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Long-term variability of glycemic markers and risk of all-cause mortality in type 2 diabetes: the Look AHEAD study

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ABSTRACT

Introduction Glycemic variability may predict poor outcomes in type 2 diabetes. We evaluated the associations of long-term variability in glycosylated hemoglobin (HbA_{1C}) and fasting plasma glucose (FPG) with cardiovascular disease (CVD) and death among individuals with type 2 diabetes.

Research design and methods We conducted a secondary, prospective cohort analysis of the Look AHEAD (Action for Health in Diabetes) data, including 3560 participants who attended four visits (baseline, 12 months, 24 months, and 36 months) at the outset. Variability of HbA_{1C} and FPG was assessed using four indices across measurements from four study visits. Participants without CVD during the first 36 months were followed for incident outcomes including a CVD composite (myocardial infarction, stroke, hospitalization for angina, and CVD-related deaths), heart failure (HF), and deaths.

Results Over a median follow-up of 6.8 years, there were 164 deaths from any cause, 33 CVD-related deaths, 91 HF events, and 340 participants experienced the CVD composite. Adjusted HRs comparing the highest to lowest quartile of SD of HbA_{1C} were 2.10 (95% CI 1.26 to 3.51), 3.43 (95% CI 0.95 to 12.38), 1.01 (95% CI 0.69 to 1.46), and 1.71 (95% CI 0.69 to 4.24) for all-cause mortality, CVD mortality, CVD composite and HF, respectively. The equivalent HRs for highest versus lowest quartile of SD of FPG were 1.66 (95% CI 0.96 to 2.85), 2.20 (95% CI 0.67 to 7.25), 0.94 (95% CI 0.65 to 1.35), and 2.05 (95% CI 0.80 to 5.31), respectively.

Conclusions A greater variability in HbA_{1C} was associated with elevated risk of mortality. Our findings underscore the need to achieve normal and consistent glycemic control to improve clinical outcomes among individuals with type 2 diabetes.

Significance of this study

What is already known about this subject?

- Glycemic variability may predict poor outcomes in type 2 diabetes.
- In assessing the adverse effects of long-term variability of glycemic measures in type 2 diabetes, previous studies have only focused on a single glycemic marker and have seldom evaluated several glycemic measures concomitantly.

What are the new findings?

- Participants in the highest quartile of SD of glycosylated hemoglobin (HbA_{1C}) had a 2.10-fold higher risk of all-cause mortality compared with those in the lowest quartile.
- Participants in the top quartile of SD of fasting plasma glucose had a 1.66-fold higher risk of all-cause mortality compared with those in the bottom quartile.
- Long-term glucose variability as assessed by HbA_{1C} was more strongly associated with all-cause mortality.

How might these results change the focus of research or clinical practice?

- Our findings indicate that higher glycemic variability predicts a greater mortality risk and underscore the need to achieve normal and consistent glycemic control to improve clinical outcomes among individuals with type 2 diabetes.

INTRODUCTION

Type 2 diabetes is highly prevalent in the USA and is responsible for significant morbidity and mortality, primarily from cardiovascular disease (CVD).[1 2] Several clinical trials of intensive glucose control have not shown a significant reduction in rates of cardiovascular outcomes.[3–6] This lack of effect of glucose-lowering strategies on CVD outcomes among individuals with diabetes has partially been attributed to the 'metabolic memory' effect.[7–9] In the aforementioned trials and numerous observational studies, hyperglycemia has traditionally been assessed by punctual measurements of fasting plasma glucose (FPG) or glycosylated hemoglobin (HbA_{1C}). Glycemic indices that reflect long-term trends in FPG or HbA_{1C} may allow a more robust assessment of the risks associated with diabetes,[6 10] as it may reflect metabolic memory.[11] Accruing evidence suggests that glycemic variability is a potential predictor

of the excess risk of CVD and death linked to hyperglycemia.[6 10 12–14] Extant reports exploring the link between glycemic variability and cardiovascular outcomes in type 2 diabetes have mainly evaluated the variability of a single glycemic marker only,[12–14] included a small sample size,[12] and lacked racially/ethnically diversity in their samples.[15–19] A limited number of studies have concomitantly assessed the long-term glycemic variability of multiple glycemic markers using a wide range of variability indices in a racially diverse sample of individuals with type 2 diabetes.

