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Healthy lifestyle factors and combined macrovascular and microvascular events in diabetes patients with high cardiovascular risk: results from ADVANCE

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Abstract

Background To explore whether healthy lifestyle factors (HLFs) predict a lower risk of major macrovascular and microvascular events and death in people with type 2 diabetes (T2D) with a high risk of vascular complications.

Methods Post hoc analyses of 11,133 participants with T2D in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial who were assigned a score ranging from 0 to 4 based on the number of baseline HLFs: never smoked, moderate-to-vigorous physical activity, ideal waist/hip ratio, and low-to-moderate alcohol consumption. Multivariable Cox models were used to determine associations of 0, 1, 2, and ≥ 3 HLFs with vascular events and all-cause mortality.

Results Compared to participants with no HLFs, hazard ratios for participants with 3 or 4 HLFs were 0.68 (95% confidence interval [CI] 0.57–0.81) for the composite of major macrovascular or microvascular events, 0.58 (0.46–0.75) for major macrovascular events, 0.78 (0.61–0.99) for microvascular events, and 0.48 (0.37–0.63) for all-cause mortality during a median follow-up of 5 years. Each increment in HLF score was significantly associated with lower rates of these outcomes. There was no heterogeneity in the effect on any outcome by HLF across randomized intensive blood glucose control and blood pressure lowering treatments.

Conclusions HLFs are associated with lower risks of major macrovascular and microvascular events and lower rates of death in high-risk adults with T2D.

Keywords Diabetes, Healthy lifestyle factors, ADVANCE, Major macrovascular events, Microvascular events

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Background

Type 2 diabetes (T2D) is a global public health issue with its prevalence rising worldwide, such that an estimated 1.31 billion people will be affected by 2050 [1]. Macrovascular complications, such as stroke and coronary artery disease, along with microvascular complications such as diabetic nephropathy and retinopathy, are the leading causes of death and disability in people with T2D [1–4]. Thus, early detection and effective intervention are crucial for improving health outcomes and quality of life.

Recent prospective observational studies indicate that an overall healthy lifestyle that includes not smoking, engaging in moderate to vigorous physical activity, adopting a healthy diet, and maintaining an ideal body weight, is associated with lower risks of macrovascular and microvascular complications in adults with T2D without established cardiovascular disease (CVD) [5–8]. Although other studies demonstrate variable rates of diabetes-related complications by ethnicity and comorbid vascular complications [9–11], there are limited data on the relation of healthy lifestyle factors (HLFs) and diabetes complications in adults with T2D patients who are at high-risk of CVD and across different ethnicities.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, as well as other studies, have shown that intensive glycemic and blood pressure (BP) management are effective in reducing macrovascular and microvascular complications in T2D [12–14]. However, to our knowledge, whether an overall healthy lifestyle modifies the effects of glucose and BP control in those with T2D is uncertain. Therefore, the aim of this study was to explore whether HLFs predict a lower risk of major macrovascular and microvascular events and death, and to determine if HLFs modify the effects of intensive glucose and BP control on outcomes in people with T2D with a high risk of vascular complications.

Methods

Study design

ADVANCE was a 2×2 factorial randomized controlled trial of intensive blood glucose control and BP lowering in patients with T2D, as described elsewhere [12–14]. In brief, a total of 11,140 adults (age ≥ 55 years) with T2D, and a history of major macrovascular or microvascular disease or at least one other risk factor for CVD, were recruited from 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America. After a 6-week run-in period, participants were randomly assigned to a fixed combination of perindopril and indapamide (2 mg/0.625 mg for the first three months and 4 mg/1.25 mg thereafter) or a matching placebo, and to either an intensive glucose control strategy (target hemoglobin A1c of ≤ 6.5%) or standard glucose control (with target glycated hemoglobin levels defined according to local guidelines) [12–14]. Ethics approval for the study was obtained from each center, and all participants provided written informed consent. The study is registered at ClinicalTrials.gov (registration no. NCT00145925).

Definition of healthy lifestyle factors

In the present study, we pre-selected four lifestyle factors based on prior knowledge [5–8, 15, 16] and available data in ADVANCE: smoking status, alcohol consumption, level of physical activity, and waist/hip ratio (WHR). Smoking status, alcohol consumption, and physical activity were self-reported using a standardized protocol, and WHR was derived from measures (waist circumference divided by hip circumference) at the initial registration visit. WHR can be considered a measure of fat distribution that may be an indicator of a person's overall physical health, lifestyle or behavior [7, 8, 15, 16]. HLFs were defined as having: (i) never smoked [17]; (ii) a moderate-to-vigorous level of physical activity (defined as moderate or vigorous exercise > 15 min at least once per week) [18]; (iii) low-to-moderate level of alcohol consumption (defined as ≤ 21 drinks per week for men, ≤ 14 drinks per week for women) [19, 20]; and (iv) an ideal WHR (defined as < 0.9 cm/cm in men, < 0.85 cm/cm in women) [21, 22]. A total score for HLF was calculated, whereby 1 point was given to those achieving each individual factor, such that the total score ranged from 0 to 4. Thus, a higher score indicated greater adherence to a healthy lifestyle.

