Excess Cardiovascular Disease and Mortality in Diabetes: Can It Be Offset With Ideal Cardiovascular Health Trajectories?

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Abstract

Objective: To describe patterns of change in cardiovascular health (CVH) measured by the Life's Simple 7 (LS7) over 6 years in participants with diabetes, and assess the association of these patterns of change with subsequent cardiovascular disease (CVD) and all-cause mortality.

Methods: We conducted a long-term prospective cohort analysis (median follow-up 19 years) using the ARIC study, a community-based, biracial cohort with participants aged 45-64 years at baseline in 1987–1989. The LS7 metrics (smoking, body mass index, physical activity, diet, total cholesterol, blood glucose, and blood pressure) were collected at baseline and 6 years later. At both time points, participants were classified as low (0-2 ideal metrics), moderate (3-4), and favorable (5-7) CVH, and 6-year CVH change categories were created. Cox proportional hazards regressions were used to estimate the association between change categories and CVD and mortality.

Results: The majority (62.2%) of participants with diabetes had a stable-low CVH at both visits, whereas 12.1% had stable-moderate and 0.4% stable-favorable, 14.9% improved, and 10.5% worsened. Compared to participants with stable-low CVH, CVD and mortality risk was lower for those who improved CVH 6 years later, or stable-moderate, or even high- or moderate-to-low CVH. This was driven by favorable changes in blood pressure, cholesterol, physical activity and smoking. Compared to participants free of diabetes with a stable-favorable CVH change, participants with diabetes had higher CVD and mortality risk regardless of their CVH trajectory. However, those with a favorable CVH trajectory displayed the same excess risk as participants without diabetes with stable-low CVH.

Conclusions: Among individuals with diabetes, maintaining or reaching ideal levels of LS7 metrics can help reduce the excess CVD incidence and mortality. A favorable CVH trajectory in people with diabetes carried approximately the same excess CVD and mortality risk than an unfavorable CVH trajectory in people free of diabetes.

Key Questions

What is already known about this subject?

Studies have shown that individuals with favorable cardiovascular health (CVH) experience markedly lower risk of incident diabetes CVD, and all-cause mortality. Whether an ideal CVH profile at midlife or a favorable evolution over time can mitigate the excess risk of CVD carried by diabetes has been understudied.

What does this study add?

Among individuals with diabetes, maintaining or reaching ideal levels on CVH metrics can help reduce the excess CVD incidence and mortality. However, in our study, maintaining favorable CVH over time did not fully attenuate the excess risk of CVD and mortality associated with diabetes.

How might this impact clinical practice?

Our results stress the importance of primordial prevention of diabetes through healthy lifestyle, and of maintaining favorable levels of blood cholesterol and blood pressure to lower the CVD burden in people suffering from diabetes.

Introduction

The number of people with diabetes has increased steadily in the last 2 decades to reach an estimated 463 million adults worldwide, which represents a global prevalence of 9.1% ^{1,2}. Patients with diabetes have a two-fold greater risk of cardiovascular events, and higher risk of death, from vascular causes but also from other causes, such as cancer ³⁻⁶. Randomized clinical trials aiming at controlling cardiometabolic risk factors in patients with diabetes or pre-diabetes, through pharmacological and lifestyle intervention, have shown encouraging results, reducing excess mortality and cardiovascular disease (CVD) risk compared to usual diabetes care ^{7,8}, although others failed to find an effect ⁹.

The American Heart Association (AHA) proposed the use of a composite marker of ideal cardiovascular health (CVH), Life's Simple 7 (LS7), focusing on key risk factors for CVD primordial prevention ¹⁰. LS7 comprises seven behavioral and physiological metrics: smoking, body mass index, physical activity, diet quality, total cholesterol, blood glucose, and blood pressure. Numerous prospective studies have shown that individuals with high LS7 experience markedly lower risk of incident diabetes ^{11,12}, CVD ¹³⁻¹⁵ CVD mortality ^{16,17}, cancer mortality ¹⁸, and all-cause mortality ^{14,15}. Changes in LS7 over time in relation to incidence of hard events or subclinical atherosclerosis have been studied as well ¹⁹⁻²², although not specifically in individuals with diabetes.

