Research Square

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Healthy lifestyle is inversely associated with the risk of sudden cardiac arrest: a population-based cohort study

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Abstract

Aims

Sudden cardiac arrest (SCA) is a major public health issue with high mortality and limited prevention. This study investigated the association between lifestyle factors and SCA risk, and the impact of lifestyle on post-SCA mortality, with major adverse cardiovascular events (MACE) as intermediate factors.

Methods and results

This population-based cohort study included 404,970 UK Biobank participants. A healthy lifestyle score (0–7) was constructed from seven factors: smoking, alcohol, physical activity, diet, sleep, sedentary behavior, and social connection, and categorized as unfavorable (0–1), moderate (2–4), or favorable (5–7). Over a median follow-up of 13.5 years, 2,294 SCA cases occurred. Each additional healthy lifestyle factor was associated with a 13% reduced SCA risk (HR = 0.87, 95% CI: 0.84–0.90, $P = 6.54\times10^{-16}$). Compared to an unfavorable lifestyle, favorable lifestyle was linked to a 64% lower SCA risk (HR = 0.36, 95% CI: 0.28–0.46, $P = 1.88\times10^{-15}$). Using multi-state models, each one-point increase in lifestyle score reduced the transition from MACE to MACE + SCA by 8% (HR = 0.92, 95% CI: 0.88–0.96, $P = 1.87\times10^{-4}$), and reduced post-SCA mortality by 9% (HR = 0.91, 95% CI: 0.86–0.97, $P = 0.002$).

Conclusion

A healthy lifestyle is associated with reduced SCA incidence and improved survival after SCA, offering insights for prevention and early intervention.

Introduction

Sudden cardiac arrest (SCA) is a life-threatening condition characterized by sudden cessation of cardiac activity, leading to hemodynamic collapse, which may progress to sudden cardiac death (SCD) if corrective action is not taken promptly[1]. The global incidence of SCA varies greatly. The average incidence of out-of-hospital cardiac arrest (OHCA) in adult was 55 per 100,000 person-years[2], and the incidence of in-hospital cardiac arrest was estimated to be ranged from 120 to 1740 per 100,000 individuals[3]. SCA carries an exceptionally high mortality rate of over 90%, accounting for 15%-20% of all deaths in adults[4]. Notably, since the majority of SCA cases occur in those without prior clinical diagnosis of heart disease, it poses significant challenges for primary prevention[4, 5], which highlighted the urgent need to identify modifiable lifestyle factors which might influence the entire spectrum of SCA. Current evidence has suggested that genetic, environmental, and behavioral factors might contribute to the development of SCA. Among these, age, sex, family history, and lifestyle factors such as smoking, physical activity, and diet have been indicated to play important roles in the onset and progression of SCA[6–10]. A case-control study in Korea found that adherence to healthy behaviors—including a balanced diet (low red meat, high fruits/vegetables), non-smoking, regular exercise, and adequate sleep—was associated with a dose-dependent reduction in SCA risk[11]. A cohort study of 81,722 women in the Nurses' Health Study investigated four specific low-risk lifestyle factors, including non-smoking, maintaining a body mass index (BMI) of < 25, daily exercise ≥ 30 minutes, and a Mediterranean-style diet rich in plant-based foods and fish, and found that the relative risk (RR) and its 95% confidence intervals (CI) of SCD was 0.54 (95% CI: 0.34–0.86) for women with 1 low-risk factor, 0.41 (95% CI: 0.25–

0.65) for 2 low-risk factors, 0.33 (95% CI: 0.20–0.54) for 3 low-risk factors, and 0.08 (95% CI: 0.03–0.23) for 4 low-risk factors[12]. More recently, a large-scale exposome-wide analysis in the UK Biobank broadened the scope of potentially modifiable determinants of SCA beyond conventional lifestyle factors, identifying 56 modifiable factors across lifestyle, psychosocial, physical, socioeconomic, and environmental domains; Mendelian randomization analyses further supported potential causal relationships for several factors[13]. Importantly, lifestyle-related factors accounted for the largest proportion of the estimated preventable burden of SCA, underscoring the potential importance of behavioral modification in SCA prevention[13]. However, existing studies, including this comprehensive investigation, have primarily focused on identifying risk factors for incident SCA rather than characterizing how modifiable lifestyle factors may influence the dynamic progression from pre-SCA conditions to SCA and subsequent mortality. Therefore, based on the large-scale population-based UK Biobank (UKB) cohort, we aimed to assess the associations of lifestyle factors including smoking, alcohol consumption, physical activity, diet, sleep duration, sedentary behavior, and social connection with the risk of incident SCA. We hypothesized that (1) adherence to a healthy lifestyle was associated with a reduced risk of SCA, (2) maintaining a healthy lifestyle was associated with a reduced risk of conversion from major adverse cardiovascular events (MACE) to SCA, and (3) healthy lifestyle might improve survival outcomes after SCA.

Materials and Methods

Study design

UKB is a large-scale population-based cohort, and from 2006 to 2010, extensive health data from around 0.5 million participants aged 40 to 69 across the United Kingdom were collected[14]. Participants visited one of the 22 assessment centers, where they provided informed consent electronically, completed self-administered touchscreen questionnaires, and engaged in brief computer-assisted interviews to furnish comprehensive socio-demographic data, lifestyle behaviors, and other personal information. Furthermore, they underwent physical and functional assessments and contributed biological samples, including blood, urine, and saliva[15]. The UKB study received ethical approval from the North West Multi-Centre Research Ethics Committee. Details of the study design and data collection procedures are available online (https://www.ukbiobank.ac.uk).

Figure 1 provides an overview of our study design, including the criteria and procedures for participants inclusion and exclusion. After excluding individuals with pre-existing SCA at baseline (n = 246), those with missing information on lifestyle factors (n = 87,187) and missing covariates (n = 9,952), a total of 404,970 participants were included in the final analysis.