Outcomes

The primary outcome was a composite of major macrovascular and microvascular events. Major macrovascular events were defined as death from a cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke. Major microvascular events were defined as new or worsening nephropathy (development of macroalbuminuria, doubling of the serum creatinine to a level of at least 200 μmol/L, need for renal replacement therapy, or death due to renal disease) or retinopathy (development of proliferative retinopathy, macular edema, diabetes mellitus–related blindness, or retinal photocoagulation therapy). Secondary outcomes were major macrovascular events, major microvascular events, all-cause mortality, new or worsening nephropathy, new or worsening retinopathy and cardiovascular death separately.

Statistical analyses

Participants were categorized into four groups based on overall HLF score (0, 1, 2, and ≥ 3). Baseline characteristics across categories were summarized as mean and standard deviation (SD) or median and interquartile

interval (IQI), as appropriate, or frequency (%) and compared using ANOVA, Wilcoxon rank-sum, or chi-squared tests, as appropriate. Cumulative incidence rates of study outcomes across HLF categories were estimated using Kaplan–Meier curves and compared using log-rank tests. Cox proportional hazards models quantified associations between each HLF (never smoked compared to previous or current smoking, moderate to vigorous level of physical activity compared to no or low physical activity, low to moderate level of alcohol consumption compared to no or higher alcohol consumption, and ideal WHR compared to non-ideal WHR) and HLF score with (0 as the reference) the primary outcome, as well as HLF score and secondary outcomes. Cox proportional hazard models were built based on prior studies and differences in baseline characteristics. Two model adjustment strategies were applied: Model 1 adjusted for age, sex, glucose treatment group allocation, and BP treatment group allocation, Model 2 further adjusted for region of residence (Asia vs not), history of macrovascular disease, history of microvascular disease, duration of diabetes, heart rate, creatinine clearance, currently treated hypertension, any lipid lowing treatment, any antiplatelet, metformin, any sulphonylureas, total cholesterol, triglyceride and hemoglobin A1c. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the four categories of overall HLF scores and per each increment of overall HLF score were calculated.

Tests of the homogeneity of the treatment effects of intensive glucose control and intensive BP lowering intervention on primary and secondary outcomes according to the HLF score were conducted by adding an interaction term in the Cox regression models. Separate analyses were undertaken for the two randomized interventions in ADVANCE: the BP lowering treatment results were obtained from the database locked at the end of the follow-up for this intervention (median follow-up of 4.4 years); and at the end of the trial (median 5 years) for the intensive glucose control strategy [14].

To assess the generality of the association between overall HLF and primary and secondary outcomes, subgroup analyses were conducted in multivariable-adjusted models stratified by age (≥65 vs. <65 years, median), sex (women, men), region of residence (Asia vs. not), diabetes duration (≥7 vs. <7 years, median), history of macrovascular disease, and history of microvascular disease. All analyses were performed with Stata 17.0 (Stata Corp, College Station, TX, USA).

Results

Among 11,140 participants with T2D in ADVANCE, there were 11,133 (mean [SD] age 65.8 [6.4] years, 4731 [42.5%] women) with available data for the present study (7 patients were excluded due to lack of baseline WHR data). Table 1 shows the distribution of number of HLFs; only 125 patients had all 4 HLF variables. In comparison to patients with fewer HLFs, those with higher HLF scores tended to be female and were recruited from Asia, had fewer co-morbidities related to macrovascular and microvascular diseases, and had a lower use of metformin, sulphonylureas, lipid lowering and antiplatelet medicines. Patients with a higher HLF score also tended to have lower body-mass index (BMI), waist circumference, hemoglobin A1c, triglycerides, creatinine clearance, urine albumin-to-creatinine ratio, and heart rate (Table 1).

During a median follow-up of 5 years, 2123 (19.1%) composite major macrovascular and microvascular events were observed. The associations between individual HLF and the composite endpoint are shown in Additional file 1: Table S1. Never smoking (HR 0.90, 95% CI 0.82–1.00) compared to previous or current smoking, moderate-to-vigorous physical activity (HR 0.80, 95%CI 0.73–0.88) compared to no or low physical activity, and low-to-moderate alcohol consumption (HR 0.86, 95% CI 0.77–0.96) compared to no or higher alcohol consumption, were all independently associated with a lower risk of the composite endpoint after adjustment for confounders (Model 2).

Figure 1A shows the Kaplan–Meier curves for composite endpoint by the HLF scores. Participants with more HLF had a lower cumulative incidence rate of composite events (log-rank $P<0.0001$). Compared to participants without any HLF, those with a 1, 2, and ≥3 HLF score had a 16% (HR 0.84, 95% CI 0.74–0.97), 28% (HR 0.72, 95% CI 0.63–0.83) and 32% (HR 0.68, 95% CI 0.57–0.81) lower risk of composite events after adjustment for confounders (Model 2), respectively (Table 2). Moreover, HLFs were associated with a dose-dependent reduction in the composite events; each increment in HLFs score was associated with a 13% (HR 0.87, 95% CI 0.83–0.92) lower risk of composite events (Table 2).