Whether an ideal cardiovascular health profile at midlife can mitigate the excess risk of CVD carried by diabetes has been understudied. Two recent nationwide prospective studies have addressed this question, in Sweden ²³ and China ²⁴. In the Swedish cohort, participants with diabetes with 5 risk factors (glycated hemoglobin, blood pressure, albuminuria, smoking and LDL cholesterol) in the optimal range at baseline were not at higher risk of mortality, acute myocardial infarction and stroke compared to a control population with normal glucose metabolism²³. In the Chinese cohort, participants with diabetes who had 5 or more other ideal LS7 metrics at baseline had lower or no excess risk of CVD events compared to individuals without diabetes ²⁴. These studies constitute a promising evidence base, however both studies assessed cardiovascular risk factors at baseline only, and the potential benefit of a positive change or detriment of a negative change in LS7 in patients diagnosed with diabetes has not been studied.

Using data from a large, biracial, population-based prospective cohort study in the United States, our objective was to describe patterns of change in CVH over 5–8 years in participants with diabetes, and assess the association of these patterns of change with subsequent CVD events and all-cause mortality.

Methods

Atherosclerosis Risk in Communities (ARIC) study

ARIC is a biracial population-based prospective cohort study conducted in four U.S. communities, and its design has been described in detail elsewhere ²⁵. The first visit took place from 1987–1989, representing the baseline of this study. LS7 metrics were measured on two occasions - visit 1 in 1987–1989 and visit 3 in 1993–1995. Participants were excluded from the investigation if they had prevalent CVD in 1987–1989 (heart failure, coronary heart disease, or stroke), or missing data (LS7 metrics, or health CVD events or mortality over the follow-up).

Assessment of diabetes

Fasting glucose was measured by the hexokinase/glucose-6-phosphate dehydrogenase method. Diabetes was defined as having any of the following: fasting glucose ≥ 126 mg/dL or non-fasting glucose ≥ 200 mg/dL, self-report of physician diagnosed diabetes, or use of antidiabetic medication in the past 2 weeks before the baseline visit. All the participants with diabetes at visit 1 were included in the “Diabetes” group, and all the participants with no diabetes at visit 1 were in the “No diabetes” group. In sensitivity analyses, we excluded all the individuals with a different diagnosis at visit 3, i.e. diabetes at visit 1 classified as no diabetes at visit 3, and no diabetes at visit 1 who developed diabetes at visit 3.

Cardiovascular health: LS7 metrics

We used the American Heart Association definition of LS7 metrics ¹⁰ at visit 1 and at visit 3, 5–8 years later. We stratified participants into three possible categories - poor, intermediate and ideal – for each metric according to criteria described in **eTable 1**. Body mass index (kg/m^2) was calculated from measured weight and standing height. Smoking status (current, former, or never) was assessed by interview. Dietary intake was assessed using the modified 66-item Harvard Food Frequency Questionnaire ²⁶. Individuals with extreme energy intake of < 600 or $> 4,200$ kcal/day for men or < 500 or $> 3,600$ kcal/day for women were excluded. Ideal dietary intake on five components was defined as follows: fruits and vegetables: ≥ 4.5 cups per day; fish: $\geq$ two 3.5-oz servings per week; fiber-rich whole grains: $\geq$ three 1-oz-equivalent servings per day; sodium: < 1500 mg per day; sugar sweetened beverages: ≤ 450 kcal (36 oz) per week. Physical activity was assessed using the Baecke questionnaire ²⁷, whereby participants report the frequency at which they engage in up to four sports and walking in the previous year. It was converted to minutes per week of moderate or vigorous physical activity ²⁸. Blood pressure was measured three times in a seated position using a random-zero sphygmomanometer after a five-minute rest. The mean of the last two measurements was used for analysis. Fasting total cholesterol was measured by enzymatic methods. Fasting glucose was measured by the hexokinase/glucose-6-phosphate dehydrogenase method. Doctor diagnosis of hypertension, hypercholesterolemia and diabetes, as well as use of antihypertensive, cholesterol-lowering, and glucose-lowering medication in the two weeks prior to each study visit was reported by participants during interview and used in the categorization of LS7 metrics.

