Association of a Healthy Lifestyle With All-Cause and Cause-Specific Mortality Among Individuals With Type 2 Diabetes: A Prospective Study in UK Biobank

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OBJECTIVE

To evaluate the association of a healthy lifestyle, involving seven low-risk factors mentioned in diabetes management guidelines (no current smoking, moderate alcohol consumption, regular physical activity, healthy diet, less sedentary behavior, adequate sleep duration, and appropriate social connection), with all-cause and cause-specific mortality among individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This study included 13,366 participants with baseline type 2 diabetes from the UK Biobank free of cardiovascular disease (CVD) and cancer. Lifestyle information was collected through a baseline questionnaire.

RESULTS

During a median follow-up of 11.7 years, 1,561 deaths were documented, with 625 from cancer, 370 from CVD, 115 from respiratory disease, 81 from digestive disease, and 74 from neurodegenerative disease. In multivariate-adjusted model, each lifestyle factor was significantly associated with all-cause mortality, and hazard ratios associated with the lifestyle score (scoring 6–7 vs. 0–2 unless specified) were 0.42 (95% CI 0.34, 0.52) for all-cause mortality, 0.57 (0.41, 0.80) for cancer mortality, 0.35 (0.22, 0.56) for CVD mortality, 0.26 (0.10, 0.63) for respiratory mortality, and 0.28 (0.14, 0.53) for digestive mortality (scoring 5–7 vs. 0–2). In the population-attributable risk analysis, 29.4% (95% CI 17.9%, 40.9%) of deaths were attributable to a poor lifestyle (scoring 0–5). The association between a healthy lifestyle and all-cause mortality was consistent, irrespective of factors reflecting diabetes severity (diabetes duration, glycemic control, diabetes-related microvascular disease, and diabetes medication).

CONCLUSIONS

A healthy lifestyle was associated with a lower risk of all-cause mortality and mortality due to CVD, cancer, respiratory disease, and digestive disease among individuals with type 2 diabetes.

In 2019, the number of individuals with diabetes has reached nearly half a billion worldwide (1). The global economic burden of diabetes and its complications would substantially increase to $2.5 trillion by 2030 (2).

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The foundational role of lifestyle management in diabetes care has been emphasized by the American Diabetes Association (ADA). However, studies have focused on a limited selection of lifestyle factors, leaving emerging factors such as sleep, sedentary behavior, and social engagement out of the lifestyle scores for the mortality risk of individuals with diabetes (3–5). As most studies regarding the relationship between lifestyle and mortality have focused on all-cause mortality, evidence on cause-specific mortality is limited, especially on noncancer, nonvascular causes (6). These causes warrant more investigations, since they account for nearly half of the deaths among individuals with diabetes—a proportion still on the rise (7). Moreover, evidence on whether and to what extent patients with different severity of diabetes could benefit from a healthy lifestyle is also limited (8). To fill the knowledge gap, we examined the association of adherence to a healthy lifestyle, defined following the prevailing guidelines on diabetes care, with all-cause and cause-specific mortality among individuals with type 2 diabetes in a large prospective cohort study. Furthermore, we investigated the potential modification by factors related to diabetes severity, such as diabetes duration, glycemic control, diabetes-related microvascular disease, and diabetes medication use.

RESEARCH DESIGN AND METHODS

Study Populations

The UK Biobank is a large, population-based prospective cohort, consisting of >500,000 participants aged 40–69 years when recruited in 2006–2010. Participants completed a touchscreen questionnaire and a verbal interview, took physical measurements, and provided biological samples in 1 of 22 assessment centers throughout England, Scotland, and Wales (9). The UK Biobank received ethics approval from the North West Multicenter Research Ethics Committee (reference no. 16/NW/0274). All participants provided written informed consent for the study.

Participants with diabetes at baseline were identified through integration of multiple data sources. Medical history and medication information were self-reported in a touchscreen questionnaire or during a verbal interview conducted by trained staff at the baseline assessment. The identification of prevalent diabetes based on self-reported data has previously been described (10). The date and cause of hospital admissions were obtained from record linkage to Health Episode Statistics (England and Wales) and the Scottish Morbidity Records (Scotland) (see https://content.digital.nhs.uk/services). Type 2 diabetes identified through hospital inpatient records was classified based on ICD-9 codes 250.00, 250.10, 250.20, and 250.90 or ICD-10 code E11. Participants who had self-reported or hospital diagnoses of type 2 diabetes were identified as diagnosed patients. Undiagnosed patients were identified, according to the ADA criteria, based on random glucose level ≥11.1 mmol/L or glycated hemoglobin (HbA_{1c}) level ≥48 mmol/mol (6.5%) (11). After exclusion of those with diagnosed type 1 diabetes, missing or implausible values of exposures, or existing cardiovascular disease (CVD) or cancer at baseline, 13,366 participants with type 2 diabetes were included in the final analysis (Supplementary Figs. 1 and 2).