During a median follow-up of 5 years, 1145 (10.3%) major macrovascular and 1131 (10.2%) major microvascular events, and 1031 (9.3%) all-cause deaths were observed. Kaplan–Meier curves show that participants with more HLF had significantly lower cumulative incidence rates of major macrovascular events (Fig. 1B, log-rank $P<0.0001$), major microvascular events (Fig. 1C, log-rank $P=0.0104$) and all-cause mortality (Fig. 1D, log-rank $P<0.0001$). After adjustment for confounders (Model 2), compared to participants without any HLFs, those with 2, and ≥3 HLFs had 34% (HR 0.66, 95% CI 0.55–0.79), and 42% (HR 0.58, 95% CI 0.46–0.75) lower risk of major macrovascular events; 23% (HR 0.77, 95% CI 0.63–0.93), and 22% (HR 0.78, 95% CI 0.61–0.99)

Table 1 Baseline characteristics of ADVANCE participants according to number of healthy lifestyle factors (HLFs)

Characteristics	Total	Numbers of HLFs				*P* value
		0	1	2	≥3	
No. of patients	11,133	1,226	4,439	4,065	1,403	
Age, y	65.8 (6.4)	65.3 (6.4)	65.8 (6.5)	65.8 (6.4)	66.0 (6.1)	0.063
Women, n (%)	4,731 (42.5)	375 (30.6)	1,977 (44.5)	1,790 (44.0)	589 (42.0)	< 0.001
Residence in Asia, n (%)	4,136 (37.2)	313 (25.5)	1,811 (40.8)	1,568 (38.6)	444 (31.6)	< 0.001
Medical and lifestyle history						
Diabetes duration, y	7.9 (6.4)	7.5 (6.3)	8.0 (6.4)	8.0 (6.2)	7.9 (6.6)	0.077
History of macrovascular disease	3,586 (32.2)	482 (39.3)	1,482 (33.4)	1,264 (31.1)	358 (25.5)	< 0.001
History of microvascular disease	1,154 (10.4)	138 (11.3)	479 (10.8)	426 (10.5)	111 (7.9)	0.011
Currently treated hypertension	7,651 (68.7)	825 (67.3)	3,095 (69.7)	2,799 (68.9)	932 (66.4)	0.082
Atrial fibrillation	700 (6.3)	72 (5.9)	284 (6.4)	243 (6.0)	101 (7.2)	0.38
Heart failure	355 (3.2)	40 (3.3)	153 (3.4)	131 (3.2)	31 (2.2)	0.15
Never smoker	6,464 (58.1)	0 (0.0)	2,333 (52.6)	2,861 (70.4)	1,270 (90.5)	< 0.001
Low to moderate alcohol drinking[a]	2,971 (26.7)	0 (0.0)	721 (16.2)	1,380 (33.9)	870 (62.0)	< 0.001
Body-mass index, kg/m^2	28.3 (5.2)	29.8 (5.5)	28.6 (5.2)	27.9 (5.1)	27.4 (5.0)	< 0.001
Waist measurement (cm)	98.5 (13.1)	104.7 (12.8)	100.1 (12.6)	96.9 (12.8)	93.0 (12.7)	< 0.001
Waist/hip ratio (cm/cm)	0.9 (0.1)	1.0 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	< 0.001
Moderate to vigorous physical activity[b]	5,109 (45.9)	0 (0.0)	1,079 (24.3)	2,722 (67.0)	1,308 (93.2)	< 0.001
Cardiovascular factors						
Systolic BP, mm Hg	145.0 (21.5)	144.8 (22.2)	145.3 (21.9)	145.1 (21.3)	143.9 (20.4)	0.21
Diastolic BP, mm Hg	80.6 (10.9)	80.3 (11.3)	80.8 (11.0)	80.7 (10.9)	80.3 (10.6)	0.33
Heart rate, bpm	74.1 (12.1)	74.3 (12.4)	74.7 (12.1)	73.9 (12.1)	72.8 (11.6)	< 0.001
Blood glucose (mmol/l)	8.5 (2.8)	8.6 (3.0)	8.5 (2.8)	8.5 (2.7)	8.3 (2.6)	0.008
Hemoglobin A1c, %	7.5 (1.6)	7.6 (1.6)	7.6 (1.6)	7.5 (1.5)	7.3 (1.4)	< 0.001
Total cholesterol, mmol/L	5.2 (1.2)	5.1 (1.2)	5.2 (1.2)	5.2 (1.2)	5.2 (1.2)	< 0.001
Triglycerides, mmol/L	1.6 (1.2–2.3)	1.8 (1.3–2.4)	1.7 (1.2–2.4)	1.6 (1.2–2.3)	1.5 (1.0–2.0)	< 0.001
LDL-cholesterol, mmol/L	3.1 (1.0)	3.0 (1.0)	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)	0.010
HDL-cholesterol, mmol/L	1.3 (0.4)	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)	1.3 (0.4)	< 0.001
Creatinine clearance	82.3 (28.5)	87.1 (30.2)	82.5 (29.6)	81.2 (27.5)	80.2 (26.1)	< 0.001
eGFR, ml/min/1.73 m^2	78.5 (17.8)	77.6 (18.4)	78.1 (18.3)	78.9 (17.5)	79.4 (16.2)	0.010
UACR, μg/mg	15.0 (7.1–39.8)	16.8 (8.0–52.2)	16.0 (7.3–44.2)	14.1 (6.9–34.8)	12.2 (6.2–28.3)	< 0.001
Randomized treatments						
Perindopril-indapamide	5,565 (50.0)	598 (48.8)	2,261 (50.9)	2,010 (49.4)	696 (49.6)	0.41
Intensive blood glucose control	5,569 (50.0)	653 (53.3)	2,189 (49.3)	2,039 (50.2)	688 (49.0)	0.085
Prior use of medications						
Any antiplatelet	5,196 (46.7)	643 (52.4)	2,065 (46.5)	1,873 (46.1)	615 (43.8)	< 0.001
Oral anticoagulant	408 (3.7)	54 (4.4)	151 (3.4)	145 (3.6)	58 (4.1)	0.29
Any lipid lowing	3,930 (35.3)	511 (41.7)	1,564 (35.2)	1,358 (33.4)	497 (35.4)	< 0.001
Any insulin	159 (1.4)	11 (0.9)	63 (1.4)	65 (1.6)	20 (1.4)	0.35
Metformin	6,751 (60.6)	784 (63.9)	2,728 (61.5)	2,452 (60.3)	787 (56.1)	< 0.001
Any sulphonylureas	7,894 (70.9)	840 (68.5)	3,202 (72.1)	2,929 (72.1)	923 (65.8)	< 0.001

