|---|---|---|---|---|---|
| **LE8 score** | **Case/*N*** | **HR (95% CI)** | ***p* value** | **Case/*N*** | **HR (95% CI)** | ***p* value** |
| Health behaviors | | | | | | |
| Per SD increment | 6371/262,864 | 0.92 (0.9, 0.95) | < 0.001 | 2754/262,864 | 0.87 (0.84, 0.91) | < 0.001 |
| Low | 473/13,332 | Ref | | 266/13,332 | Ref | |
| Moderate | 5289/211,911 | 0.82 (0.76, 0.89) | | 2305/211,911 | 0.77 (0.68, 0.87) | |
| High | 609/37,621 | 0.78 (0.71, 0.85) | < 0.001* | 183/37,621 | 0.67 (0.59, 0.77) | < 0.001* |
| Health factors | | | | | | |
| Per SD increment | 6371/262,864 | 0.94 (0.91, 0.96) | 0.001 | 2754/262,864 | 0.79 (0.76, 0.83) | < 0.001 |
| Low | 473/13,332 | Ref | | 266/13,332 | Ref | |
| Moderate | 5289/211,911 | 0.83 (0.78, 0.89) | | 2305/211,911 | 0.70 (0.63, 0.76) | |
| High | 609/37,621 | 0.86 (0.79, 0.94) | < 0.001* | 183/37,621 | 0.54 (0.47, 0.62) | < 0.001* |

HRs and 95% CIs were estimated via Fine–Gray competing risk models adjusted for age, sex, race, household income, education level, the Townsend deprivation index, alcohol use, and baseline diabetes, hypertension, and cardiovascular disease. The health factor comprises four variables: body mass index, non–HDL cholesterol, blood glucose, and blood pressure. Behavior was based on four variables: diet, physical activity, nicotine exposure, and sleep. In the subscale analyses, the two scores were mutually adjusted. Ref refers to the group with low LE8 score, which was used as the reference category for comparison.
AS = aortic valve stenosis; CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ratio; Ref = reference; SD = standard deviation; VHD = degenerative valvular heart disease.
**p* for trend.