Assessment of Lifestyle Factors

All lifestyle information was self-reported at baseline (2006–2010). In the current study, we considered 7 modifiable behavioral factors, including 4 conventional factors (smoking, physical activity, alcohol consumption, and diet) and 3 emerging factors (sleep duration, sedentary behavior, and social connection), to generate a lifestyle score. Details of the assessment of each lifestyle factor can be found in Supplementary Material. No current smoking was classified as low risk. Regular physical activity was defined as at least 150 min/week of moderate activity or 75 min/week of vigorous activity (or an equivalent combination). Low-risk alcohol consumption was defined as moderate drinking (no more than one drink/day for women and two drinks/day for men; one drink is measured as 8 g ethanol in the U.K. [12]) on a relatively regular frequency. Participants who reported no drinking or drinking on special occasions only were regarded as nonregular drinkers. For diet, a low risk level was defined as an adequate intake of at least one-half of 10 food groups recommended as dietary priorities for cardiometabolic health: increased consumption of fruits, vegetables, whole grains, fish, dairy, and vegetable oils and reduced consumption of refined grains, processed/unprocessed meats, and sugar-sweetened beverages (13,14). Given the established J-shaped association between total daily sleep duration and mortality (15), adequate sleep duration (7–8 h/day) was classified as low risk. According to a previous study (16), we used television watching as the proxy for total leisure sedentary behavior and defined a low risk level as <4 h/day. Information on the number in the household, frequency of friend/family visits, and participation in leisure/social activity was used to evaluate the social connection level (17). A low risk level was defined as not socially isolated. For each factor, a low risk level was assigned 1 point and otherwise 0 points. The lifestyle score was constructed as the sum of all seven factors, ranging from 0 to 7, with a higher score indicating better adherence to an overall healthy lifestyle. For avoidance of extreme groups with limited cases, the lifestyle score was subsequently categorized into five groups (0–2, 3, 4, 5, and 6–7). Given that weight change is considered one of the typical symptoms during diabetes progression and is affected by medical treatment (8), BMI at baseline may not serve as a proxy for weight management, especially among participants with different stages of diabetes as in the current study.

Ascertainment of Outcomes

Date and cause of death were obtained from death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Detailed information about the linkage procedure is available from https://content.digital.nhs.uk/services. Person-time was calculated from baseline to the occurrence of study outcomes or the end of follow-up (28 February 2021)—whichever came first. The outcomes of this study were all-cause and cause-specific mortality (cancer, CVD, respiratory disease, neurodegenerative disease, digestive disease, and other causes) based on the ICD-10 code (Supplementary Table 1).

Assessment of Covariates

Possible confounding factors included sociodemographic factors, i.e., age, sex, ethnicity, education, employment, Townsend deprivation index, and family history of diabetes; health conditions, i.e., BMI, waist-to-hip ratio (WHR), and prevalent diseases (neurodegenerative disease, digestive disease, respiratory disease, depression, hypertension, and hyperlipemia); and related factors of diabetes severity, i.e., diabetes duration, diabetes-related microvascular disease, HbA_{1c} level, and diabetes medication use. Information on age, sex, ethnicity, education, employment, family history, and medication use was collected through questionnaires or verbal interviews at baseline. Townsend deprivation index, a composite measure of deprivation based on unemployment, non–car ownership, non–home ownership, and household overcrowding, was calculated with national census data and assigned with use of postal codes, with a lower score indicating a higher area level of socioeconomic status (18). Nurses conducted physical measurements and collected data on height, weight, and waist and hip circumference at baseline. BMI was calculated as weight in kilograms divided by the square of height in meters and classified into three categories based on the World Health Organization's criteria: underweight/normal (<25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥ 30 kg/m^2). WHR was calculated as waist circumference in centimeters divided by hip circumference in centimeters and classified into a high or low category with 0.85 for women and 0.90 for men as the cutoff value (19). Information on prevalent diseases was obtained through self-reported and hospital inpatient records (Supplementary Table 2). HbA_{1c} level was measured by the UK Biobank with high-performance liquid chromatography using the VARIANT II TURBO analyzer (Bio-Rad Laboratories). According to the ADA guideline, baseline HbA_{1c} levels were categorized into two groups: <53 or ≥ 53 mmol/mol (7.0%) (20). Diabetes duration was calculated as the years between the first occurrence of diabetes and baseline assessment for diagnosed patients and assigned as 0 years for undiagnosed patients.

Statistical Analyses

For variables with a missing rate of $>5\%$ (i.e., HbA_{1c} level), missing data were coded as an independent category; otherwise, missing data were imputed as median values for continuous variables or mode values for categorical variables. Detailed information on missing covariates can be found in Supplementary Table 3. Variables of baseline characteristics are shown as *n* (%) if categorical, mean (SD) if normally distributed, and median [interquartile range] if nonnormally distributed. The distribution of baseline characteristics by categories of lifestyle score was compared using a χ^2 test, ANOVA, and a Kruskal-Wallis test, respectively. However, it should be noted that these tests would be significant even for small differences, given the large sample size.

Cox proportional hazards models were applied to examine the associations of each lifestyle factor and the overall lifestyle score with all-cause and cause-specific mortality risk. The results were reported as hazard ratios (HRs) with 95% CIs. We assigned a median value to each lifestyle score category to test the linear trend. Three multivariable-adjusted models were constructed to account for potential confounding: model 1, adjustment for age (years), sex (women or men), ethnicity (White British or other), education (college/university degree or other), Townsend deprivation index (quintiles), employment (currently employed or not), and family history of diabetes (yes or no); model 2, additional adjustment for BMI (<25.0, 25.0–29.9, or ≥ 30 kg/m^2), WHR (high or low), and prevalent diseases (yes or no) based on model 1; model 3, further adjustment for diabetes duration (<1, 1–5, 5–10, or ≥ 10 years), HbA_{1c} level (<53 or ≥ 53 mmol/mol [7.0%]), diabetes-related microvascular disease (yes or no), and diabetes medication use (oral antidiabetes drug only, insulin, or neither) based on model 2. For analyses on individual lifestyle factors, all lifestyle factors were simultaneously adjusted. Besides, we examined the association of single and combined emerging low-risk lifestyle factors with all-cause mortality risk among participants with different adherence to the conventional low-risk lifestyle factors. The HRs with 95% CIs between the combination of emerging and conventional low-risk factors (nine categories with 0–1 emerging and 0–1 conventional low-risk factor as reference) and all-cause mortality were also calculated. The proportional hazards assumption was examined by a likelihood ratio test comparing models with and without a time-dependent exposure that was constructed using the time-transform functionality, and we found no significant violation of the assumption. To examine the proportion of all-cause mortality in the study population that theoretically would not have occurred if all participants had adhered to 6–7 low-risk lifestyle factors, we used the R package AF to calculate the population-attributable risk (PAR) under the assumption of a causal relationship between lifestyle and mortality risk (21,22).