Exposure Definition

As a main exposure, we used the following categories, based on the number of ideal LS7 metrics met: Low CVH, 0–2 ideal metrics; Moderate CVH, 3–4 ideal metrics; and Favorable CVH 5–7 ideal metrics. We used as main exposure seven categories of change in CVH over time: Low to Low, Low to Moderate/Favorable, Moderate to Low, Moderate to Moderate, Moderate to Favorable, Favorable to Low/Moderate, Favorable to Favorable. We also grouped them in three broader categories: Stable, Improvement (Low/Moderate to Moderate/Favorable) and Deterioration (Moderate/Favorable to Low/Moderate). Moreover, as a secondary exposure, we calculated a “total LS7 score” as follows: for each individual metric a score of 0 was assigned for poor, 1 for intermediate, and 2 for ideal; the total LS7 score was calculated as the sum of the seven scores, ranging 0–14.

We also investigated the change in individual LS7 metrics and created seven change categories for each of them: Poor to Poor, Poor to Intermediate/Ideal, Intermediate to Poor, Intermediate to Intermediate, Intermediate to Ideal, Ideal to Poor/Intermediate, Ideal to Ideal. We also grouped Intermediate and Poor together into “Non-ideal”, yielding 4 trajectories: Non-ideal to Non-ideal, Non-ideal to Ideal, Ideal to Non-ideal, Ideal to Ideal.

Outcome definition

The outcomes were incident CVD event and all-cause mortality. All participants were followed from the second measure of LS7 (visit 3, 1993–1995) to the date of the CVD event, death, loss to follow-up, or otherwise to December 31, 2014.

CVD was defined as the composite of incident coronary heart disease, ischemic stroke and hospitalized heart failure, as described in earlier reports of ARIC²⁹. Incident coronary heart disease events included fatal coronary heart disease, definite or probable myocardial infarction, and silent myocardial infarction (as determined by ARIC examination Electrocardiogram). Stroke events were defined as ischemic strokes; definite or probable hospitalized embolic or thrombotic strokes were determined from diagnosis codes (*ICD-9* codes 430–437), hospital records, and neuroimaging reports. Eligible stroke cases were classified by a computer algorithm and a physician reviewer, and differences were adjudicated. Heart failure hospitalization was determined by diagnostic code (*ICD-9* code 428) from hospital discharges until 2004 and by additional adjudication by an expert panel after 2004.

All-cause mortality was defined from deaths ascertained through the review of hospital discharge records and death certificates, supplemented by informant interviews or physician questionnaires for out-of-hospital deaths.

Covariates

Data on covariates were extracted from the interviews accompanying the clinical examinations and included: age, sex, university education (yes/no), and race (White, Black).

Statistical Analysis

Comparison between characteristics at visit 1 and visit 3 were made using Chi-squared tests for categorical variables or dependent sample t-tests for continuous variables. We used two approaches to examine the association of change in CVH with adverse outcomes. First, in people with diabetes only, we evaluated how the change in CVH between 1987–1989 and 1993–1995 was associated with subsequent CVD event and mortality. Second, we investigated these associations compared with individuals without diabetes. For all analyses, Cox proportional hazards regression models were used, with age as the time-scale, rounded to the nearest year of age of event or censoring. We used as main exposure the seven categories of change in CVH over time (see Exposure definition). We also grouped them in broader 3 categories: Stable, Improvement and Deterioration. Change in continuous total LS7 score was used as a secondary exposure. The latter two analyses were adjusted for baseline values of total LS7 score. Finally, we investigated the change in every individual LS7 metric in 7 trajectories and in 4 trajectories. All analyses used age as the time-scale and were adjusted for gender, race, and education.