Ascertainment of outcomes

Participants diagnosed with SCA were obtained from hospital inpatient data, which were defined by the International Classification of Diseases 10th Revision (ICD-10) code. SCA was further divided into three distinct categories: (i) SCA with successful resuscitation (I46.0); (ii) SCA with confirmed death (I46.1, corresponding to SCD); and (iii) SCA with unspecified prognosis (I46.9).

Additionally, to assess the potential intermediate role of cardiovascular disease (CVD) on SCA, we focused on MACE, which were defined as ischemic heart disease, stroke, and arrhythmia and heart failure, selected on the basis of their direct relationships with the pathogenesis of SCA[1, 4]. Briefly, ischemic heart was defined as code I20 – I25, arrhythmia and heart failure as code I47 – I50, and stroke as code I60 – I64.

Participants were followed from their initial visit to the assessment centers until the time of diagnosis of SCA, loss to follow-up, death, or the end of the follow-up (Oct 31, 2022), whichever came first.

Assessment of Lifestyle factors and construction of healthy lifestyle score

Based on previous studies[16–18], seven modifiable lifestyle factors were considered in the current study as lifestyle factors, including smoking, alcohol consumption, physical activity, diet, sleep duration, sedentary behavior, and social connection. All lifestyle information was self-reported by each participant at baseline. More detailed information of the assessment of each lifestyle factor can be found in **Supplementary Table 1**. Briefly, for smoking, we defined never smoking or smoking cessation as a healthy lifestyle. For alcohol consumption, less than 28 grams of alcohol per day (14 grams for women) was considered healthy[19]. Regular physical activity was defined as meeting one of the following criteria: (□) Frequency: vigorous physical activity once or moderate activity at least 5 days per week; (□) Duration: vigorous activity for at least 75 minutes or moderate activity for 150 minutes per week[20]. The healthy diet score was calculated based on the intake of seven components: vegetables, fruit, fish, whole grains, refined grains, processed meat, and unprocessed meat, defined by the latest US Dietary Guidelines[21, 22], and reaching more than half (i.e., 4 or more) of the healthy diet components was considered healthy[17]. For sleep duration, 7 to 9 hours of sleep was considered as a healthy sleep pattern according to the recommendations of the National Health Service, the American Academy of Sleep Medicine and the Sleep Research Society[23]. Sedentary behavior was assessed based on the sum of self-reported daily television viewing and computer use on the Global Physical Activity Questionnaire[24]. According to the recommendations of the World Health Organization[25] and previous studies[18], sedentary time of less than 4 hours per day was considered to be a low-moderate level of sedentary behavior[18]. The social isolation index (SII) was used to assess social connections on the following criteria: (i) number of household members (1 point for living alone); (ii) frequency of visits to friends/family (1 point for monthly, every few months, never, or almost never); and (iii) participation in leisure/social activities (1 point for no participation)[26]. Participants with the lowest (score of 0) or moderate (score of 1) SII were defined as well socially connected[18, 26].

A 0–7 point of healthy lifestyle score was constructed based on the aforementioned seven lifestyle factors, with 1 point assigned for each factor reaching the “healthy criteria”, and a higher score represented healthier lifestyle[17]. In this study, healthy lifestyle score was also categorized into three categories in the Cox proportional hazards models, including favorable lifestyle (5–7 points), moderate lifestyle (2–4 points), and unfavorable lifestyle (0–1 points), with unfavorable lifestyle as the reference group[27].

Covariates

The selection of covariates was based on biological plausibility and previous literature[3, 17, 28, 29], including sociodemographic factors (age, sex, ethnicity, education level, Townsend deprivation index [TDI], and assessment center), BMI, and patient's pre-baseline diagnosis of hypertension, dyslipidemia, type 2 diabetes (T2D). The detailed definition of each variable is shown in **Supplementary table 2.**

Statistical analysis

Associations of lifestyle factors with SCA risk were assessed using multivariable Cox proportional hazards regression models, calculating hazard ratios (HRs) and 95% CIs. We also examined the association between each lifestyle factor and the incidence of SCA. Two models were constructed: Model a was adjusted for age and sex, and Model b additionally adjusted for ethnicity, education level, TDI, BMI, assessment center, patient's pre-baseline diagnosis of hypertension, dyslipidemia, and T2D. The proportional hazard assumption was assessed using the Schoenfeld residual method, and no evidence was found contradicting the assumption (all *P* values > 0.05, **Supplementary Fig. 1**). Non-linear dose-response relationships were explored using restricted cubic spline (RCS) models with four knots, selected based on Akaike Information Criterion[30]. We further conducted a series of stratified analyses, and between strata heterogeneity was assessed using Cochran's Q test, with a *P*-value greater than 0.05 suggesting no statistically significant heterogeneity.

The multi-state model was applied, which is an extension of the competing risks survival analysis and allows estimation of the role of a certain factor in different phases of a process[31]. To assess the role of lifestyle in the trajectories from baseline to MACE, to SCA and to all-cause mortality, we constructed three main transition pathways and four competing transition pathways, assessed how lifestyle might simultaneously influence different progression stages[32]. As shown in Fig. 2, the three main transition pathways referred to: (i) baseline health → incident MACE; (ii) incident MACE → incident MACE + SCA; (ii) incident MACE + SCA → all-cause mortality. Four competing transition pathways referred to: (i) baseline health → incident SCA; (ii) baseline health → all-cause mortality; (iii) incident MACE → all-cause mortality; (iv) incident SCA → all-cause mortality. Meanwhile, we constructed three subgroups by dividing MACE into three disease groups by ICD-10 definition (i.e. ischemic heart disease [IHD], arrhythmia and heart failure, and stroke). If a participant was diagnosed with both MACE and SCA on the same date, we assumed that the order of onset was MACE first, followed by SCA, and subtracted 0.5 days for the onset of MACE[33, 34].