Analyses were performed with stratification by age at diabetes diagnosis (≤ 55 or >55 years), sex (women or men), ethnicity (White British or other), Townsend deprivation index (tertiles), education (college/university degree or other), employment (currently employed or not), BMI (underweight/normal, overweight, or obese), WHR (low or high), diabetes duration (<1, 1–5, 5–10, or ≥ 10 years), HbA_{1c} level (<53 or ≥ 53 mmol/mol [7.0%]), diabetes-related microvascular disease (yes or no), and diabetes medication use (oral antidiabetes drug only, insulin, or neither). Statistical significance of interactions with lifestyle was tested by a likelihood ratio test with comparison of models with and without cross product terms between the stratifying variables and the lifestyle score.

Several sensitivity analyses were conducted to test the robustness of our results: First, we used multiple imputations with chained equations to assign missing values of exposure or covariates to test the influence of missing values (23). Second, we excluded participants with a history of the corresponding disease at baseline when examining the association between lifestyle score and risk of mortality from neurodegenerative disease, respiratory disease, or digestive disease to minimize the reverse causation. Third, we used the competing risk proportional subdistribution hazards regression model for cause-specific mortality analysis to account for the presence of competing events. Fourth, participants with undiagnosed diabetes were excluded in case lifestyle might change drastically due to the awareness of diabetes. Fifth, we constructed a weighted

lifestyle score (Supplementary Material) considering the varying magnitudes of association between each lifestyle factor and mortality risk. Sixth, BMI was included in the lifestyle score with 18.5–25 kg/m^2 defined as the low risk level. Seventh, the low risk level for alcohol consumption was redefined as no heavy drinking. Eighth, we stratified by self-reported health status or excluded participants with poor self-reported health to reduce the influence of undiagnosed diseases or poor health on lifestyle behaviors. Finally, we excluded participants who died within the first 2 or 4 years after recruitment to reduce potential reverse causation. All statistical analyses were performed with R, version 3.6.0. A two-sided $P < 0.05$ was considered statistically significant. We used Bonferroni correction to account for multiple testing in the cause-specific analysis and stratified analysis.

RESULTS

Population Characteristics

Baseline characteristics of the study population were shown in Table 1. Of the 13,366 participants with type 2 diabetes at baseline (median age 61.0 years, 35.7% women), the proportion of those scoring 0–2, 3, 4, 5, and 6–7 was 12.2%, 22.0%, 31.0%, 23.9%, and 10.8%, respectively. Participants with a lower lifestyle score were younger, less educated, more socioeconomically deprived, and more likely to be women, have higher HbA_{1c} levels, and take diabetes medication. Comorbidities and higher BMI were more prevalent among those with poor adherence to low-risk lifestyle factors. Participants excluded from the current analysis were older, less educated, less likely to be employed, more socioeconomically deprived, more likely to be women, on diabetes medication, and to have comorbidities, and less likely to be White British and have a family history of diabetes (Supplementary Table 3).

Association of Individual and Combined Lifestyle Factors With All-Cause Mortality

During a median follow-up of 11.7 years (interquartile range 11.0, 12.6), 1,561 all-cause deaths were documented. As shown in Table 2, each lifestyle factor was significantly associated with all-cause mortality. Adoption of 3 emerging low-risk factors, compared with scoring 0–1, was associated with 37% (HR 0.63 [95% CI 0.51, 0.78]), 24% (0.76 [0.61, 0.94]), and 35% (0.65 [0.47, 0.88]) lower mortality risk for participants adhering to ≤1, 2, and 3 conventional low-risk lifestyle factors, respectively (Supplementary Table 4 and Supplementary Fig. 3). When all 7 lifestyle factors were combined, HR for participants scoring 3, 4, 5, and 6–7, as compared with those scoring 0–2, was 0.72 (0.62, 0.83), 0.58 (0.50, 0.67), 0.50 (0.43, 0.59), and 0.42 (0.34, 0.52) (P for trend <0.001). For each 1-point increase, HR was 0.81 (0.78, 0.84). For participants with relatively poor adherence to a healthy lifestyle (scoring 0–5), the PAR of all-cause mortality was 29.4% (95% CI 17.9%, 40.9%) at median follow-up time. Estimates of the PAR by the duration of follow-up and the PARs for individual factors can be found in Supplementary Fig. 4 and Supplementary Table 5.

Association of Lifestyle Score With Cause-Specific Mortality

During the follow-up, we documented 625 cancer deaths, 370 CVD deaths, 115 respiratory disease deaths, 81 digestive disease deaths, 74 neurodegenerative disease deaths, and 296 deaths from causes other than those listed above. The lifestyle score was inversely associated with the risk of mortality from cancer, CVD, respiratory disease, digestive disease, and other causes (all P for trend <0.001), while the association with neurodegenerative disease mortality risk was not significant (Table 3). In comparisons of participants with higher overall lifestyle score (5–7 for analysis on digestive disease mortality and 6–7 for others) with those scoring 0–2, the multivariate-adjusted HR was 0.57 (95% CI 0.41, 0.80) for cancer mortality, 0.35 (0.22, 0.56) for CVD mortality, 0.26 (0.10, 0.63) for respiratory disease mortality, 0.28 (0.14, 0.53) for digestive disease mortality, and 0.35 (0.21, 0.60) for other mortality.

Subgroup Analyses

Consistent results were observed in analyses with stratification by sex, ethnicity, Townsend deprivation index, education, BMI category, WHR category, diabetes duration, HbA_{1c} level, diabetes-related microvascular disease, and diabetes medication use (Fig. 1 and Supplementary Table 6). The association between lifestyle score and all-cause mortality risk turned out to be stronger among participants with earlier diabetes onset and those who were not employed at baseline (P for interaction = 0.02 for both) but became nonsignificant for both after Bonferroni correction.