In a first set of sensitivity analyses, we restricted the definition of the “Diabetes” group to participants with a diabetes status both at visit 1 and 3. Similarly, the definition of the “No diabetes” group was restricted to participants with no diabetes at both visit 1 and 3. Another set of sensitivity analysis was done excluding the blood glucose component of the LS7 calculation, so the total number of metrics was 6. Therefore, the total score ranged 0–12 and the Favorable category being people with either 5 or 6 ideal metrics. All analyses were two-tailed and a p-value of less than 0.05 was chosen for statistical significance. Statistical analyses were undertaken using SAS software version 9.4 (SAS Institute Inc., Cary, NC) and R software, version 3.3.2.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

The flow diagram of the selection of the sample based on available data is presented in **e-Figure 1**. As shown in Table 1, compared to individuals free of diabetes (n = 7702), participants with diabetes (n = 788) were much more likely to display a low LS7 status both at baseline and at the following visit (median time between visits: 6 years). This was largely due to poor blood glucose metric as expected, but also poor Body Mass Index (BMI) metric (50% in individuals with diabetes vs 30% in those without to present poor BMI at v3), and poor blood pressure metric (50% vs 31%), and poor cholesterol to a lower extent (23% vs 19%). Diet quality was somewhat less poor in the Diabetes group (21% vs 30%), and no marked differences between the groups in the smoking and physical activity metric was observed.

Table 1
Characteristics of the ARIC population at visit 1 and visit 3 according to diabetes status

	Participants with Diabetes			Participants without Diabetes		
	N = 788			N = 7702		
	1987– 1989	1993– 1995	p- value	1987– 1989	1993– 1995	p- value
Age, mean (SD)	55.4 (5.8)	61.4 (5.8)	< 0.0001	53.9 (5.7)	59.9 (5.7)	< 0.0001
Male, N (%)	375 (47.6)			3136 (40.7)		
University Education, N (%)	565 (71.7)			6406 (83.2)		
White, N (%)	512 (65)			6450 (83.7)		
High income, N (%)	127 (17)	152 (20.2)	< 0.0001	2213 (30.2)	2500 (33.4)	< 0.0001
Current drinker, N (%)	348 (44.3)	290 (36.8)	< 0.0001	4758 (61.9)	4315 (56.1)	< 0.0001
Cigarette smoking, N (%)	149 (18.9)	123 (15.6)	< 0.0001	1698 (22.1)	1298 (16.9)	< 0.0001
BMI (kg/m ²), mean (SD)	31.1 (5.7)	30.8 (5.8)	0.0003	27 (4.9)	28.1 (5.3)	< 0.0001
Glucose (mg/dL), mean (SD)	181.4 (70.9)	194.3 (79.9)	< 0.0001	98.4 (9.1)	102.4 (21.7)	< 0.0001
Glucose lowering medication, N (%)	332 (46.6)	533 (69.6)	< 0.0001	0 (100)	112 (1.5)	< 0.0001
Cholesterol (mg/dL), mean (SD)	220.2 (45)	209.3 (43.8)	< 0.0001	214.3 (40.4)	208.2 (36.9)	< 0.0001
Cholesterol lowering medication, N (%)	39 (5)	115 (14.7)	< 0.0001	214 (2.8)	671 (8.7)	< 0.0001
SBP (mmHg), mean (SD)	127.5 (18.8)	130.9 (19.7)	< 0.0001	118.5 (16.9)	123.6 (18.7)	< 0.0001
Antihypertensive medication, N (%)	331 (42)	403 (51.1)	< 0.0001	1652 (21.5)	2215 (28.8)	< 0.0001
Overall CVH Status, N (%)			< 0.0001			< 0.0001