Several sensitivity analyses were conducted to verify the robustness of the results. First, since the impact of each lifestyle factor on SCA and SCA-associated disease trajectories might vary, we introduced a weighted healthy lifestyle score and competing transition pathways to confirm the main findings of our study. The algorithm for calculating the weighted lifestyle score is shown in **Supplementary appendix**. Second, to eliminate the potential effect of delayed diagnosis of SCA, we repeated the analysis after excluding patients diagnosed with SCA within the first two years of enrollment. Third, we excluded participants with a history of cancer prior to baseline (Field ID 40005).

Two-sided *P*-values less than 0.05 were considered statistically significant. All analyses were performed using the R software (version 4.3.1), and the multi-state model was performed using *"mstate"* R package.

Results

Association between healthy lifestyle and SCA incidence

Among 404,970 UK Biobank participants, 2,294 experienced SCA within a median follow-up time of 13.51 years. Table 1 shows the baseline characteristics of the study population. Individuals with SCA were older and more likely to be male. Unhealthy lifestyle behaviors were more prevalent in the SCA group, including smoking, physically inactivity, unhealthy diet, weak social connection, and prolonged sedentary time (all $P < 0.001$). Additionally, pre-baseline comorbidities such as T2D, hypertension, and dyslipidemia were more common in those with SCA (all *P* <

0.001). Overall, a higher proportion of SCA cases fell into the unfavorable or intermediate lifestyle categories, compared with non-SCA participants (60.9% vs. 51.7%, $P < 0.001$).

Table 1
Baseline characteristics of participants from UK Biobank at baseline.

Characteristics	Total population (N = 404970)	Non-SCA cases No (N = 351631)	SCA cases Yes (N = 2294)	*P*
Age, year, mean ± SD	56.54 (8.05)	56.51 (8.05)	60.74 (6.90)	< 0.001
Sex, N (%)				
Female	211249 (52.2)	210609 (52.3)	640 (27.9)	< 0.001
Male	193721 (47.8)	192067 (47.7)	1654 (72.1)	
Ethnicity, N (%)				
White	385252 (95.1)	383093 (95.1)	2159 (94.1)	0.027
Non-white	19718 (4.9)	19583 (4.9)	135 (5.9)	
Education, N (%)				
College and above	140087 (34.6)	139485 (34.6)	602 (26.2)	< 0.001
Others	264883 (65.4)	263191 (65.4)	1692 (73.8)	
TDI, N (%)				
Most affluent	84586 (20.9)	84183 (20.9)	403 (17.6)	< 0.001
Affluent	83328 (20.6)	82903 (20.6)	425 (18.5)	
Middle	81061 (20.0)	80613 (20.0)	448 (19.5)	
Deprived	81402 (20.1)	80902 (20.1)	500 (21.8)	
Most deprived	74593 (18.4)	74075 (18.4)	518 (22.6)	
BMI, kg/m^2, mean ± SD	27.23 (4.62)	27.23 (4.61)	28.65 (5.30)	< 0.001
Assessment center, N (%)				
England	362605 (89.5)	360503 (89.5)	2102 (91.6)	0.002
Scotland	26505 (6.5)	26396 (6.6)	109 (4.8)	
Wales	15860 (3.9)	15777 (3.9)	83 (3.6)	
Smoking status, N (%)				
Current smoking	40961 (10.1)	40575 (10.1)	386 (16.8)	< 0.001
Never/previous smoking	364009 (89.9)	362101 (89.9)	1908 (83.2)	
Drinking status, N (%)				
Excessive drinking	178791 (44.1)	177732 (44.1)	1059 (46.2)	0.054
Never/Moderate drinking	226179 (55.9)	224944 (55.9)	1235 (53.8)	

Definition of abbreviations: BMI = body mass index; SCA = sudden cardiac arrest; T2D = Type 2 diabetes; TDI = Townsend deprivation index.

Characteristics	Total population (N = 404970)	Non-SCA cases No (N = 351631)	SCA cases Yes (N = 2294)	*P*
Sleep duration, N (%)				
Unfavorable	287658 (71.0)	286019 (71.0)	1639 (71.4)	0.677
Favorable	117312 (29.0)	116657 (29.0)	655 (28.6)	
Physical activity, N (%)				
Unfavorable	83775 (20.7)	83154 (20.7)	621 (27.1)	< 0.001
Favorable	321195 (79.3)	319522 (79.3)	1673 (72.9)	
Diet, N (%)				
Unhealthy	239065 (59.0)	237620 (59.0)	1445 (63.0)	< 0.001
Healthy	165905 (41.0)	165056 (41.0)	849 (37.0)	
Social connection, N (%)				
Bad social connection	53871 (13.3)	53499 (13.3)	372 (16.2)	< 0.001
Well social connection	351099 (86.7)	349177 (86.7)	1922 (83.8)	
Sedentary time, N (%)				
Unhealthy	176560 (43.6)	175268 (43.5)	1292 (56.3)	< 0.001
Healthy	228410 (56.4)	227408 (56.5)	1002 (43.7)	
T2D, N (%)				
No	398382 (98.4)	396245 (98.4)	2137 (93.2)	< 0.001
Yes	6588 (1.6)	6431 (1.6)	157 (6.8)	
Dyslipidemia, N (%)				
No	391683 (96.7)	389662 (96.8)	2021 (88.1)	< 0.001
Yes	13287 (3.3)	13014 (3.2)	273 (11.9)	
Hypertension, N (%)				
No	374399 (92.5)	372624 (92.5)	1775 (77.4)	< 0.001
Yes	30571 (7.5)	30052 (7.5)	519 (22.6)	

Definition of abbreviations: BMI = body mass index; SCA = sudden cardiac arrest; T2D = Type 2 diabetes; TDI = Townsend deprivation index.