Values are mean (SD) for continuous variables (except for triglycerides and UACR), median (interquartile range) for triglycerides and UACR, and number (%) for categorical variables

Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)

BP indicates blood pressure, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *HLFs* healthy lifestyle factors, *LDL* low-density lipoprotein, *UACR* urine albumin-to-creatinine ratio

[a] Low to moderate alcohol drinking: defined as ≤ 21 drinks weekly for men and ≤ 14 drinks for women

[b] Moderate to vigorous physical activity: defined as moderate or vigorous exercise > 15 min at least once per week

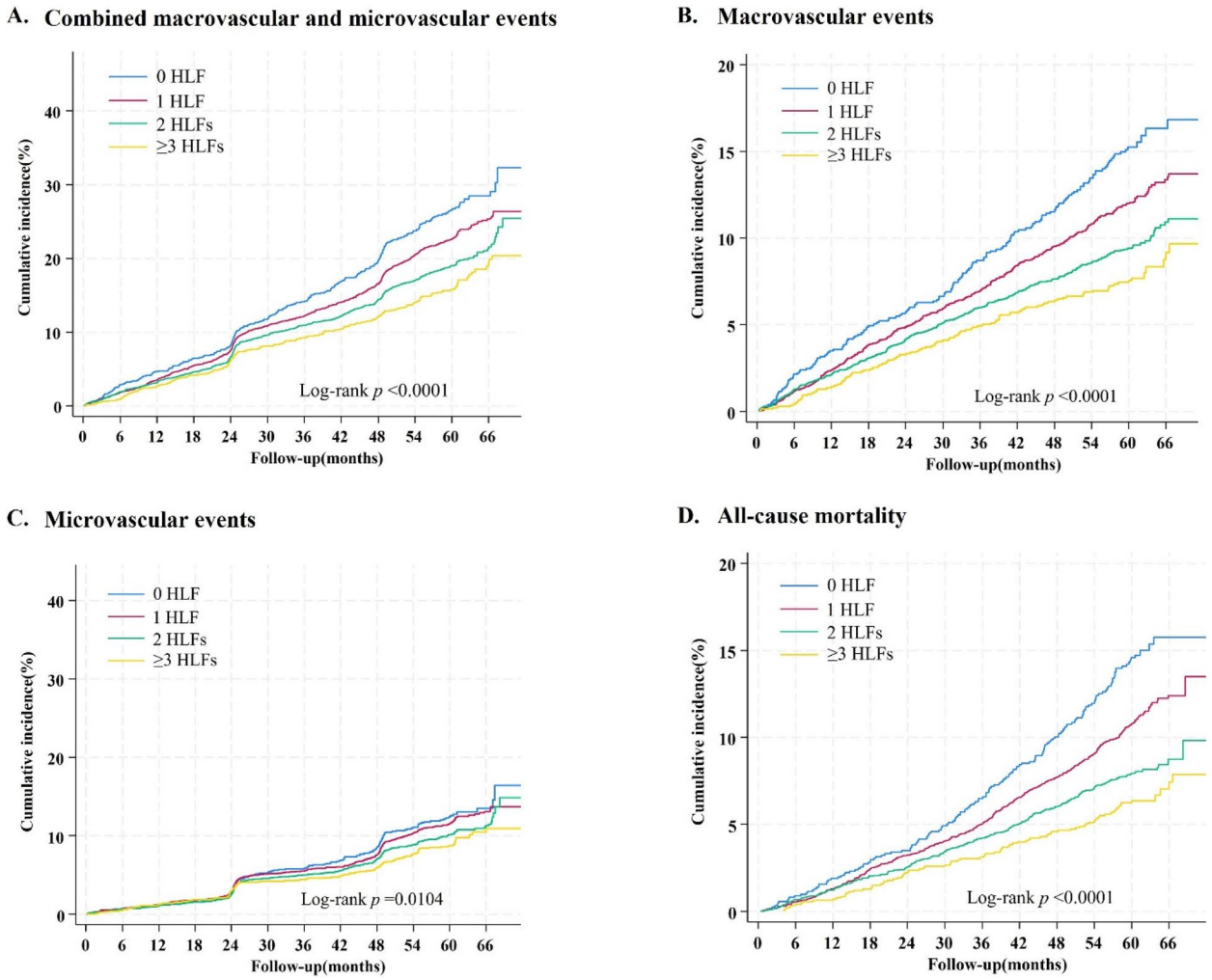

Fig. 1 Kaplan–Meier curves for cumulative incidence rates of study outcomes across HLFs score. **A** Composite macrovascular and microvascular events; **B** Major macrovascular events; **C** Major microvascular events; **D** All-cause mortality