Sensitivity Analyses

In sensitivity analyses, the results were not materially changed when missing values of covariates and exposure were estimated with use of multiple imputations with chained equations (Supplementary Table 7 and Supplementary Table 8), when participants with a history of the corresponding disease at baseline were excluded (Supplementary Table 9), when the competing risk of cause-specific mortality was taken into account (Supplementary Table 10), when analyses were restricted to patients diagnosed with type 2 diabetes (Supplementary Table 11), when the weighted lifestyle score was applied (Supplementary Table 12), when BMI was included in the lifestyle score (Supplementary Table 13), when the low risk level of alcohol consumption was redefined as no heavy drinking (Supplementary Table 14), with stratification by self-reported health status or exclusion of participants with poor self-reported health (Supplementary Table 15 and Supplementary Table 16), and when deaths occurred within the first 2 or 4 years after recruitment were excluded (Supplementary Table 17).

CONCLUSIONS

In this prospective cohort study among participants with type 2 diabetes at baseline, we found that a healthy lifestyle defined by 7 low-risk lifestyle factors was significantly associated with a lower risk of all-cause mortality and mortality from cancer, CVD, respiratory disease, and digestive disease. Among participants with varying adherence to the conventional low-risk lifestyle factors, a significant, inverse association was observed between adopting the emerging low-risk factors and all-cause mortality risk. The association between lifestyle and all-cause mortality was independent of other potential confounders, including those related to diabetes severity.

Table 1—Baseline characteristics of participants with type 2 diabetes by lifestyle score category

	Lifestyle score					
	0–2 (*n* = 1,636)	3 (*n* = 2,946)	4 (*n* = 4,138)	5 (*n* = 3,199)	6–7 (*n* = 1,447)	*P*
Age, years	60.0 [53.0, 64.0]	60.0 [54.0, 65.0]	61.0 [55.0, 65.0]	61.0 [55.0, 65.0]	62.0 [56.0, 66.0]	<0.001
Women	618 (37.8)	1,079 (36.6)	1,490 (36.0)	1,125 (35.2)	463 (32.0)	0.010
White British	1,341 (82.0)	2,433 (82.6)	3,404 (82.3)	2,622 (82.0)	1,188 (82.1)	0.973
Townsend deprivation index	0.2 [−2.5, 3.4]	−1.2 [−3.1, 2.2]	−1.6 [−3.3, 1.3]	−2.0 [−3.6, 0.8]	−2.2 [−3.6, 0.3]	<0.001
College/university degree	502 (30.7)	1,081 (36.7)	1,818 (43.9)	1,522 (47.6)	745 (51.5)	<0.001
Currently employed	573 (35.0)	1,309 (44.4)	2,028 (49.0)	1,613 (50.4)	696 (48.1)	<0.001
Family history of diabetes	705 (43.1)	1,317 (44.7)	1,866 (45.1)	1,453 (45.4)	647 (44.7)	0.629
BMI, kg/m^2	32.0 [28.3, 36.5]	31.3 [28.2, 35.5]	30.6 [27.6, 34.4]	30.0 [26.9, 33.3]	28.8 [26.1, 32.1]	<0.001
Low WHR*	198 (12.1)	404 (13.7)	658 (15.9)	653 (20.4)	326 (22.5)	<0.001
Previous diseases						
Hypertension	1,103 (67.4)	1,952 (66.3)	2,685 (64.9)	1,973 (61.7)	862 (59.6)	<0.001
Hyperlipidemia	1,147 (70.1)	2,038 (69.2)	2,799 (67.6)	2,148 (67.1)	951 (65.7)	0.041
Depression	217 (13.3)	238 (8.1)	240 (5.8)	158 (4.9)	58 (4.0)	<0.001
Respiratory disease	110 (6.7)	125 (4.2)	107 (2.6)	67 (2.1)	19 (1.3)	<0.001
Diabetes-related microvascular disease	44 (2.7)	62 (2.1)	86 (2.1)	64 (2.0)	16 (1.1)	0.042
Digestive disease	40 (2.4)	38 (1.3)	48 (1.2)	23 (0.7)	7 (0.5)	<0.001
Neurodegenerative disease	7 (0.4)	7 (0.2)	10 (0.2)	4 (0.1)	2 (0.1)	0.288
Diabetes duration, years						
<1	383 (23.4)	666 (22.6)	891 (21.5)	672 (21.0)	292 (20.2)	0.224
1–5	545 (33.3)	1,040 (35.3)	1,477 (35.7)	1,186 (37.1)	526 (36.4)	
5–10	405 (24.8)	715 (24.3)	1,057 (25.5)	808 (25.3)	358 (24.7)	
≥10	303 (18.5)	525 (17.8)	713 (17.2)	533 (16.7)	271 (18.7)	
HbA_{1c}						
mmol/mol	50.7 [44.7, 60.0]	50.6 [44.5, 59.0]	50.1 [44.0, 58.0]	49.5 [43.2, 57.3]	49.3 [42.9, 56.3]	<0.001
%	6.8 [6.2, 7.6]	6.8 [6.2, 7.5]	6.7 [6.2, 7.5]	6.7 [6.1, 7.4]	6.7 [6.1, 7.3]	<0.001
Missing	101 (6.2)	177 (6.0)	253 (6.1)	187 (5.8)	90 (6.2)	
Diabetes medication						
Oral antidiabetes drug only	811 (49.6)	1,493 (50.7)	2,006 (48.5)	1,483 (46.4)	665 (46.0)	<0.001
Insulin	199 (12.2)	308 (10.5)	378 (9.1)	346 (10.8)	163 (11.3)	
Neither	626 (38.3)	1,145 (38.9)	1,754 (42.4)	1,370 (42.8)	619 (42.8)	