The Look AHEAD (Action for Health in Diabetes) study, a multicenter trial of intensive lifestyle intervention, included a large and diverse sample of adults with type 2 diabetes who had serial annual measurements of HbA_{1C} and FPG. We conducted a cohort analysis of the Look AHEAD study to evaluate the associations of long-term variability in HbA_{1C} and FPG with incident cardiovascular outcomes and mortality. We hypothesized that higher glycemic variability would be associated with higher risks of cardiovascular outcomes and deaths.

METHODS

Study design

The Look AHEAD study was a multicenter, randomized clinical trial designed to evaluate effects on cardiovascular outcomes of Intensive Lifestyle Intervention versus Diabetes Support and Education in individuals with type 2 diabetes (ClinicalTrials.gov number: NCT00017953).[20] A total of 5145 overweight or obese adults with type 2 diabetes aged 45 to 76 years were recruited between August 2001 and April 2004 across 16 sites in the USA in the trial, which ended on September 14 2012.

For the current investigation, we included participants with complete data on HbA_{1C} and FPG at the baseline, 12-month, 24-month, and 36-month visits. We excluded participants who had CVD, HF events or died before the 36-month visit (n=650), those with consent restrictions (n=244), or prevalent CVD at baseline (n=691). Following these exclusions, 3560 participants were included in our analyses. Participants were followed for events from their 36-month visit until the occurrence of an outcome or the end of study.

The research protocol was approved by the institutional review board at each participating site and each participant gave an informed consent.[20] We were granted access by the NIH to the publicly available datasets in the NHLBI Biorepository (BioLINCC).

Assessment of variability of glycemic markers

At each visit, participant provided venous blood samples after 12 hours of fasting. Blood assays were performed at the Look AHEAD Central Biochemistry Laboratory. HbA_{1C} was assayed using a dedicated ion exchange high-performance liquid chromatography method (Bio-Rad Variant II). FPG was measured using the glucokinase method.[20]

For each glycemic marker (HbA_{1C} or FPG), long-term variability was defined using four metrics: (1) the intra-individual standard deviation (SD) across the four visits, (2) the coefficient of variation (CV), (3) the average successive variability (ASV) defined as the average absolute difference between consecutive values, and (4) the variability independent of the mean (VIM) computed as $100*SD/mean^{\alpha}$, where α is the regression coefficient based on the natural logarithm of SD on the natural logarithm of the glycemic measure's mean.[13]

As there is no consensus on the gold standard measure of variability, we included multiple indices, which allow the capture of various aspects of glycemic variability.[21]

Ascertainment of clinical outcomes

We assessed four outcomes: (1) all-cause mortality, (2) cardiovascular mortality, (3) a CVD composite (composite of myocardial infarction, hospitalization for angina, stroke, and death from cardiovascular causes), and (4) incident heart failure (HF). The ascertainment process of cardiovascular events in Look AHEAD has been described previously, including the adjudication process.[22]

Covariates

The covariates were selected a priori based on their role as potential confounders. The baseline characteristics included age, sex, race/ethnicity, randomization arm, cigarette smoking status, alcohol consumption, body mass index (BMI), use of antihypertensive medication, duration of diabetes, and estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[23] Additionally, data obtained from baseline through the fourth visit were used to compute average systolic and diastolic blood pressures (BP), average ratio of total to high-density lipoprotein (HDL) cholesterol, average FPG, and average HbA_{1C}.[22]

Statistical analyses

For each glycemic marker, participants were categorized into quartiles of the intraindividual SD. The characteristics of participants were reported across these quartiles as proportions for categorical variables and mean (SD) or median (interquartile range (IQR)) for continuous variables. Categorical variables were compared using the χ^2 test, and continuous variables were compared using the analysis of variance or Kruskal-Wallis test as relevant.

Kaplan-Meier curves were used to assess the time-to-event distributions and were compared using the log-rank test. Cox proportional hazards regression models were used to model each outcome and to compute adjusted HRs and 95% CIs. For both HbA_{1C} and FPG, each measure of variability (SD, CV, ASV, and VIM) was modeled as a continuous variable and quartiles (with the lowest quartile serving as the reference group). Regression models were built in a sequential manner. The first model adjusted for age, sex, race/ethnicity, and randomization

arm (model 1). The second model included covariates in model 1 plus BMI, current smoking, alcohol drinking, use of BP-lowering medication, average total-to-HDL cholesterol ratio, eGFR, duration of diabetes, and average systolic BP (model 2). To explore the effect of glycemic variability independent of glycemic level, we constructed an additional model (model 3), further accounting for average HbA_{1C} (when assessing variability of HbA_{1C}) or average FPG (when assessing FPG variability), except for the VIM metric which already accounts for the mean of HbA_{1C} or FPG.