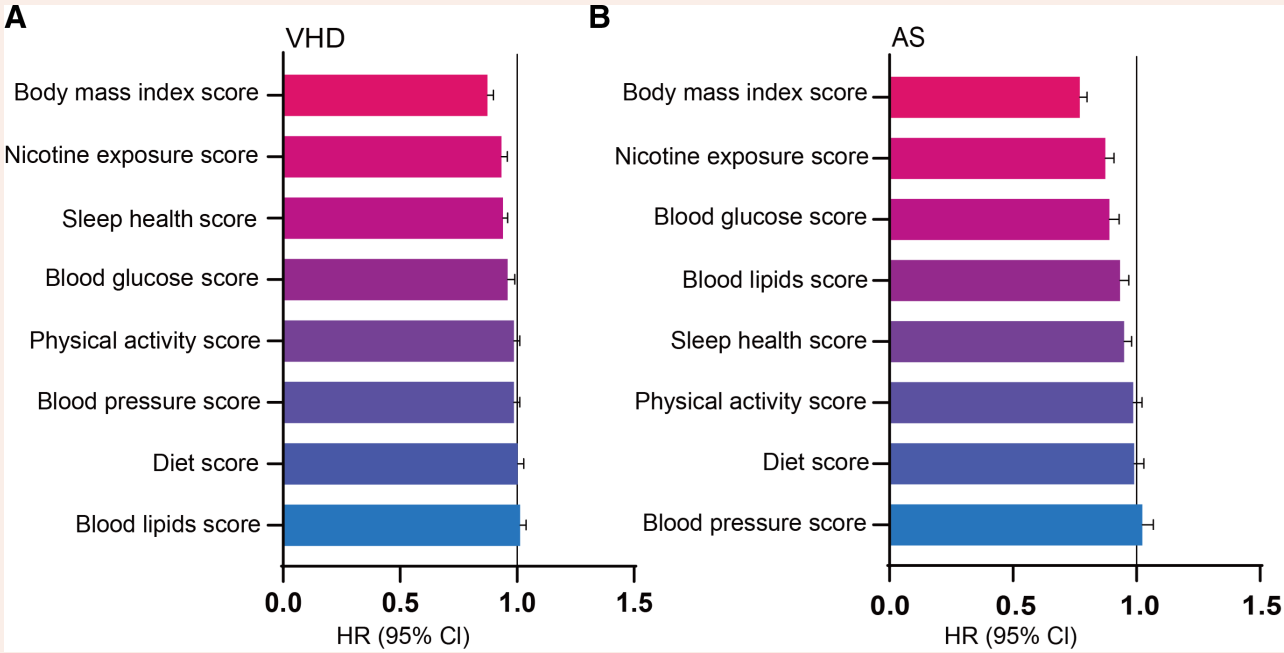


**Figure 3.** Associations between the 8 components of LE8 and the risk of incident degenerative VHD. (A) Associations between each LE8 component and the risk of incident VHD. (B) Associations between each LE8 component and the risk of incident AS. HRs and 95% CIs per 1-standard deviation increase in each LE8 component were estimated using Fine–Gray competing risk models adjusted for age, sex, race, household income, education level, Townsend deprivation index, alcohol use, baseline diabetes, hypertension, cardiovascular disease, and the other 7 LE8 components. AS = aortic valve stenosis; CI = confidence interval; HR = hazard ratio; VHD = degenerative valvular heart disease.

by the moderately small sample size. Our study used the newly published LE8 score to further examine its inverse association with VHD, particularly AS. Compared with prior research, the current analysis was based on a larger sample size and extended follow-up duration. Compared with prior studies, this work extends the literature by leveraging a larger cohort with longer follow-up, the updated LE8 construct, and stratification by genetic susceptibility. These findings suggest an inverse association between CVH and VHD risk, underscoring the potential relevance of LE8-guided approaches, especially among high-risk and socioeconomically disadvantaged populations.

Our findings indicate that the influence of lifestyle-related factors appears to differ among valvular lesions.

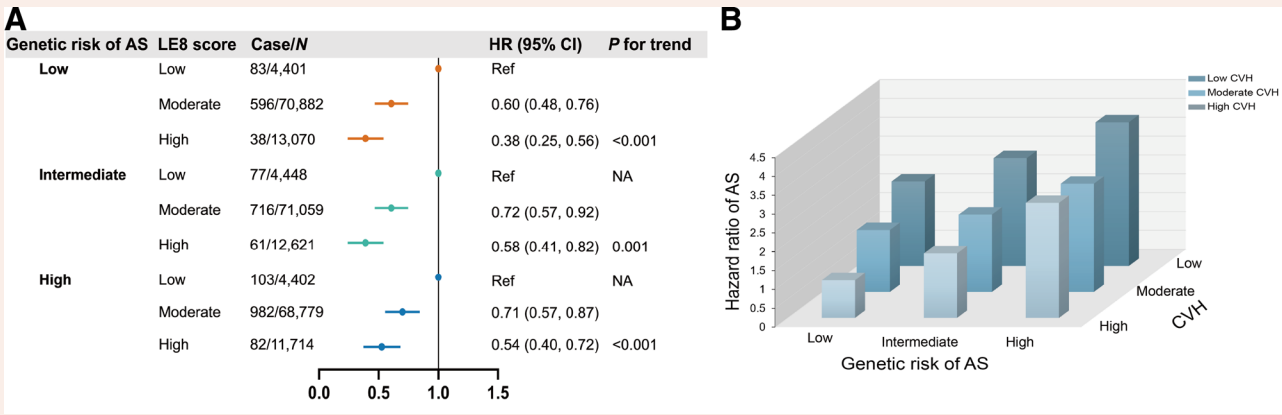


**Figure 4.** Associations of LE8 and polygenic risk with AS risk. (A) Associations between CVH and the risk of AS across categories of genetic risk for AS. (B) Joint associations of LE8 and the genetic risk of AS. *p* for interaction was calculated using multiplicative terms in fully adjusted Fine–Gray competing risk models. HRs and 95% CIs were estimated using Fine–Gray competing risk models adjusted for age, sex, race, household income, education level, Townsend deprivation index, alcohol use, and baseline diabetes, hypertension, and cardiovascular disease. AS = aortic valve stenosis; CI = confidence interval; CVH = cardiovascular health; HR = hazard ratio; LE8 = Life's Essential 8; Ref = refers to the group with low LE8 score.