Continued on p. 324

Table 1—Continued

	Lifestyle score					
	0–2 (*n* = 1,636)	3 (*n* = 2,946)	4 (*n* = 4,138)	5 (*n* = 3,199)	6–7 (*n* = 1,447)	*P*
Smoking						
Never	521 (31.8)	1,287 (43.7)	2,006 (48.5)	1,685 (52.7)	788 (54.5)	<0.001
Previous	518 (31.7)	1,213 (41.2)	1,848 (44.7)	1,414 (44.2)	646 (44.6)	
Current	597 (36.5)	446 (15.1)	284 (6.9)	100 (3.1)	13 (0.9)	
Alcohol consumption						
Never	375 (22.9)	531 (18.0)	626 (15.1)	355 (11.1)	106 (7.3)	<0.001
On special occasions only	486 (29.7)	693 (23.5)	783 (18.9)	457 (14.3)	102 (7.0)	
Regular, ≤16 g/day†	171 (10.5)	516 (17.5)	1,197 (28.9)	1,449 (45.3)	1,065 (73.6)	
Regular, >16 g/day†	604 (36.9)	1,206 (40.9)	1,532 (37.0)	938 (29.3)	174 (12.0)	
Healthy diet‡	52 (3.2)	236 (8.0)	634 (15.3)	955 (29.9)	934 (64.5)	<0.001
Regular physical activity§	206 (12.6)	884 (30.0)	2,070 (50.0)	2,362 (73.8)	1,347 (93.1)	<0.001
Less television watching time‖	278 (17.0)	1,159 (39.3)	2,558 (61.8)	2,606 (81.5)	1,364 (94.3)	<0.001
Adequate sleep duration¶	318 (19.4)	1,282 (43.5)	2,690 (65.0)	2,633 (82.3)	1,342 (92.7)	<0.001
Appropriate social connection	912 (55.7)	2,435 (82.7)	3,804 (91.9)	3,080 (96.3)	1,434 (99.1)	<0.001

Data are median [interquartile range] for continuous variables or *n* (%) for categorical variables. *P* values were calculated with a Kruskal-Wallis test and χ^2 test for continuous and categorical variables, respectively. *Waist-to-hip ratio no more than 0.85 for women and 0.90 for men. †Refers to participants who reported drinking frequency ≥1–3 times/month. ‡Refers to adequate intake of at least one-half of 10 recommended food groups. §Refers to ≥150 min/week of moderate activity or ≥75 min/week of vigorous activity, or an equivalent combination. ‖Refers to <4 h per day of television watching. ¶Refers to sleep duration of 7 or 8 h/day.

Table 2—HR (95% CI) of all-cause mortality according to individual and combined lifestyle factors

	No. of cases/person-years*	HR (95% CI)†		
		Model 1	Model 2	Model 3
Smoking				
Current	252/16,070	1	1	1
Previous	759/64,558	0.70 (0.60, 0.81)	0.69 (0.59, 0.80)	0.68 (0.59, 0.79)
Never	550/72,940	0.56 (0.48, 0.65)	0.56 (0.48, 0.65)	0.55 (0.48, 0.65)
Alcohol consumption				
Never	285/22,781	1.37 (1.17, 1.59)	1.35 (1.16, 1.58)	1.32 (1.13, 1.54)
On special occasions only	297/28,974	1.14 (0.98, 1.32)	1.12 (0.97, 1.31)	1.08 (0.93, 1.26)
Regular, ≤16 g/day‡	400/50,600	0.83 (0.73, 0.95)	0.84 (0.73, 0.96)	0.83 (0.72, 0.94)
Regular, >16 g/day‡	579/51,214	1	1	1
Diet				
<5 recommended components	1,257/121,039	1	1	1
≥5 recommended components	304/32,529	0.87 (0.77, 0.99)	0.87 (0.77, 0.99)	0.88 (0.77, 0.99)
Physical activity§				
Irregular	828/74,415	1	1	1
Regular	733/79,154	0.83 (0.75, 0.91)	0.85 (0.76, 0.94)	0.86 (0.77, 0.95)
Sleep duration, h/day				
≤6	443/41,212	1.17 (1.04, 1.32)	1.15 (1.03, 1.30)	1.14 (1.02, 1.28)
7–8	890/95,335	1	1	1
≥9	228/17,021	1.18 (1.02, 1.37)	1.15 (0.99, 1.33)	1.15 (0.99, 1.34)
Television watching time, h/day				
0	40/3,333	1.14 (0.82, 1.57)	1.17 (0.85, 1.61)	1.18 (0.86, 1.63)
0.5–4	757/88,688	0.87 (0.79, 0.97)	0.90 (0.81, 1.00)	0.90 (0.81, 1.00)‖
≥4	764/61,547	1	1	1
Social connection				
Isolated	279/19,070	1	1	1
Moderately active	673/62,752	0.80 (0.69, 0.92)	0.80 (0.70, 0.92)	0.78 (0.67, 0.90)
Active	609/71,746	0.64 (0.55, 0.75)	0.65 (0.56, 0.75)	0.63 (0.54, 0.74)
Overall lifestyle¶				
0–2	308/18,245	1	1	1
3	400/33,792	0.71 (0.61, 0.82)	0.71 (0.61, 0.83)	0.72 (0.62, 0.83)
4	436/47,722	0.55 (0.48, 0.64)	0.57 (0.49, 0.66)	0.58 (0.50, 0.67)
5	299/37,006	0.48 (0.41, 0.56)	0.50 (0.42, 0.59)	0.50 (0.43, 0.59)
6–7	118/16,803	0.39 (0.32, 0.49)	0.42 (0.34, 0.52)	0.42 (0.34, 0.52)
P for trend		<0.001	<0.001	<0.001
Per score point		0.80 (0.76, 0.83)	0.81 (0.77, 0.84)	0.81 (0.78, 0.84)
PAR, %#		32.06 (20.98, 43.15)	29.91 (18.45, 41.36)	29.39 (17.90, 40.89)