Table 2 shows the association of healthy lifestyle score and lifestyle category with the risk of incident SCA. After adjusted for potential confounders, each 1-point increase in the healthy lifestyle score was associated with a 13% (95% CI: 10%-16%, $P = 6.54\times10^{-16}$) reduction in the incidence of SCA. Compared to those with unfavorable lifestyle, participants maintaining a moderate lifestyle or a favorable lifestyle were associated with a 58% (95% CI: 46%~67%) and a 64% (95% CI: 54%-72%) reduced risk of SCA, respectively. We also examined the association of independent lifestyle factors and the incidence of SCA, which showed that never smoking or smoking cessation (HR = 0.51, 95%

CI: 0.45–0.57), engaging in regular physical activity (HR = 0.77, 95% CI: 0.70–0.84), maintaining good socialization (HR = 0.82, 95% CI: 0.73–0.92) and limiting sedentary time (HR = 0.86, 95% CI: 0.79–0.94) were associated with a reduced risk of developing SCA (**Supplementary table 3**).

Table 2
The associations between lifestyle score, lifestyle category and the risk of SCA.

	Total	Person years	Events	Model a		Model b	
				HR (95% CI)	*P*	HR (95% CI)	*P*
Lifestyle score	404970	5353589.73	2294	0.83(0.80,0.86)	2.25×10^{-29}	0.87(0.84,0.90)	6.54×10^{-16}
Unfavorable lifestyle	4630	57736.73	66	Ref		Ref	
Moderate lifestyle	193554	2544638.76	1260	0.39(0.30,0.50)	8.62×10^{-14}	0.42(0.33,0.54)	1.22×10^{-11}
Favorable lifestyle	206786	2751214.24	968	0.30(0.23,0.38)	1.67×10^{21}	0.36(0.28,0.46)	1.88×10^{-15}
model a: age and sex.							
model b: age, sex, ethnicity, education level, assessment center, TDI, BMI, T2D, hypertension, and dyslipidemia.							
Definition of abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; SCA = sudden cardiac arrest. T2D = type 2 diabetes; TDI = Townsend deprivation index.							

Supplementary Fig. 2 shows the results of the stratified analyses. Briefly, when stratified by age, each 1-point increase in the healthy lifestyle score was associated with a reduced risk of SCA (HR = 0.79, 95% CI: 0.73–0.85) among those < 55 years of age, whereas among those ≥ 55 years of age, the association effect estimate was relatively weak (HR = 0.89, 95% CI: 0.86–0.92), a statistically significant difference between age groups were found (*P* for heterogeneity = 0.003). Similarly, the impact of healthy lifestyle score was more pronounced among women (HR = 0.81, 95% CI: 0.76–0.86) than in men (HR = 0.88, 95% CI: 0.85–0.92) (*P* for heterogeneity = 0.015). The inverse associations were similar in different education and BMI strata (education level: *P* for heterogeneity = 0.148; BMI: *P* for heterogeneity = 0.568). However, the association of healthy lifestyle was statistically significant among participants with TDI ≥ 3 group (HR = 0.81, 95% CI: 0.78–0.84), while no association was found among those with TDI < 3 (HR = 0.96, 95% CI: 0.91–1.02) (*P* for heterogeneity = 4.54×10^{-6}).

Association of healthy lifestyle with the development trajectory of SCA

As shown in Fig. 2, after excluding those who developed MACE and SCA before baseline, a total of 382,749 participants were included in the analysis assessing the association of healthy lifestyle with the development trajectory of SCA using MACE as an intermediate disease. During follow-up, a total of 55,583 participants (14.52%) were diagnosed with at least one disease of MACE including IHD (n = 30,627), stroke (n = 8,644), or arrhythmia and heart failure (n = 33,243). Among these, 1,223 patients progressed to SCA (transition, 2.20%), 737 died from all causes (transition, 60.26%), and 9,373 participants (transition, 16.86%) progressed directly from MACE to all-cause mortality.

The results of the main transition pathways of the disease trajectories are illustrated in Table 3. A higher healthy lifestyle score was associated with an 8% (95% CI: 0.88–0.96) reduction in the risk of progressing from MACE to MACE + SCA ($P = 1.87 \times 10^{-4}$). Among specific MACE conditions, we observed a 6% (95% CI: 1%-11%) reduction in the transition from IHD to IHD + SCA ($P = 0.025$) and a 11% (95% CI: 6%-16%) reduction for arrhythmia and heart failure ($P = 8.98 \times 10^{-6}$). We also found that an increase of healthy lifestyle score was related with a 9% (95% CI: 3%-14%) reduction in mortality risk among individuals who experienced MACE + SCA ($P = 0.002$), and for IHD and arrhythmia and heart failure, the rate was 12% (95% CI: 6%-18%, $P = 3.75 \times 10^{-4}$) and 11% (95% CI: 5%–16%, $P = 0.001$), respectively. However, the effect of the lifestyle score on either the transition pathways stroke → stroke + SCA ($P = 0.175$) or stroke + SCA → death ($P = 0.196$) did not reach statistical significance. These may suggest that lifestyle may reduce the incidence of SCA more by reducing the incidence of IHD and arrhythmias and heart failure.

Table 3
The associations between lifestyle score and main transition pathways of SCA development trajectory.

	Cases	Transition proportions*	Lifestyle score*	
			HR (95%CI)	*P* value
MACE as intermediate disease				
Baseline → MACE	55583	14.52%	0.93 (0.92,0.94)	7.52×10^{-92}
MACE → MACE + SCA	1223	2.20%	0.92 (0.88,0.96)	1.87×10^{-4}
MACE + SCA → death	737	60.26%	0.91 (0.86,0.97)	0.002
IHD as intermediate disease				
Baseline → IHD	30627	8.00%	0.93 (0.92,0.94)	2.28×10^{-55}
IHD → IHD + SCA	916	2.99%	0.94 (0.89,0.99)	0.025
IHD + SCA → death	512	55.90%	0.88 (0.82,0.94)	3.75×10^{-4}
Arrhythmia and heart failure as intermediate disease				
Baseline → arrhythmia and heart failure	33243	8.69%	0.94 (0.93,0.95)	1.09×10^{-37}
arrhythmia and heart failure → arrhythmia and heart failure + SCA	915	2.75%	0.89 (0.84,0.94)	8.98×10^{-6}
arrhythmia and heart failure + SCA→ death	557	60.87%	0.89 (0.84,0.95)	0.001
Stroke as intermediate disease				
Baseline → Stroke	8609	2.25%	0.90 (0.88,0.92)	3.84×10^{-32}
Stroke→ Stroke + SCA	111	1.29%	1.11 (0.95,1.29)	0.175
Stroke + SCA → death	82	73.87%	1.20 (0.91,1.59)	0.196

*Transition proportions refer to the proportion of people transitioning from the former state to the latter state.