Abbreviations: LS7, AHA Life's simple seven; BMI, body mass index; SBP, systolic blood pressure

	Participants with Diabetes		Participants without Diabetes	
Low (0–2)	601 (76.3)	568 (72.1)	2789 (36.2)	3120 (40.5)
Moderate (3–4)	179 (22.7)	208 (26.4)	3799 (49.3)	3612 (46.9)
Favorable (5–7)	8 (1)	12 (1.5)	1114 (14.5)	970 (12.6)
LS7 metrics				
Smoking, N (%)	< 0.0001		< 0.0001	
Poor	149 (18.9)	123 (15.6)	1698 (22.1)	1298 (16.9)
Intermediate	23 (2.9)	9 (1.1)	211 (2.7)	121 (1.6)
Ideal	616 (78.2)	656 (83.3)	5793 (75.2)	6283 (81.6)
Body Mass Index, N (%)	< 0.0001		< 0.0001	
Poor	402 (51)	396 (50.3)	1737 (22.6)	2328 (30.2)
Intermediate	293 (37.2)	290 (36.8)	3061 (39.7)	3031 (39.4)
Ideal	93 (11.8)	102 (12.9)	2904 (37.7)	2343 (30.4)
Physical Activity, N (%)	< 0.0001		< 0.0001	
Poor	339 (43)	309 (39.2)	2498 (32.4)	2582 (33.5)
Intermediate	187 (23.7)	169 (21.5)	2029 (26.3)	1779 (23.1)
Ideal	262 (33.3)	310 (39.3)	3175 (41.2)	3341 (43.4)
Diet, N (%)	< 0.0001		< 0.0001	
Poor	219 (27.8)	169 (21.5)	2413 (31.3)	2303 (29.9)

Abbreviations: LS7, AHA Life's simple seven; BMI, body mass index; SBP, systolic blood pressure

	Participants with Diabetes			Participants without Diabetes		
Intermediate	527 (66.9)	571 (72.5)		4946 (64.2)	5039 (65.4)	
Ideal	42 (5.3)	48 (6)		343 (4.5)	360 (4.7)	
Blood Glucose, N (%)			0.03			< 0.0001
Poor	726 (92.1)	625 (79.3)		0 (0)	505 (6.6)	
Intermediate	62 (7.9)	143 (18.2)		3153 (40.9)	3026 (39.3)	
Ideal	0	20 (2.5)		4549 (59.1)	4171 (54.2)	
Blood Cholesterol, N (%)			< 0.0001			< 0.0001
Poor	239 (30.3)	177 (22.5)		1807 (23.5)	1430 (18.6)	
Intermediate	284 (36)	313 (39.7)		2962 (38.5)	3218 (41.8)	
Ideal	265 (33.6)	298 (37.8)		2933 (38.1)	3054 (39.7)	
Blood Pressure, N (%)			< 0.0001			< 0.0001
Poor	342 (43.4)	395 (50.1)		1739 (22.6)	2379 (30.9)	
Intermediate	250 (31.7)	244 (31)		2331 (30.3)	2499 (32.5)	
Ideal	196 (24.9)	149 (18.9)		3632 (47.2)	2824 (36.7)	
Number of ideal LS7 metrics						
0	38 (4.8)	31 (3,9)	< 0.0001	127 (1.7)	114 (1.5)	< 0.0001
1	270 (34.3)	226 (28.7)		887 (11.5)	1015 (13.2)	
2	293 (37.2)	311 (39.5)		1775 (23.1)	1991 (25.9)	

Abbreviations: LS7, AHA Life's simple seven; BMI, body mass index; SBP, systolic blood pressure

	Participants with Diabetes		Participants without Diabetes	
3	139 (17.6)	159 (20.2)	2155 (28)	2163 (28.1)
4	40 (5.1)	49 (6.2)	1644 (21.4)	1449 (18.8)
5	7 (0.9)	10 (1.3)	842 (10.9)	738 (9.6)
6	1 (0.1)	2 (0.3)	263 (3.4)	220 (2.9)
7	0 (0)	0 (0)	9 (0.1)	12 (0.2)
Abbreviations: LS7, AHA Life's simple seven; BMI, body mass index; SBP, systolic blood pressure				