lower risk of major microvascular events; 43% (HR 0.57, 95% CI 0.47–0.69), and 52% (HR 0.48, 95% CI 0.37–0.63) lower risk of all-cause mortality, respectively. Additionally, each one-point increase in HLF score was significantly associated with reduced risks of major macrovascular events, major microvascular events, and all-cause mortality (Table 2). Similar results were observed for adoption to HLF and lower risk of new or worsening nephropathy, and cardiovascular death, but not new or worsening retinopathy in patients with T2D (Additional file 1: Table S2).

Compared with standard glucose control, intensive glucose control reduced composite events (HR 0.91, 95% CI 0.83–0.99), and major microvascular events alone (HR 0.87, 95% CI 0.78–0.98) (Fig. 2A). There was no evidence of heterogeneity in the effect of randomized glucose control treatment across subgroups by HLF score (all P for interaction ≥ 0.573). Similarly, compared to placebo, active BP lowering treatment lowered the risk of composite events (HR 0.89, 95% CI 0.81–0.98), and all-cause mortality (HR 0.84, 95% CI 0.74–0.97) (Fig. 2B). There was no evidence of significant heterogeneity in the effect of active BP lowering treatment by HLFs score on all these outcomes (all P for interaction ≥ 0.270).

There were similar associations between HLFs and lower risk of composite events observed in all subgroups by age, region of residence, sex, diabetes duration, history of macrovascular disease and history of microvascular disease, such that no significant interactions between HLFs and subgroup variables were detected (*P*-interaction ≥ 0.206 for all) (Table 3). A lower risk of major macrovascular events, major microvascular events, and all-cause mortality among patients with higher HLFs scores were confirmed across all subgroups (Additional file 1: Table S3-S5). There was a significant interaction between overall HLFs and sex for the major

Table 2 HRs (95% CIs) for primary and secondary outcomes by HLFs score in ADVANCE

	Number of HLFs				*P* trend	Per point increase in HLFs score
	0	1	2	≥3		
Combined macrovascular and microvascular events						
Events, n (%)	286 (23.3)	907 (20.4)	716 (17.6)	214 (15.3)		
Model 1	1.00	0.87 (0.76–1.00)	0.73 (0.64–0.84)	0.62 (0.52–0.74)	< 0.001	0.85 (0.81–0.89)
Model 2	1.00	0.84 (0.74–0.97)	0.72 (0.63–0.83)	0.68 (0.57–0.81)	< 0.001	0.87 (0.83–0.92)
Macrovascular events						
Events, n (%)	171 (14.0)	500 (11.3)	369 (9.1)	105 (7.5)		
Model 1	1.00	0.81 (0.68–0.97)	0.64 (0.54–0.77)	0.52 (0.40–0.66)	< 0.001	0.80 (0.75–0.86)
Model 2	1.00	0.81 (0.68–0.97)	0.66 (0.55–0.79)	0.58 (0.46–0.75)	< 0.001	0.83 (0.78–0.89)
Microvascular events						
Events, n (%)	140 (11.4)	480 (10.8)	390 (9.6)	121 (8.6)		
Model 1	1.00	0.95 (0.79–1.15)	0.83 (0.68–1.00)	0.73 (0.57–0.93)	0.001	0.89 (0.83–0.95)
Model 2	1.00	0.87 (0.72–1.06)	0.77 (0.63–0.93)	0.78 (0.61–0.99)	0.007	0.91 (0.85–0.97)
All-cause mortality						
Events, n (%)	166 (13.5)	463 (10.4)	314 (7.7)	88 (6.3)		
Model 1	1.00	0.76 (0.64–0.91)	0.56 (0.46–0.67)	0.44 (0.34–0.57)	< 0.001	0.75 (0.70–0.81)
Model 2	1.00	0.76 (0.64–0.91)	0.57 (0.47–0.69)	0.48 (0.37–0.63)	< 0.001	0.77 (0.72–0.83)

HLFs indicates healthy lifestyle factors

Model 1. Adjusted for age, sex, glucose treatment group allocation, and BP treatment group allocation

Model 2. Further adjusted for region of residence (Asia vs. not), history of macrovascular disease, history of microvascular disease, duration of diabetes, heart rate, creatinine clearance, currently treated hypertension, any lipid lowing treatment, any antiplatelet, metformin, any sulphonylureas, total cholesterol, triglycerides and hemoglobin A1c

macrovascular events ($P=0.028$ for interaction, Additional file 1: Table S3). The association between higher baseline HLFs and reduced risk of major macrovascular events was significant only in men but not women. There was no significant interaction (P interaction > 0.05 for all) between overall HLFs and other subgroup variables for major macrovascular events (Additional file 1: Table S3) as well as microvascular events (Additional file 1: Table S4), and all-cause mortality (Additional file 1: Table S5).