*The model adjusted for age, sex, ethnicity, education level, assessment center, TDI, BMI, T2D, hypertension, and dyslipidemia.

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; IHD = ischemic heart disease; MACE = major adverse cardiovascular events; SCA = sudden cardiac arrest.

Potential nonlinear associations of healthy lifestyle score and SCA developmental trajectories were assessed using the RCS models (Fig. 3). Statistically significant dose-response relationships were found between the lifestyle score and the main transition pathways of the disease development trajectories for MACE, IHD, or arrhythmia and heart

failure as intermediate diseases (all $P < 0.05$). We also found a nonlinear association between lifestyle score and the transition pathways from MACE → MACE + SCA (P for non-linearity 0.033), as well as a similar nonlinear association for IHD, and arrhythmia and heart failure (P for non-linearity: 0.013 for IHD and 0.011 for arrhythmia and heart failure).

Sensitivity analysis

Supplementary table 4 further revealed the associations of healthy lifestyle score with competing pathways (death) for SCA transition pathways. It indicated that the healthy lifestyle score was associated with a reduced risk of each competing pathway, and the associations were statistically significant. In addition, since not all of the lifestyle factors investigated were statistically significantly associated with the risk of SCA in our study, and their association effect estimates varied, we constructed a weighted lifestyle score and repeated statistical analysis, and a similar association was yielded (HR = 0.89, 95% CI: 0.87–0.90, $P = 8.78\times10^{-41}$) (**Supplementary Tables 5**).

Moreover, sensitivity analysis excluding participants who developed SCA within two years of entering the cohort and analysis excluding participants diagnosed with cancer obtained similar associations of lifestyle scores with SCA, as well as the main transition pathways of SCA development trajectory, suggesting the robustness of our main findings (**Supplementary Tables 5, Supplementary Tables 6 and Supplementary Tables 7**).

Discussion

Main Findings

In this study, by leveraging data from a large-scale population-based cohort, we found that a healthy lifestyle was associated with a reduced risk of SCA. Moreover, by utilizing a multi-state model to assess the effect of lifestyle on SCA trajectory with MACE as an intermediate disease, we found that high healthy lifestyle score was associated with lower risks of the transition pathways (e.g. MACE → MACE + SCA and MACE + SCA → all-cause mortality).

Disease-Specific Pathways

In this study, we explored the effect of lifestyle with the risk of SCA incidence, and we also explored the impact of a healthy lifestyle on the trajectory of SCA. The results suggested that a healthy lifestyle might reduce the risk of transformation from MACE to SCA. However, when we subdivided MACE into three intermediate diseases, namely IHD, arrhythmia and heart failure, and stroke, healthy lifestyle showed a statistically significant protective effect on the main pathways involving IHD and arrhythmia and heart failure, but no statistically significant evidence was observed for the pathway involving stroke as intermediate disease. This phenomenon might reflect the unique mechanisms of different intermediate diseases in the SCA pathway trajectory, which not only reveals the heterogeneity of intermediate diseases in the SCA development trajectory, but also suggests the need to stratify management according to the characteristics of intermediate diseases in health intervention strategies. For pathways with IHD, arrhythmia and heart failure as intermediate diseases, the promotion of lifestyle interventions centered on smoking cessation, healthy diet, and moderate physical activities should be prioritized, since these measures might improve heart health and therefore reduce SCA risk[35–39]. For stroke-related pathways, it may be difficult to achieve significant results with traditional lifestyle interventions alone. This discrepancy may arise from both methodological and biological factors. Methodologically, to prevent the effect of co-morbidity of more than two MACE disorders, we excluded people with two other MACE disorders prior to stroke when examining the stroke-associated pathway, resulting in only 111 SCA events out of 8,644 stroke cases in a total of 382,749 participants.

The number of SCA cases was significantly fewer than in the other two MACE pathways, which may have led to inadequate statistical power. Biologically, stroke-related SCA may involve neurogenic mechanisms (e.g., autonomic dysfunction post-insular stroke, brain-heart interactions) less amenable by lifestyle modification[40, 41], whereas IHD/arrhythmia pathways are driven by ischemia or electrical instability directly modifiable via adherence to a healthy lifestyle[42]. Overall, our findings suggest that individualized intervention strategies tailored to different disease characteristics are key to optimizing primary and secondary prevention of SCA, which also provide a scientific basis for developing more precise public health policies for SCA.

Our stratified analyses identified three subgroups that might have amplified benefits from healthy lifestyles: younger adults (< 55 years), women, and socioeconomically disadvantaged individuals (TDI ≥ 3). These results provided special guidance for maintaining a good lifestyle to prevent SCA, for example, the prevention of SCA by maintaining a healthy lifestyle should be more emphasized at a young age, females and those living in communities with limited healthcare access, where behavioral modifications may yield a pronounced risk reduction of SCA.

Comparison with Previous Studies

A large number of studies have suggested the association of lifestyle factors with the development of SCA. Consistent with our findings, smoking cessation has been reported to be associated with a reduced risk of SCA[38, 43]. Similarly, regular physical exercise was found to enhance cardiac health and cardiac function, improve the heart's metabolic capacity and blood flow regulation, and thus reduce the occurrence of cardiac arrhythmia and ultimately the incidence of SCA[39], although excessive exercise has been linked to an elevated probability of SCA[44]. Sedentary behavior was also identified as a risk factor for SCA, and maintaining less sedentary time reduces the incidence of SCA and most of cardiovascular diseases[45], which was consistent with our results.