*Due to rounding, the sum of person-years may not be exactly the same. †HRs were calculated in Cox proportional hazards model: model 1, adjustment for age (years), sex (women or men), ethnicity (White British or other), education (college/university degree or other), Townsend deprivation index (quintiles), employment (currently employed or not), and family history of diabetes (yes or no); model 2, further adjustment for BMI (<25.0, 25.0–29.9, or ≥30 kg/m^2), WHR (≤0.85/0.90 or >0.85/0.90 for women/men, respectively), and prevalent diseases (yes or no) based on model 1; model 3, further adjustment for diabetes duration (<1, 1–5, 5–10, or ≥10 years), HbA_{1c} level (<53 or ≥53 mmol/mol [7.0%]), diabetes-related microvascular disease (yes or no), and diabetes medication use (oral antidiabetes drug only, insulin, or neither) based on model 2. Lifestyle factors were simultaneously adjusted for analyses on the association of each individual lifestyle factor with all-cause mortality risk. ‡Refers to participants who reported drinking frequency ≥1–3 times/month. §Regular physical activity was defined as ≥150 min/week of moderate activity, or ≥75 min/week ofvigorous activity, or an equivalent combination. ‖*P* = 0.047. ¶Low-risk lifestyle factors: no current smoking, regular physical activity (≥150 min/week of moderate activity or ≥75 min/week of vigorous activity, or an equivalent combination), healthy diet (adequate intake of at least one-half of 10 recommended food groups), moderate alcohol consumption (no more than 1 drink/day for women and 2 drinks/day for men on a relatively regular frequency), adequate sleep duration (7–8 h/day), less television watching time (<4 h/day), and appropriate social connection (not isolated). #The percentage of all-cause mortality theoretically attributable to nonadherence to 6 or 7 low-risk lifestyle factors among participants included in the current study. PAR at the median follow-up time of the study population was reported.

Our findings on all-cause mortality and CVD mortality are consistent with a recent meta-analysis of eight observational studies (6), in which the pooled HR was 0.44 (95% CI 0.33, 0.60) for all-cause mortality and 0.51 (0.30, 0.86) for CVD mortality in comparisons of extreme healthy lifestyle score groups. Meanwhile, an inverse association between a healthy lifestyle and cancer mortality was detected when three existing studies were pooled (HR 0.69 [95% CI 0.47, 1.00]) (24–26), which is similar to the finding in the current study. Our study adds new evidence to this field

Table 3—HR (95% CI) of cause-specific mortality according to lifestyle score category

	Score category*						
	0–2	3	4	5	6–7	*P* for trend	HR (95% CI) per score point*
Cancer							
No. of cases/person-years	106/18,245	147/33,792	181/47,722	133/37,006	58/16,803		
Model 1	1	0.74 (0.58, 0.95)	0.65 (0.51, 0.83)	0.60 (0.47, 0.78)	0.55 (0.40, 0.76)	<0.001†	0.87 (0.81, 0.92)
Model 2	1	0.74 (0.58, 0.96)	0.66 (0.51, 0.84)	0.61 (0.47, 0.80)	0.57 (0.41, 0.79)	<0.001†	0.87 (0.82, 0.93)
Model 3	1	0.75 (0.58, 0.96)	0.66 (0.52, 0.85)	0.62 (0.47, 0.80)	0.57 (0.41, 0.80)	<0.001†	0.87 (0.82, 0.93)
CVD							
No. of cases/person-years	77/18,245	86/33,792	114/47,722	69/37,006	24/16,803		
Model 1	1	0.59 (0.43, 0.81)	0.55 (0.41, 0.74)	0.42 (0.30, 0.59)	0.30 (0.19, 0.48)	<0.001†	0.77 (0.71, 0.83)
Model 2	1	0.61 (0.44, 0.83)	0.58 (0.43, 0.78)	0.45 (0.32, 0.63)	0.34 (0.21, 0.54)	<0.001†	0.79 (0.72, 0.85)
Model 3	1	0.61 (0.45, 0.84)	0.60 (0.45, 0.81)	0.46 (0.33, 0.65)	0.35 (0.22, 0.56)	<0.001†	0.79 (0.73, 0.86)
Respiratory disease							
No. of cases/person-years	27/18,245	31/33,792	34/47,722	17/37,006	6/16,803		
Model 1	1	0.64 (0.38, 1.08)	0.53 (0.31, 0.88)	0.34 (0.18, 0.63)	0.25 (0.10, 0.60)	<0.001†	0.72 (0.62, 0.83)
Model 2	1	0.65 (0.39, 1.09)	0.54 (0.32, 0.90)	0.35 (0.19, 0.65)	0.26 (0.10, 0.63)	<0.001†	0.73 (0.63, 0.84)
Model 3	1	0.64 (0.38, 1.07)	0.53 (0.32, 0.89)	0.35 (0.19, 0.65)	0.26 (0.10, 0.63)	<0.001†	0.73 (0.63, 0.84)
Neurodegenerative disease							
No. of cases/person-years	8/18,245	22/33,792	15/47,722	19/37,006	10/16,803		
Model 1	1	1.46 (0.65, 3.29)	0.66 (0.28, 1.57)	0.98 (0.42, 2.29)	1.01 (0.39, 2.61)	0.514	0.94 (0.79, 1.14)
Model 2	1	1.45 (0.64, 3.28)	0.66 (0.28, 1.58)	0.97 (0.41, 2.28)	1.06 (0.40, 2.75)	0.557	0.95 (0.79, 1.15)
Model 3	1	1.47 (0.65, 3.35)	0.64 (0.26, 1.53)	0.95 (0.40, 2.24)	1.00 (0.38, 2.63)	0.472	0.94 (0.78, 1.13)
Digestive disease‡							
No. of cases/person-years	25/18,245	18/33,792	21/47,722	17/53,809			
Model 1	1	0.41 (0.22, 0.76)	0.37 (0.20, 0.66)	0.26 (0.14, 0.50)		<0.001†	0.66 (0.55, 0.78)
Model 2	1	0.42 (0.23, 0.78)	0.39 (0.21, 0.70)	0.28 (0.15, 0.53)		<0.001†	0.67 (0.56, 0.80)
Model 3	1	0.42 (0.23, 0.78)	0.38 (0.21, 0.70)	0.28 (0.14, 0.53)		<0.001†	0.67 (0.56, 0.80)
Other§							
No. of cases/person-years	65/18,245	96/33,792	71/47,722	45/37,006	19/16,803		
Model 1	1	0.84 (0.61, 1.16)	0.46 (0.32, 0.64)	0.37 (0.25, 0.55)	0.33 (0.20, 0.56)	<0.001†	0.73 (0.67, 0.80)
Model 2	1	0.85 (0.62, 1.17)	0.47 (0.34, 0.67)	0.39 (0.27, 0.58)	0.35 (0.21, 0.60)	<0.001†	0.74 (0.68, 0.81)
Model 3	1	0.85 (0.62, 1.17)	0.48 (0.34, 0.68)	0.40 (0.27, 0.58)	0.35 (0.21, 0.60)	<0.001†	0.74 (0.68, 0.81)