Consistently, a recent cohort study reported a negative correlation between physical activity and AS but not with AR or MR,[35] underscoring the specificity of hemodynamic and biomechanical factors in valvular pathogenesis. AS shares pathophysiological similarities with atherosclerosis and is closely linked to established cardiovascular risk determinants. AS is driven by progressive valvular calcification linked to cardiometabolic and inflammatory pathways captured by the LE8 construct.[36] Increasing data suggest that poor lifestyle choices might drive AS progression through chronic inflammatory states, oxidative damage, and lipid buildup, resulting in valvular injury.[37–39] In contrast, valvular regurgitation involves distinct mechanisms and is weakly associated with metabolic disturbances.[40–42] AS progression is driven primarily by osteogenic transformation of valvular interstitial cells and calcific accumulation, whereas AR is typically caused by cusp prolapse due to medial degeneration,[43] and MR is commonly linked to leaflet myxomatous changes in mitral valve prolapse.[40] Unlike stenotic lesions, regurgitant lesions such as AR and MR are less influenced by metabolic or inflammatory pathways.[44,45] Consistent with this, aortic and mitral regurgitation exhibit substantially lower degrees of valvular calcification and are more commonly attributable to structural abnormalities rather than metabolic or inflammatory injury.[36,40,43–45] This pathophysiological difference aligns with our findings. Therefore, the protective effects of a healthy lifestyle may be more pronounced in AS, potentially through improved endothelial function, reduced visceral adiposity and blood viscosity, improved glycemic control, and attenuated systemic inflammation.[46–50] Similarly, we observed that LE8 components were related to a reduced incidence of AS, whereas no significant associations were found for AR or MR. Although evidence regarding the overall association between CVH status and degenerative VHD remains limited, examining individual components of the LE8 metrics may help clarify their specific associations with degenerative VHD and provide insights into differential risk patterns. Previous studies have demonstrated associations between several modifiable behaviors and the risk of VHD. These behaviors include physical activity, lipid disorders, smoking habits, sleep quality, and body mass index.[16,17,33,44,51,52] In our analyses of the individual components of the LE8 metrics, body mass index, sleep duration, and nicotine exposure showed the strongest associations with valvular outcomes. The increased likelihood of AS associated with greater adiposity may be partly mediated by elevated blood pressure and increased concentrations of atherogenic lipids.[53,54] While sleep itself is not a direct cause of AS, sleep-related disturbances may increase the risk of AS or exacerbate its clinical manifestations. For example, central sleep apnea may reflect underlying neurological dysfunction that contributes to the development of AS.[55] Elevated blood glucose can lead to diabetes, resulting in left ventricular hypertrophy and impaired cardiac function. These alterations may increase atrial afterload and promote atrial enlargement, thereby facilitating the development of AS.[56] Contact with environmental tobacco smoke has been linked to higher concentrations of inflammatory markers, potentially contributing to a greater occurrence of AS.[57,58] In contrast, the lipid score was not significantly associated with VHD overall; however, a distinct association with AS was observed, consistent with the so-called "cholesterol paradox."[59] In particular, subclinical hyperthyroidism may partly account for this relationship, as it can reduce total cholesterol and low-density lipoprotein cholesterol levels and is also associated with an increased risk of AS.[40] Taken together, the individual components of LE8 appear to act through distinct yet interrelated biological pathways that may collectively influence the development of VHD, particularly AS.

Previous studies have demonstrated that both lifestyle factors and genetic predispositions independently contribute to the development of VHD.[18] However, no prior research has comprehensively assessed the impact of genetic factors concerning the association of CVH with AS. Our investigation confirmed that better CVH conditions, as evaluated by the LE8 score, are consistently related to a lower likelihood of VHD, especially for AS, regardless of genetic risk background. Notably, individuals with both high PRSs and low CVH values presented the highest incidence of AS, and this association was robust across subgroups and sensitivity analyses. These results emphasize the importance of adhering to high lifestyle behaviors to mitigate the risk of AS, particularly among individuals with high genetic susceptibility. In stratified analyses, higher LE8 scores were particularly beneficial among individuals with lower socioeconomic status. Given that AS lacks effective pharmacological therapies and relies primarily on costly surgical valve replacement,[39] this evidence points to the necessity of prevention. Promoting CVH through lifestyle modification may offer a resource-efficient, scalable strategy to mitigate the effects of AS, particularly in underserved populations where access to advanced treatment is limited.