Our findings are also broadly consistent with a recent exposome-wide analysis conducted in the UK Biobank, which systematically evaluated 125 potentially modifiable factors and identified 56 factors associated with incident SCA across lifestyle, psychosocial, physical, socioeconomic, and environmental domains[13]. Notably, lifestyle-related factors contributed the largest proportion of the estimated preventable burden of SCA, and the authors estimated that 40% to 63% of SCA cases might theoretically be prevented by improving unfavorable risk profiles[13]. These findings further support the importance of lifestyle modification as a potentially high-yield strategy for SCA prevention. However, the previous study primarily focused on identifying individual modifiable risk factors and estimating their attributable burden, whereas our study further examined whether a multidimensional healthy lifestyle was associated with different stages of the SCA disease trajectory. In particular, our multi-state analysis suggested that the potential benefits of a healthy lifestyle may extend beyond the prevention of incident SCA to the reduction of progression from MACE to SCA and mortality following SCA. Thus, our findings complement the existing evidence by providing a dynamic perspective on how lifestyle may influence the progression of SCA across different disease states.

Although some studies have reported that good socialization was associated with the mortality rate of CVD[18, 46], evidence regarding its relationship with SCA remains limited. The recent exposome-wide study also identified psychosocial and social activity-related factors among the potentially modifiable determinants of SCA[13]. Consistent with this emerging evidence, our study found that good social connection was associated with a lower risk of SCA, further supporting the potential relevance of psychosocial well-being in SCA prevention. Some studies have suggested that moderate alcohol consumption was associated with a decrease in the incidence of SCA[37, 47], which was not consistent with our results. However, it has also been documented that even low levels of alcohol

intake might lead to increased rates of CVD[48]. The effect of alcohol intake on disease risk may vary depending on how it was calculated, and the type of alcohol consumed[48], which still needs further exploration. Interestingly, the recent exposome-wide study also reported potential protective associations of fruit intake and certain wine consumption patterns with SCA, with some of these associations supported by Mendelian randomization analyses[13]. Nevertheless, these findings should be interpreted cautiously given the complexity of dietary and alcohol-related exposures and the potential for pleiotropy or other sources of bias in causal inference.

In this study, we did not find a robust association between diet score and the risk of SCA, although previous studies found that a healthy diet was significantly associated with SCA[11, 12]. Though a statistically significant association of diet and SCA was found in Model a, the association vanished in Model b, suggesting that there might be other confounding factors. The situation might also be due to the dietary criteria and scoring methods we used[49]. In previous studies, sleep duration was found to be associated with SCA as well as cardio-metabolic disorders[11, 50], but this was not found in our study. The aforementioned lifestyle factors might not only reduce the risk of SCA, but also the incidence of cardiovascular[39, 45, 48, 50] and cardiometabolic diseases[48, 50], which were considered to be important triggers of SCA[5, 42], therefore healthy lifestyle might influence the risk of SCA by reducing the incidence of these intermediate diseases, which might be a potential explanation of our findings that lifestyle reduced the risk of transitioning from MACE to MACE + SCA.

Study Limitations

To the best of our knowledge, this is the first large cohort study to examine the relationship between lifestyle and the development trajectory of SCA. However, this study has several limitations. First, we used data from the UK Biobank and conducted an observational cohort study, and as such, residual confounding bias could not be ruled out. Second, the lifestyle score used in this study was based on self-reported data, which could introduce reporting bias. Additionally, while lifestyle data were collected at baseline, these data only reflected participants' behaviors during that period, and did not account for changes in lifestyle over time. Long-term consistency and changes in lifestyle might be likely to influence SCA risk, but this variation was not fully captured in our study. Another limitation is that the study sample was predominantly from a White population (> 90%). While we adjusted for ethnicity in the multivariate regression models, the racial composition of the sample may limit the external validity of the results. Since the relationship between lifestyle and SCA risk may differ across racial groups, future studies should include more racially diverse cohorts to improve the generalizability of our findings. Furthermore, though we used a multi-state model to explore the impact of lifestyle on disease progression, this model relies on certain assumptions when dealing with disease state transitions. For example, when MACE and SCA were diagnosed on the same day, we assumed MACE occurred first. This assumption might not fully reflect the real pathological sequence of events. Although we conducted extensive data processing and sensitivity analyses, further validation of this assumption is needed. Finally, although this study analyzed the relationship between lifestyle and SCA using Cox regression and multi-state models, we cannot infer causality due to the observational nature of the data. This consideration is particularly relevant given recent evidence from Mendelian randomization analyses suggesting potential causal relationships between several modifiable factors and SCA[13]. Nevertheless, Mendelian randomization has its own assumptions and limitations, and the causal effects of a multidimensional healthy lifestyle on the sequential progression of SCA remain uncertain. Future studies integrating longitudinal lifestyle assessments, causal inference approaches, and prospective intervention designs are warranted to determine whether sustained lifestyle modification can alter the course of SCA from its antecedent cardiovascular conditions to post-SCA outcomes.

Conclusions

In this large-scale cohort study, we observed that a healthy lifestyle was associated with both reduced risk of SCA and decreased incidence of transition pathways in the SCA disease trajectory with MACE as the intermediate process and all-cause mortality as the final outcome. Our study provides evidence that maintaining a good lifestyle is associated with primary and secondary prevention measures for sudden cardiac arrest and may be linked to improved prognosis in patients with SCA. However, further studies are needed to explore the underlying mechanisms between lifestyle factors and the incidence and progression of SCA.

Declarations

Ethics approval and consent to participate

Ethical approval was available from the North West Multi-Centre Research Ethics Committee and informed consent was provided by all participants. The present analyses were conducted under UK Biobank application number 113769.