*HRs were calculated in Cox proportional hazards model: model 1, adjustment for age (years), sex (women or men), ethnicity (White British or other), education (college/university degree or other), Townsend deprivation index (quintiles), employment (currently employed or not), and family history of diabetes (yes or no); model 2, further adjustment for BMI (<25.0, 25.0–29.9, or ≥30 kg/m^2), WHR (≤0.85/0.90 or >0.85/0.90 for women/men, respectively), and prevalent diseases (yes or no) based on model 1; model 3, further adjustment for diabetes duration (<1, 1–5, 5–10, or ≥10 years), HbA_{1c} level (<53 or ≥53 mmol/mol [7.0%]), diabetes-related microvascular disease (yes or no), and diabetes medication use (oral antidiabetes drug only, insulin, or neither) based on model 2. †*P* value for trend <0.05 after Bonferroni correction. ‡Lifestyle score was categorized into four groups (0–2, 3, 4, 5–7) due to limited case numbers. §Mortality from causes other than cancer, CVD, respiratory disease, neurogenerative disease, or digestive disease.

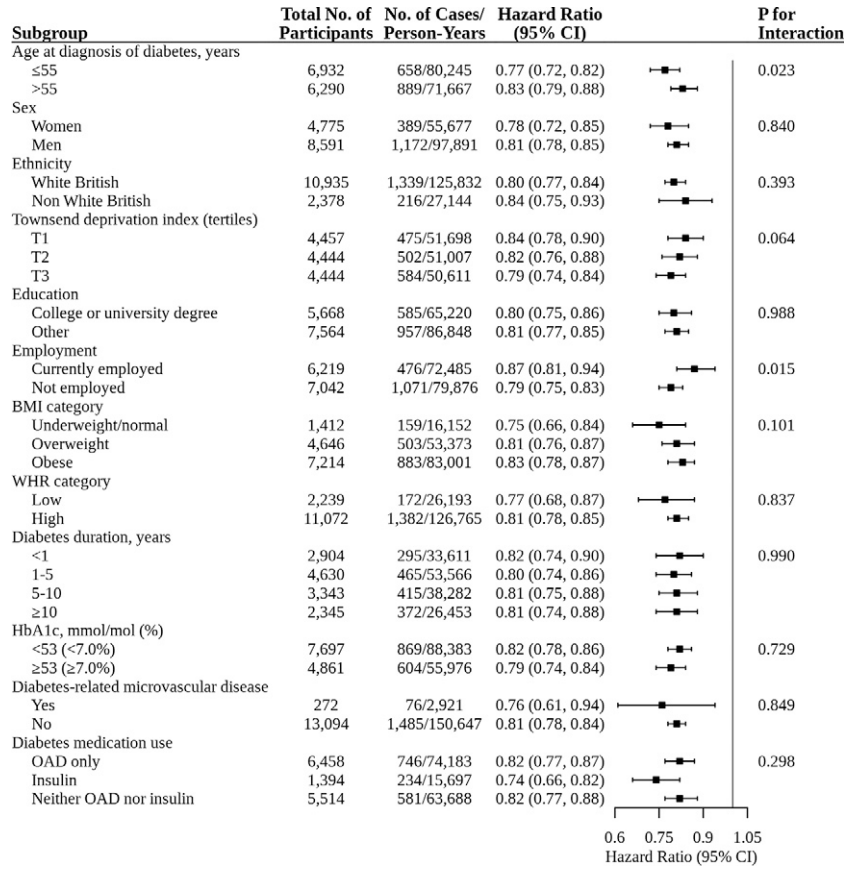

Figure 1—Association between lifestyle score and all-cause mortality risk stratified by potential risk factors. HRs (95% CIs) were calculated in Cox proportional hazards model after adjusting for age (years), sex (women or men), ethnicity (White British or other), education (college/university degree or other), Townsend deprivation index (quintiles), employment (currently employed or not), family history of diabetes (yes or no), BMI (underweight/normal, <25.0 kg/m^2; overweight, 25.0–29.9 kg/m^2; or obese, ≥30 kg/m^2), WHR (low, ≤0.85/0.90, or high, >0.85/0.90, for women/men, respectively), prevalent diseases (yes or no), diabetes duration (<1, 1–5, 5–10, or ≥10 years), HbA_{1c} level (<53 or ≥53 mmol/mol [7.0%]), diabetes-related microvascular disease (yes or no), and diabetes medication use (oral antidiabetes drug only, insulin, or neither). The strata variable was not included in the model when stratifying by itself. All *P* values for interaction were nonsignificant after Bonferroni correction. OAD, oral antidiabetes drug.

that a higher healthy lifestyle score is associated with a lower risk of mortality from respiratory disease and digestive disease. Previous investigations suggested the potential benefits of a healthy lifestyle on lowering the risk of neurodegeneration (27,28), which has also been observed in the current study (Supplementary Table 18), while the evidence on mortality due to neurodegenerative disease is limited. We specifically investigated the role of a healthy lifestyle on the risk of neurodegenerative disease mortality and reported a null association. The lack of relationship could be explained by the nature of the neurodegenerative disease, namely, not being a life-threatening disease such as heart disease or stroke. In addition, our study included relatively young participants with an average age of 59.2 years, while neurodegenerative disease (e.g., Alzheimer disease) is more prevalent in the elderly. We hypothesized that a longer follow-up time, when our middle-aged participants reach older ages, could have shown a significant relationship between a healthy lifestyle and neurodegenerative disease mortality.