Discussion

In the present analysis of over eleven thousand participants with T2D and a high-risk of vascular complications from 20 countries in the ADVANCE trial, we demonstrated that adoption of baseline HLFs defined by never smoking, engaging in moderate-to-vigorous physical activity, low-to-moderate alcohol consumption, and maintaining ideal WHR, was associated with a lower risk of major macrovascular and microvascular events, combined and individually. Moreover, the association between HLFs and lower risk of adverse vascular outcomes was consistent across various ages, in residents of Asia vs not, and in individuals with prior macrovascular or microvascular disease history. In addition, baseline overall HLFs did not modify the treatment effect of intensive BP lowering and intensive glycemic control, although less consistent than intensive BP lowering, on all the outcomes.

Recent studies indicate that greater adherence to HLFs is associated with a reduced risk of major macrovascular and microvascular complications in patients with T2D without vascular disease [5–8, 23, 24]. For example, data from Nurses' Health Study and the Health Professionals Follow-Up Study of 11,527 US females with T2D without CVD found that adherence to a HLF, including having a healthy diet, not smoking, engaging in moderate-to-vigorous physical activity and drinking alcohol in moderation, were significantly associated with a lower risk of CVD events and microvascular complications [5, 7]. Our study comprehensively investigated the association of HLF with composite and separate major macrovascular and microvascular events in adults with T2D. Compared to participants without any HLF, those with two or more HLFs were found to have lower risks of composite major macrovascular and microvascular events, major macrovascular alone, major microvascular alone and all-cause mortality. We also found a dose-dependent inverse relationship between HLF score and these outcomes.

This study addresses some of the limitations of prior studies [5–8, 23] where people have been exclusively recruited from a single country or were free from CVD.

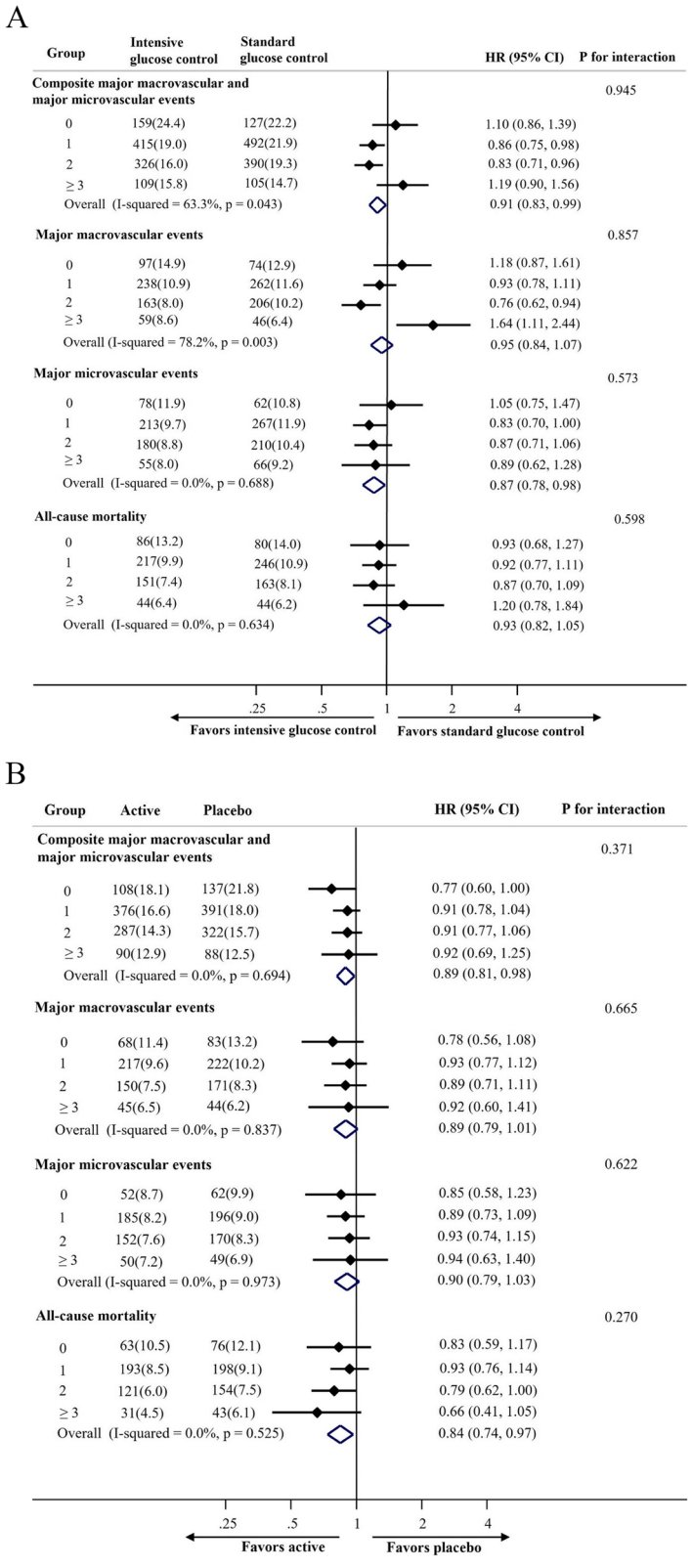

Fig. 2 **A** HRs (95% CIs) for the effect of intensive glucose control (vs standard control) on outcomes by HLFs score in ADVANCE. **B** HRs (95% CIs) for the effect of active blood pressure lowering treatment (vs placebo) on outcomes by HLFs score in ADVANCE