### 4.1. Strengths and limitations

This investigation's principal advantages lie in leveraging an extensive, community-derived longitudinal cohort, prolonged observation duration and comprehensive adjustment for potential confounding factors to control bias. The application of a comprehensive CVH metric enables a multidimensional evaluation of lifestyle and clinical factors. Building on these strengths, we demonstrate a robust, population-level inverse association between LE8 and AS, but not aortic or mitral regurgitation, thereby underscoring etiological heterogeneity across degenerative valvular phenotypes. By integrating a GWAS-derived PRS, we further show that favorable CVH consistently reduces AS risk across genetic risk strata, helping address the limited evidence on the joint effects of lifestyle-based indices and genetic susceptibility in AS. Moreover, component-level analyses identify body mass index, sleep

duration, and nicotine exposure as key modifiable contributors to AS risk. Finally, by accounting for nonvalvular mortality using Fine–Gray competing risk models, our findings provide robust and clinically relevant evidence supporting CVH as a central, modifiable determinant of AS risk. Nonetheless, several limitations warrant consideration. First, the 8 LE8 metrics were captured solely at enrollment and were largely based on self-reported information, risking recall inaccuracy and exposure misclassification because unmonitored changes could have occurred over the observation period. Lifestyle-related behaviors, including diet, physical activity, smoking, and sleep, may change over time. Therefore, reliance on a single baseline assessment may underestimate the cumulative impact of sustained improvements or deteriorations in CVH and may introduce random misclassification bias. Second, despite adjustment for multiple known confounders, residual or unknown confounding factors may still be present. Third, the UK Biobank sample is predominantly of European ancestry, thereby limiting the generalizability of the findings to ethnically diverse groups. Fourth, a substantial number of participants were excluded because of missing data on LE8 components and covariates, potentially introducing selection bias. Fifth, reliance on ICD-10 codes may preferentially capture advanced AS and underestimate early or subclinical disease, although these data sources have shown good reliability in prior validation studies.[60] Imaging-based studies are needed to improve phenotypic characterization and assessment of disease severity. Sixth, the European ancestry-based PRS may limit generalizability, although sensitivity analyses in White participants yielded consistent results. Seventh, although competing risk analyses were performed to mitigate bias, residual confounding and potential reverse causation remain concerns. Eighth, the observational design limits causal inference. Therefore, the associations observed between LE8 and valvular disease should be interpreted cautiously, and future causal inference studies are required to establish causality. Ninth, (cardiac magnetic resonance) CMR-derived subclinical hemodynamic markers were not assessed in this study, and future imaging-based analyses are needed to clarify the underlying mechanisms. Given the voluntary nature of UK Biobank participation, the cohort may not fully represent the general UK population; thus, findings should be validated in ethnically and geographically diverse populations. In addition, the limited ethnic diversity of the UK Biobank, the use of baseline-only LE8 assessments, and reliance on ICD-10 codes for AS ascertainment underscore the need for future studies in more diverse populations with longitudinal CVH assessment and imaging-based AS detection.

### *4.2. Conclusions*

On the basis of this large cohort, our study demonstrates that higher LE8 scores are significantly associated with a lower incidence of VHD overall, with the most pronounced association observed for AS. Notably, higher LE8 scores were consistently associated with a lower risk of AS across all genetic risk strata. An inverse association between CVH and AS risk was observed even among individuals with high genetic susceptibility. Together, these findings suggest that the LE8 score may serve as a complementary tool for AS risk assessment and risk stratification.

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## Ethical statement

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820), and the use of data for this analysis was approved by the UK Biobank (Approved Research ID: 429905). All participants provided written informed consent prior to enrollment, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

## Conflict of interest

The authors have no conflicts of interest to disclose.

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## Data availability statement

Data and materials are available via the UK Biobank at www.ukbiobank.ac.uk.

## Author contributions

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**Writing—review and editing:** All authors.

All the authors contributed to the interpretation of the results and critically revised the manuscript for important intellectual content. All designated authors meet the International Committee of Medical Journal Editors criteria for authorship, take collective responsibility for the work's integrity, and have approved its publication.

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