Change in CVH, CVD and mortality in people with diabetes

There were 788 people with diabetes with valid data to calculate LS7 at visit 1 and visit 3, which represent 8.2% of the total sample (n = 8490). The majority of participants with diabetes remained in the same overall CVH category at both waves with 62.2%, 12.1% and 0.4% having persistently Low, Moderate, and Favorable CVH, respectively. Improvement in CVH occurred in 14.9% of diabetes participants, while deterioration in CVH occurred in 10.5% over the 6 years between the measurements.

Over the median follow-up of 19 years (interquartile range (IQR): 13 to 21 years), there were 325 incident CVD cases and over a median follow-up of 20 years (IQR: 16 to 21), 463 of deaths of all-cause. The 6-year change in total LS7 score ranged from - 5 to + 8, and a one-point increase in total LS7 score was associated with a 13% lower CVD risk (HR = 0.87; 95% CI 0.81, 0.93). The association with mortality was slightly weaker (HR = 0.91; 95%CI: 0.86, 0.96).

As shown in Fig. 1, in participants with diabetes, compared to those with persistent Low CVH (Low-Low, reference category), the risk of CVD decreased for those who improved by the second visit (HR = 0.59; 95%CI: 0.41, 0.85). It was also lower for those with stable Moderate CVH (HR = 0.59; 95%CI: 0.40, 0.85), or improved to Favorable CVH, although the confidence interval was wide due to lack of power in that category (n = 6, 1 incident CVD case, HR = 0.29; 95%CI: 0.04, 2.05). The risk was also lower for participants who showed a deterioration of their CVH, but started with Moderate CVH (moderate to low [HR = 0.60; 95%CI: 0.40, 0.90]). The results for participants starting with Favorable CVH at baseline are difficult to interpret due to the small number of participants. Results for all-cause mortality followed the same pattern as with CVD incidence. The only difference was that the diabetes population who improved from Low to Moderate CVH displayed only a weak association (HR = 0.82; 95% CI: 0.62, 1.07) (Fig. 1). When grouping the categories into Stable, Improvement or Deterioration (**eTable 2**), adjusting for the total LS7 score at baseline, compared to those whose CVH worsened, those who remained stable did not show a decreased risk of CVD neither mortality, but those who improved experienced a lower risk of CVD (HR = 0.63; 95% CI 0.48, 0.84) and of mortality (HR = 0.70; 95% CI: 0.55, 0.89).

Inspecting individual metrics separately, a strong association with CVD risk was observed in those who remained in the ideal category of smoking, cholesterol, blood pressure and to a lesser extent physical activity (**eFigure 2**). Regarding all-cause mortality, the metrics with a favorable trajectory that were associated with a lower risk were smoking, physical activity, and blood pressure (**eFigure 3**).

Comparison with individuals without diabetes

Compared to those without diabetes, participants with diabetes were overall at higher risk for CVD and mortality, regardless of baseline and change in CVH (Fig. 2). Overall, however, there was a gradient of risk observed related to CVH trajectories, with the highest Hazards Ratio (HR) observed in those with stable Low CVH. In the no diabetes group, those who started low and improved had HR of similar magnitude as those who started moderate and deteriorated to low (2-fold higher risk). Those who started moderate had similar intermediate HR whether they remained stable or improved, and those who started favorable and deteriorated had only marginally higher risk of all-cause mortality (HR = 1.33; 95% CI: 0.99, 1.78).