Table 3 HRs (95% CIs) for combined macrovascular and microvascular events by HLFs score in key ADVANCE subgroups

	Number of HLFs					
	0	1	2	≥3	*P* trend	*P* for interaction
Combined macrovascular and microvascular events						
Region of residence						0.329
Asia	1.00	0.90 (0.71–1.14)	0.76 (0.60–0.97)	0.75 (0.55–1.02)	0.007	
Not Asia	1.00	0.81 (0.68–0.95)	0.69 (0.58–0.82)	0.65 (0.52–0.81)	< 0.001	
Sex						0.301
Men	1.00	0.84 (0.72–0.98)	0.69 (0.58–0.81)	0.67 (0.54–0.84)	< 0.001	
Women	1.00	0.88 (0.67–1.14)	0.79 (0.60–1.03)	0.72 (0.51–1.00)	0.017	
Age, years						0.511
< 65	1.00	0.90 (0.72–1.13)	0.71 (0.57–0.90)	0.79 (0.59–1.06)	0.004	
≥ 65	1.00	0.81 (0.68–0.96)	0.72 (0.60–0.86)	0.62 (0.49–0.78)	< 0.001	
Diabetes duration, years						0.828
< 7	1.00	0.73 (0.59–0.90)	0.66 (0.53–0.81)	0.63(0.48–0.84)	< 0.001	
≥ 7	1.00	0.92 (0.77–1.10)	0.75 (0.62–0.90)	0.71 (0.56–0.90)	< 0.001	
History of macrovascular disease						0.206
No	1.00	0.88 (0.73–1.06)	0.79 (0.65–0.96)	0.72 (0.57–0.91)	0.001	
Yes	1.00	0.82 (0.67–1.00)	0.64 (0.52–0.79)	0.66 (0.49–0.88)	< 0.001	
History of microvascular disease						0.919
No	1.00	0.82 (0.70–0.95)	0.72 (0.62–0.84)	0.64 (0.53–0.79)	< 0.001	
Yes	1.00	0.93 (0.69–1.26)	0.70 (0.51–0.95)	0.82 (0.54–1.24)	0.022	

HLFs indicates healthy lifestyle factors. Models adjusted for age, sex, region of residence (Asia vs. not), history of macrovascular disease, history of microvascular disease, duration of diabetes, glucose treatment group allocation, and BP treatment group allocation, heart rate, creatinine clearance, currently treated hypertension, any lipid lowing treatment, any antiplatelet, metformin, any sulphonylureas, total cholesterol, triglycerides and hemoglobin A1c

Participants in ADVANCE were from 20 countries across four continents, and they had a high-risk of vascular complications at baseline: 32% of patients had a history of major macrovascular, 10.4% had microvascular disease or at least one other risk factor for vascular disease. In the subgroup analysis, we found a significant association between HLFs and lower risk of composite major macrovascular and microvascular events, and these events separately, across both Asian and non-Asian populations, irrespective of the presence or absence of macrovascular or microvascular complications. These findings expand the evidence for a general protective effect of maintaining a HLF for the prevention of macrovascular and microvascular complications in T2D. In present study, we also found adoption to HLFs was associated with lower risk of diabetic nephropathy but not diabetic retinopathy, which was consistent with previous findings that baseline HLF was more effective on diabetic nephropathy than diabetic retinopathy [7, 8].

In subgroup analysis, we found the associations between overall HLFs and major macrovascular events differed between men and women, showing significance only in men. The possible explanation is that men had less baseline overall HLFs but more major macrovascular events than women in ADVANCE. In addition, we observed a similar reduction in all-cause mortality and CVD-related deaths with each increase in HLF score. These findings suggest that higher baseline HLFs are associated with a reduced risk of all-cause mortality, largely driven by a lower risk of CVD-related death.

Evidence of lifestyle intervention on complications in T2D has been inconsistent [25–27]. Data from the Steno-2 Study of 160 patients with T2D and microalbuminuria indicates that target-driven behavior modification and pharmacologic therapy significantly reduces the risk of CV and microvascular events over approximately 8-years of follow-up [25]. Conversely, the Look AHEAD (Action for Health in Diabetes) study enrolled 5145 adults with T2D and were overweight or obese to show that an intensive lifestyle intervention focused on weight loss did not reduce cardiovascular events after a median of 9.6 years of follow-up [26, 27]. The difference in these findings may be partially attributed to the distinct intervention strategies and small number of participants. Our analysis suggests that that future clinical research should focus on achieving multiple healthy lifestyle benchmarks rather than any single one

alone, which may represent a more effective strategy for reducing the risk of diabetes complications.