Previous studies mostly include four well-characterized modifiable factors (smoking, alcohol consumption, physical activity, and diet) to define an overall healthy lifestyle, and emerging lifestyle factors, such as sleep, sedentary behavior, and social connection, have rarely been taken into account (6,29). It is known that inadequate sleep duration is associated with glycemic control among patients with diabetes (30), and a recent study reported a J-shaped relationship between sleep duration and all-cause and cause-specific mortality risk (31). Several clinical trials have demonstrated the benefits of interrupting prolonged sitting on glycemic control, which would, directly and indirectly, affect the long-term health of patients with diabetes (32,33). Besides, in a cross-sectional study among patients with type 2 diabetes, investigators observed that a smaller social network size was associated with macrovascular complications (34). Our findings support previous studies by showing independent associations of these emerging lifestyle factors with all-cause mortality risks, especially within a varying level of adherence to conventional lifestyle factors, and call for further investigations to explore novel lifestyle factors that may further facilitate the long-term survival of patients with diabetes.

In our study, nearly one-third of all-cause deaths in this population with type 2 diabetes could be attributed to a lack of adherence to 6 or 7 low-risk lifestyle factors, which is lower than that in the general population (35). One possible explanation is the greater adherence to an overall low-risk lifestyle in the current population and higher cutoffs in calculation of the PAR (10.8% of participants with 6–7 low-risk lifestyle factors vs. 89.2% with ≤5 in our population; 1.3% of participants with 5 low-risk lifestyle factors vs. 98.7% with ≤4 in the study of the general population). Another reason might be the smaller effect size in this group, which might be due to a larger contribution of nonlifestyle factors to mortality among patients, such as diabetes severity.

In the current study, we observed a consistent, inverse association between lifestyle score and all-cause mortality risk irrespective of factors reflecting the diabetes severity, including years lived with diabetes, glycemic control, the prevalence of diabetes-related microvascular disease, and diabetes medication use. Intervention studies have highlighted the potential benefits of lifestyle modification: for individuals in the early stage of diabetes, the lifestyle intervention could potentially delay the need for antihyperglycemic drug therapy or induce partial remission of type 2 diabetes (36,37); for those in the

more advanced stage, it could potentially improve glycemic control and avoid pharmacological intensification (38). In addition, we observed a stronger inverse association between lifestyle score and all-cause mortality risk among participants who were not employed at baseline or those with earlier-onset diabetes, though the interactions were not statistically significant after Bonferroni correction. Given that 80.1% of unemployed participants were retired (n = 5,641), a possible explanation might be the increased flexibility of lifestyle choices while being out of the labor market and the intensification of some lifestyle factors after retirement. For example, retired participants who are socially isolated might be more severely isolated than their employed counterparts. Besides, individuals with an early onset of diabetes might be less likely to have intensive management of risk factors when diagnosed compared with those with later onset, leading to a stronger effect of individual lifestyle modification (39).

The strengths of our study include the large sample size and rich data resources, which enabled detailed analyses on mortality from multiple causes and stratification according to potential risk factors. Several limitations also warrant comments. First, participants in the UK Biobank were primarily Caucasians, limiting the generalizability of findings to other ethnic groups. Second, individuals with type 2 diabetes who were excluded from the analysis were more likely to be less educated, less employed, and more likely to live in areas with lower socioeconomic levels. Given that the association between an unhealthy lifestyle and mortality risk became stronger with increasing levels of socioeconomic deprivation (40), the influence of adherence to an overall healthy lifestyle might be underestimated. However, the results remained similar after imputation of missing exposures and covariates. Third, lifestyle factors were measured only at baseline, and lifestyle changes could not be captured. Nevertheless, the results remained consistent after exclusion of undiagnosed patients for whom we assumed that the lifestyle might change drastically due to the awareness of diabetes. Fourth, a lifestyle score with the assignment of the same weights to each lifestyle factor might function to ignore the varying magnitudes of associations between individual factors and mortality risk. However, we generated a weighted lifestyle score based on our study population and observed similar results. Fifth, lifestyle behaviors could be influenced by undiagnosed diseases or poor health at baseline. Although no significant interaction was detected with stratification by self-rated health status and the results were similar after exclusion of those with poor self-rated health and exclusion of deaths that occurred within the first 2 or 4 years of follow-up, the possibility of reverse causation cannot be eliminated. Finally, due to the nature of the observational study, residual confounding was inevitable and we cannot derive causality between lifestyle modification and mortality in patients with type 2 diabetes, which warrants more well-conducted interventional studies to verify.

In conclusion, adherence to a healthy lifestyle is consistently associated with lower risks of all-cause and cause-specific mortality among individuals with varying diabetes severity. Furthermore, our study supports independent roles of additional lifestyle factors, such as sleep, social connection, and sedentary behaviors, that have been included in diabetes management guidelines. These findings highlight that a wide range of lifestyle strategies could be adopted to facilitate the long-term survival of patients. Further studies are needed to explore the potential benefits of other behaviors within this population to align with their personal preferences and medical requirements.

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