When grouped into smaller categories, taking improvement in non-diabetic participants as the reference (Fig. 3), participants with diabetes who also improved their CVH over time still had excess risk, with a 42% (HR 1.42; 95%CI 1.17, 1.72) higher risk of CVD and a 23% (HR 1.23; 95%CI 1.05, 1.43) higher risk of mortality, but this excess risk was much lower than in those with diabetes who worsened (HR 2.49; 95%CI 2.01, 3.08 for CVD and HR 1.84; 95%CI: 1.53, 2.20 for all-cause mortality).

Results from sensitivity analyses with a stricter definition of diabetes display the same trends, with slightly less power (**eTable 3 and eTable 4**). Finally, when the glucose metric was excluded, the gradient observed in people with diabetes was similar (**eTable 5**) but the comparison with people without diabetes showed a stronger gradient. There was nearly a 10-fold increased risk of CVD in people with diabetes with a stable low CVH, compared to individuals without diabetes with a favorable CVH evolution (**eTable 6**).

Discussion

In people with diabetes, a favorable CVH at baseline or an improvement over 6 years at midlife were associated with a lower risk of incident CVD and all-cause mortality over 19 years of follow-up, compared to those who displayed consistently low CVH. Despite having impaired glucose metabolism, maintaining or reaching ideal levels on other cardiometabolic indicators and a healthy lifestyle may help reduce the excess risk in individuals with diabetes. In particular, this seemed to be driven by smoking, physical activity, blood cholesterol and blood pressure. Causal inference is plausible given the demonstrated causal associations for each of the LS7 metrics with CVD events. Compared to participants free of diabetes with stable favorable CVH, participants with diabetes had a higher CVD and mortality risk regardless of their CVH trajectory. However, those with a favorable CVH trajectory displayed the same excess risk as participants without diabetes with constantly low CVH.

Intensive lifestyle intervention studies in diabetes are scarce with mixed findings. The Steno-2 Study in Denmark found clear effects of a 7.8-year intensive therapy in reducing mortality and CVD incidence in

the subsequent 5.5 years as compared to conventional therapy ⁷. The Da Qing Diabetes Prevention study in China found long-term effects of a 6-year intervention in people with impaired glucose tolerance, with a reduction in mortality and CVD over 23 years of follow-up. On the other hand, the Look-AHEAD trial in the USA failed to show an effect on cardiovascular outcomes of an intensive lifestyle intervention over 10 years of follow-up ⁹, observing benefit only when restricting the analyses to participants who lost more than 10% of their body weight ³⁰. Our results show that a favorable 6-year evolution of a cluster of key cardiovascular risk factors at midlife in diabetes participants is associated with lower CVD and mortality compared to those with consistently low CVH. It appeared to be driven by a stabilization of blood cholesterol and blood pressure at optimal levels, non-smoking, and engaging in more physical activity, but not by a change in body weight or diet. In the Look-AHEAD trial, baseline BMI was 36 kg/m², allowing for a greater possible weight loss than in our study where baseline BMI in those with diabetes was 31 kg/m² and the vast majority (84%) remained in the non-ideal category of BMI. That may explain the apparent lesser importance of weight loss in our study compared with the Look-AHEAD trial.

Two long-term observational studies have investigated the excess risk of mortality and CVD among individuals with diabetes according to risk factors at ideal levels ^{23,24}, and only one of them specifically used the AHA LS7 metrics ²⁴. Both studies examined risk factors at baseline and not change in risk factors and therefore are not directly comparable to our findings. The study by Wang and colleagues was a Chinese nationwide cohort of 111,765 adults followed for a mean of 3.8 years, was more powered than the present study but with a much shorter follow-up time. They found that, in people with diabetes, compared with individuals with ≤ 1 ideal LS7, any higher number of ideal LS7 metrics was associated with a lower risk of CVD events, which is in line with our results, despite only measuring the LS7 metrics at baseline. However, when comparing to people free of diabetes (all LS7 profiles combined), individuals with diabetes who had 5 or more ideal LS7 metrics did not carry excess CVD risk (HR = 0.80; 95% CI 0.56, 1.15). In our study, the very low number of individuals with diabetes with consistently favorable LS7 does not allow drawing clear conclusions, but when evaluating the broader “improvement” trajectory in the diabetes group, they were still at greater risk of CVD compared to those without diabetes following such a trajectory. The relative risk was essentially similar to the one observed in people without diabetes following an unfavorable LS7 trajectory. This highlights the intrinsic excess risk carried by diabetes alone, which may not be completely attenuated by an otherwise favorable trajectory of cardiovascular risk factors. Therefore, our results emphasize that primordial prevention of diabetes, in particular through obesity prevention programs and attaining higher levels of LS7, is paramount to reduce CVD burden.