Consent for publication

Not applicable.

Competing interests

None declared.

Clinical trial number

Not applicable.

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Author Contribution

FW drafted the initial and subsequent versions of the manuscript. FW, PL and YM contributed to data verification, formal analysis. JY, PZ and JQ contributed to review and editing this study. All authors revised the manuscript for important intellectual content. FW, PL and YM had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Data Availability

Data were accessed from https://www.ukbiobank.ac.uk. Data and code for this study are available from the correspondent authors upon reasonable request.

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Figures

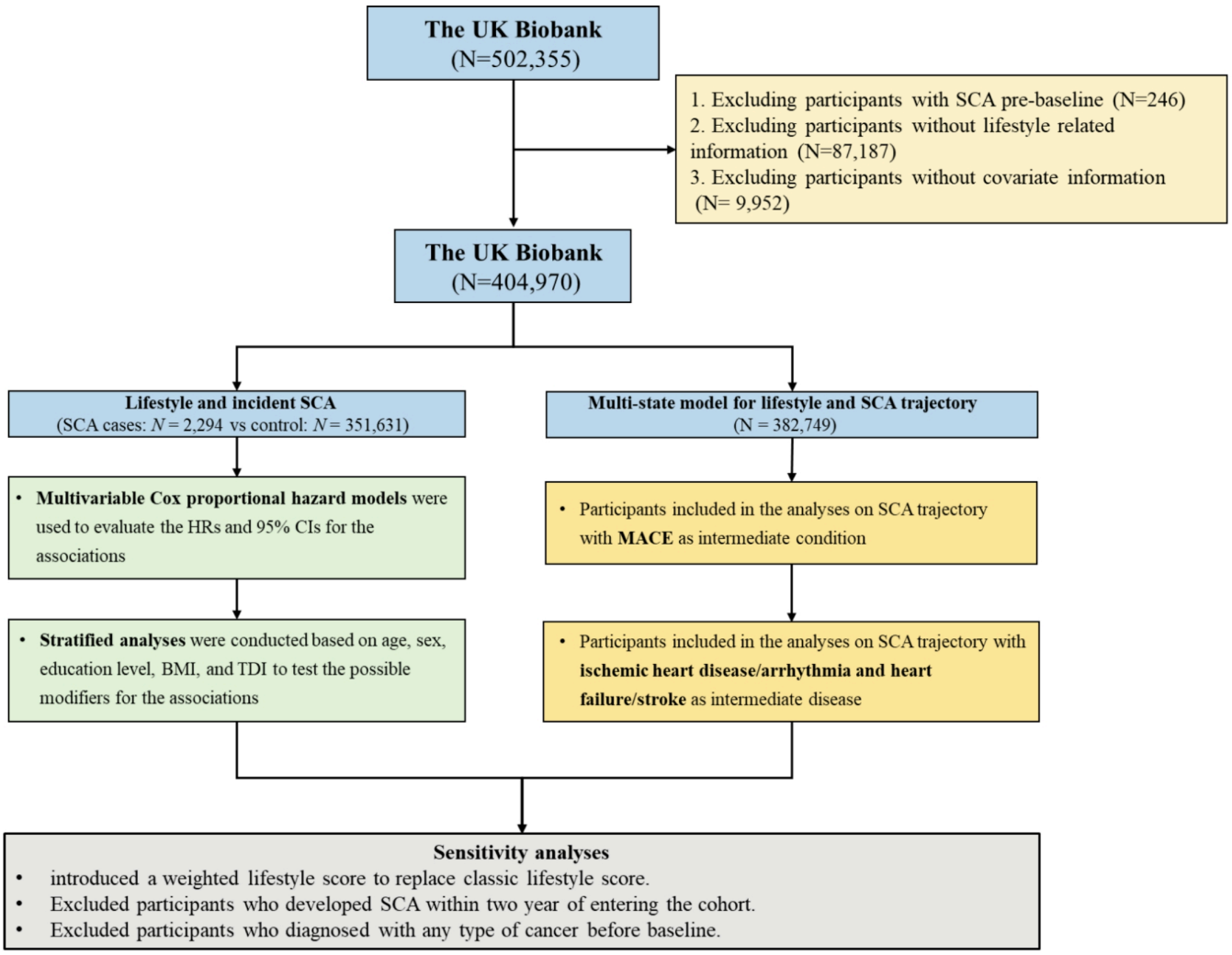


Figure 1

Overall design of the present study. Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events; SCA = sudden cardiac arrest; TDI = Townsend deprivation index;