Intensive blood glucose control and active BP lowering treatment have been confirmed to be effective interventions for reducing T2D complications [13, 14, 28]. In the present analysis, we confirmed that the effectiveness of both intensive blood glucose control and active BP lowering treatment in reducing composite major macrovascular and microvascular events across the baseline HLFs. There was no modification of the effect of intensive BP lowering and blood glucose control treatment according to the baseline overall HLF on the composite and individual outcomes. Apart from an anomalous result showing a higher risk of major macrovascular events for ≥ 3 HLFs in those on intensive glucose lowering compared to standard glucose control. However, this is likely a chance finding, and the p value did not indicate significant heterogeneity by HLF ($p = 0.857$) in the glucose treatment effect. Our findings suggest that both intensive BP lowering, and blood glucose control treatment are effective in reducing vascular complications and can be applied to all people with T2D, regardless of level of HLF.

Major strengths of these analyses are the inclusion of a large number of individuals with T2D and high atherosclerotic CVD risk from 20 countries across 4 continents, with comprehensive baseline data on clinical parameters and prespecified endpoints during follow-up. In addition, we are the first to report that overall HLFs at baseline do not modify the intensive blood glucose control and BP lowering treatment effect on macrovascular and microvascular complications in individuals with T2D. Even so, there are several limitations. First, we did not collect information on diet biomarkers nor daily dietary habits, which is an important lifestyle factor associated with a reduced risk of diabetic complications [29, 30], however we did include WHR, a measure of fat distribution, which may be considered an indication for overall physical health. Second, our study consisted of post-hoc analyses from a clinical trial population, although the results of ADVANCE have been shown to be broadly generalizable to those with T2D in community practice [31]. Finally, the possibility of residual confounding could not be fully eliminated in an observational analysis, despite several important potential confounders being controlled for in multivariable-adjusted models.

Conclusions

In summary, our study shows that adults with T2D and a high CVD risk, who had a greater HLF score at baseline, were at a lower risk of future composite major macrovascular and microvascular events, major macrovascular alone, major microvascular alone and all-cause mortality. These associations were consistent across different participant characteristics. The effects of intensive blood glucose control and BP lowering treatment on diabetic complications were consistent across different numbers of overall HLFs.

Abbreviations

ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
BP	Blood pressure
BMI	Body-mass index
CI	Confidence interval
CVD	Cardiovascular disease
HR	Hazard ratio
HLFs	Healthy lifestyle factors
IQI	Interquartile interval
SD	Standard deviation
T2D	Type 2 diabetes
WHR	Waist/hip ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03932-3.

Additional file 1: Table S1. HRs (95% CIs) for combined macrovascular and microvascular events by individual healthy lifestyle factors (HLFs) in ADVANCE. Table S2. HRs (95% CIs) for other outcomes (new or worsening nephropathy, new or worsening retinopathy, cardiovascular death) by HLFs score in ADVANCE. Table S3-S5. HRs (95% CIs) for outcomes by HLFs score in ADVANCE: key subgroups analysis. Table S3 [macrovascular events], Table S4 [microvascular events], Table S5 [all-cause mortality].

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None.

Authors' contributions
JC, MW, QL, DEG, SH, GM, BW, NP, LL, MM, PH conceived, designed and acquired the ADVANCE trial data. SY, DZ and KH contributed to the concept and rationale for the present study. SY and QL conducted statistical analyses with supervision from KH and MW. SY and KH were responsible for the first draft; all authors for major revisions. All authors participated in review and approval of the final manuscript and take responsibility for its content and interpretation. KH is the guarantor of this work.

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Data availability
Restrictions apply to the availability of these data, which were used by agreement of the ADVANCE Management Committee for the current study and are not publicly available.

Declarations

Ethics approval and consent to participate
Ethics approval came from the institutional review board of each center as outlined in:

• Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840.
• Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572.

All participants provided written informed consent to participate in ADVANCE.

Consent for publication
This study was approved for publication by the ADVANCE Management Committee.

Competing interests
SY holds China Scholarship Council (CSC) grant, the National Natural Science Foundation of China (82471226), Jiangsu Provincial Medical Key Discipline (ZDXK202217) and the 6th Jiangsu Province 333 High Level Talents Training Project. JC reports research grants from the NHMRC and from Servier International for the ADVANCE trial and the ADVANCE-ON follow-up study, all before 2014. MW also reports research support from the NHMRC, as well as consultancy work for Freeline in the recent past. CSA holds a Senior Investigator Fellowship of the NHMRC and reports receipt of advisory board fees from AstraZeneca, Australia. GM has received compensations as speaker/chairman/consultant from: Berlin Chemie, IPCA Laboratories, Medtronic Inc USA, Menarini Int, Merck Healthcare KGaA, Omnicuris, Recordati, Sanofi, Servier, Sun Laboratories. NP has received personal speaker fees from Servier, Takeda and Novo Nordisk, and advisory board activities from AstraZeneca and Novo Nordisk, and has received grants for his research group relating to diabetes mellitus from Diabetes UK, NIHR Efficacy and Mechanism Evaluation Programme (EME), Julius Clinical and the British Heart Foundation with a pending grant from Novo Nordisk. N.P. holds no stocks or shares in any such companies All other authors declare that they have no competing interest.

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