The literature on behavior change in diabetes has shown conflicting results. Some theoretical models suggest that being made aware of a health problem and the long-term complications may entice a behavior change, and others show that ingrained unhealthy habits are hard to overcome ³¹. Overall, observational studies have found that behavior change following diagnosis of diabetes is hard to achieve, apart from smoking ³². In our results, a substantial (30%) proportion of participants with diabetes with a non-ideal smoking profile at baseline moved to ideal smoking profile 6 years later. That figure was 27% for physical activity, whereas it was only 5% for diet quality and body mass index. This

positive behavior evolution in smoking and physical activity was more salient in individuals with diabetes, compared to those without.

Strengths and Limitations

This study is the first to describe CVH change patterns using Life's Simple 7 in diabetes and to assess the potential additional benefit of a positive change in CVH in diabetes. Methodological strengths include the use of a large dataset with a wide age range, a long follow-up of nearly 20 years, and the ability to classify CVH over time. Our investigation has several limitations. First, the ARIC cohort is community-based but not nationally representative. This may affect the estimation of the prevalence of CVH change patterns but not the association between CVH and outcomes. Secondly, although measurement of major risk factors was well standardized across visits, measurement of diet and physical activity was not. Nevertheless, the ARIC estimates for healthy diet and physical activity are similar to other US representative estimates.

Conclusion

In participants with diabetes in a well-characterized biracial cohort, achieving or maintaining higher number of ideal LS7 metrics over 6 years was associated with lower 19-year risk of CVD and mortality compared to those with consistently low CVH. Having diabetes was associated with a higher CVD and mortality, regardless of the CVH trajectory, compared to people without diabetes following a favorable trajectory. However, a favorable CVH trajectory in people with diabetes carried approximately the same excess CVD and mortality risk than an unfavorable CVH trajectory in people free of diabetes. Taken together, our results stress the importance of primordial prevention of diabetes through promotion of a healthy lifestyle, and of maintaining favorable levels blood cholesterol and blood pressure to lower the CVD burden in people suffering from diabetes.

Abbreviations

AHA American Heart Association

ARIC Atherosclerosis Risk in Communities study

CVD Cardiovascular Disease

CVH Cardiovascular Health

LS7 Life's Simple 7 score

Declarations

Ethical approval: The ARIC study protocol was approved by the institutional review board of each participating university.

Data availability statement The Atherosclerosis Risk in Communities Study (ARIC) data are available for request on BioLINCC (<https://biolincc.nhlbi.nih.gov/home/>). Also included are data from ancillary studies.

Author contributions: BG and CL requested the data; BG and CL designed the study; EV conducted the data analysis; BG and CL drafted the manuscript; BG, DLJ, XJ, JJJ, and CL interpreted the results; BG, DLJ, XJ, JJJ, SK, and CL read and critically revised the manuscript.

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Figures

Figure 1

Multivariable associations of 6-year CVH change categories with 19-year risk of CVD incidence and all-cause mortality in participants with Type 2 Diabetes, ARIC n=788

Figure 2

Multivariable association of 6-year CVH change categories with risk of CVD incidence and all-cause mortality comparing patients with and without type 2 diabetes, ARIC n=8490

Figure 3

Multivariable association of 6-year CVH change categories with CVD and all-cause mortality risk comparing patients with and without diabetes, ARIC n=8490

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