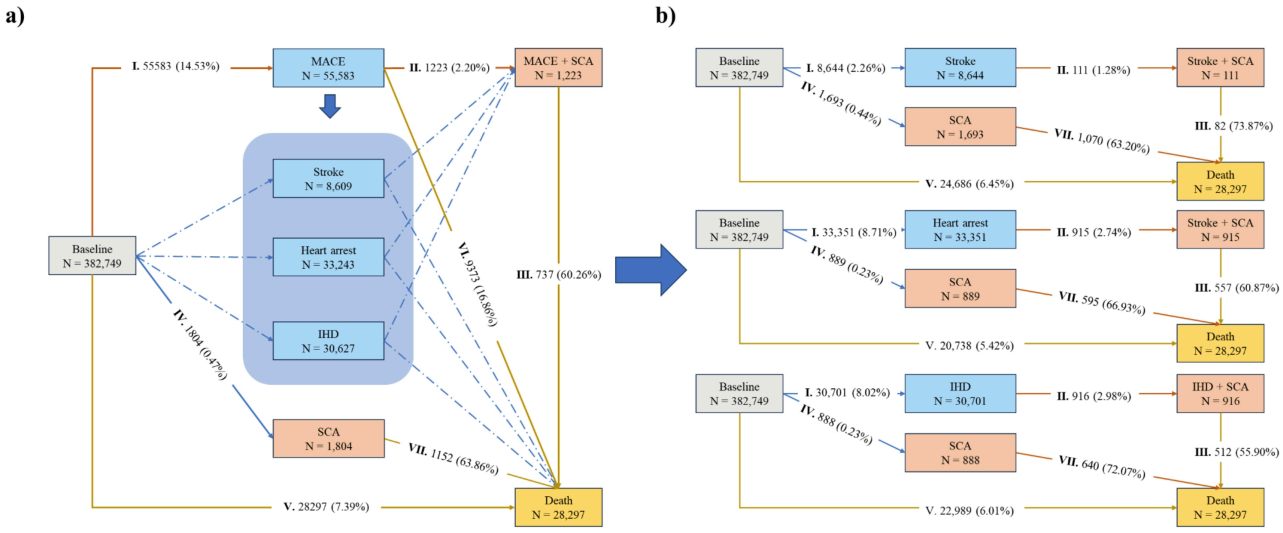


Figure 2

The specific transition pathways and the population details. (Ⅰ) baseline health → incident MACE; (Ⅱ) incident MACE → incident MACE + SCA; (Ⅲ) incident MACE + SCA → all-cause mortality; (Ⅳ) baseline health → incident SCA; (Ⅴ) baseline health → all-cause mortality; (Ⅵ) incident MACE → all-cause mortality; (Ⅶ) incident SCA → all-cause mortality.

Abbreviations: IHD = ischemic heart disease; MACE = major adverse cardiovascular events; SCA = sudden cardiac arrest;

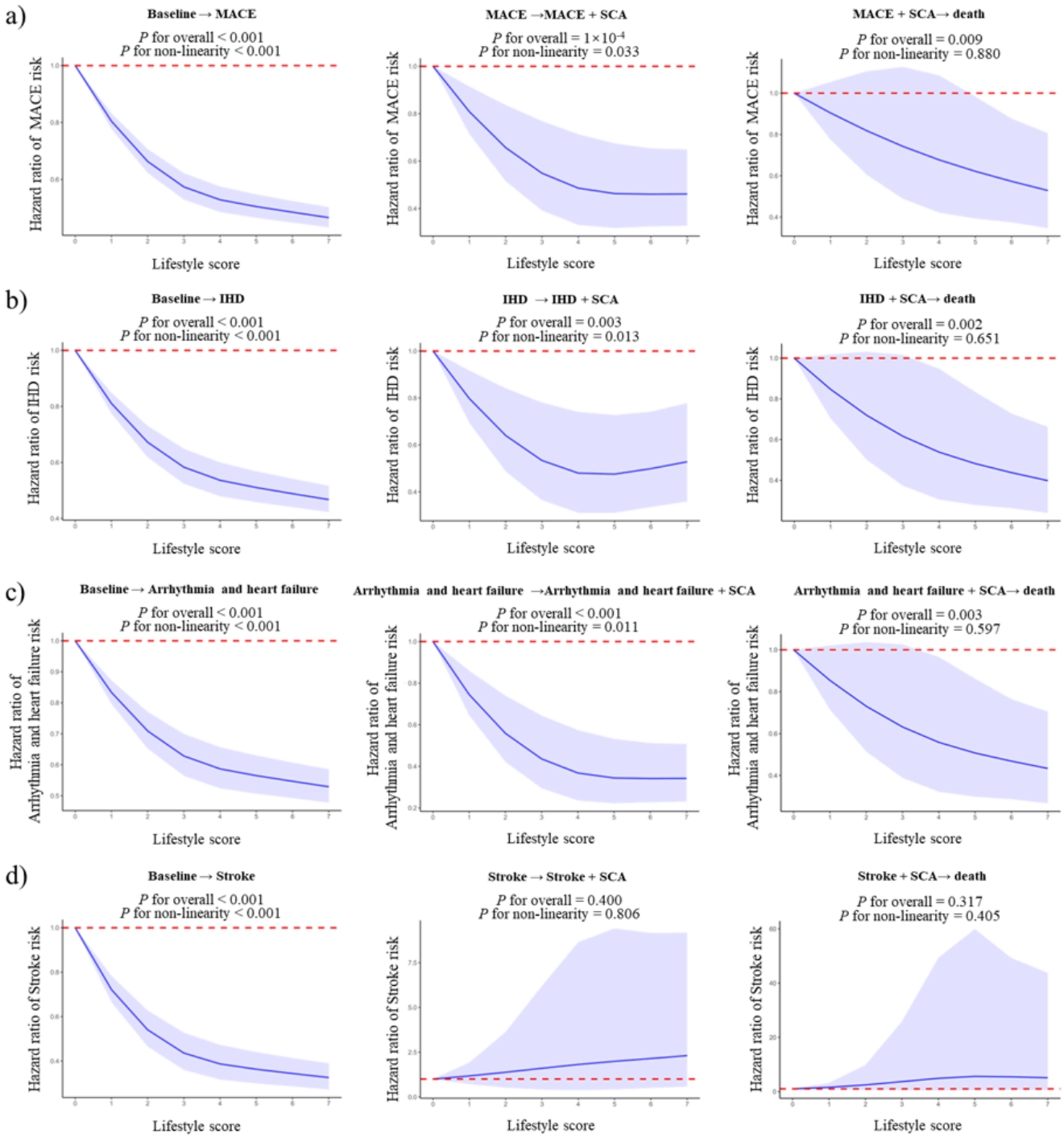


Figure 3

Dose-response relationship curves between lifestyle score and the main transition pathways (transition pathway , , and) of SCA-related development trajectory with MACE as an intermediate disease.

Abbreviations: IHD = ischemic heart disease; MACE = major adverse cardiovascular events; SCA = sudden cardiac arrest; The model adjusted for age, sex, ethnicity, education level, assessment center, TDI, BMI, T2D, hypertension, and dyslipidemia.

Supplementary Files

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- SupplementalAppendix.docx