All analyses were conducted using STATA 14.2 (Stata, College Station, Texas, USA). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Characteristics of study participants

A total of 3560 participants were included in our analyses. Table 1 displays the characteristics of participants by quartiles of SD of HbA_{1C}. Compared with those in the lowest quartile, participants in the highest quartile were younger and more frequently Black or Hispanic. Additionally, they had higher BMI, BP values, ratios of total-to-HDL cholesterol, HbA_{1C}, FPG as well as a longer duration of diabetes. Participants in the lowest quartile were more likely to be women or Caucasians.

The distribution of study participants by quartiles of SD of FPG was generally comparable to that by quartiles of SD of HbA_{1C} (online supplemental table S1).

Over a median follow-up period of 6.8 years (IQR 6.0–7.4), there were a total of 164 deaths from any cause, 33 cardiovascular deaths, 91 HF events, and 340 participants were categorized as having the CVD composite.

Kaplan-Meier curves for all-cause mortality, cardiovascular mortality, CVD composite and incident HF by quartiles of SD of HbA_{1C} are displayed in figure 1. In unadjusted comparisons, higher HbA_{1C} variability was significantly associated with greater risks of all-cause mortality, cardiovascular mortality, and HF, but not the CVD composite (figure 1 and online supplemental figure S1). After multivariable adjustment, these associations remained significant only for all-cause mortality and cardiovascular mortality (table 2).

Long-term variability of HbA_{1c} and clinical outcomes

The adjusted HRs per SD increment in intraindividual SD of HbA_{1C} are displayed in table 2. After full adjustment, each SD increase in the intraindividual SD of HbA_{1C} was associated with HRs of 1.34 (95% CI 1.14 to 1.57, p<0.001) for all-cause mortality, 1.44 (95% CI 1.01 to 2.05, p=0.045) for cardiovascular mortality, 0.95 (95% CI 0.83 to 1.08, p=0.416) for CVD composite and 1.03 (95% CI 0.80 to 1.31, p=0.842) for incident HF (table 2). Similarly, the HRs per SD increase in the VIM of HbA_{1C} were 1.31 (95% CI 1.14 to 1.50, p<0.001), 1.30 (95% CI 0.94 to 1.81, p=0.115), 0.98 (95% CI 0.87 to 1.10, p=0.718), and 1.01 (95% CI 0.80 to 1.29, p=0.911) for all-cause mortality, cardiovascular mortality, CVD composite and incident HF, respectively (online supplemental table S2). The adjusted HRs per SD increment in the CV and ASV of HbA_{1C} are shown in online supplemental tables S3 and S4).

When compared with the lowest quartile, the adjusted HRs associated with the highest quartile of SD of HbA_{1C} were 2.10 (95% CI 1.26 to 3.51), 3.43 (95% CI 0.95 to 12.38), 1.01 (95% CI 0.69 to 1.46), and 1.71 (95% CI 0.69 to 4.24) for all-cause mortality, cardiovascular mortality, CVD composite and incident HF, respectively (table 2). Likewise, the HRs for the highest quartile (vs lowest quartile) of the VIM of HbA_{1C} were 1.59 (95% CI 1.02 to 2.46), 4.54 (95% CI 0.97 to 21.29), 0.90 (95% CI 0.66 to 1.25), and 1.30 (95% CI 0.61 to 2.75) for all-cause mortality, cardiovascular mortality, CVD composite and incident HF, respectively (online supplemental table S2). Similar results were obtained for the CV of HbA_{1C} (online supplemental table S3).

Long-term variability of FPG and clinical outcomes

After multivariable adjustment, the HRs per SD increase in the intraindividual SD of FPG were 1.29 (95% CI 1.08 to 1.53, p=0.005), 1.25 (95% CI 0.84 to 1.86, p=0.272), 1.03 (95% CI 0.91 to 1.18, p=0.609), and 1.17 (95% CI 0.91 to 1.50, p=0.231) for all-cause deaths, cardiovascular deaths, CVD composite and incident HF, respectively (table 3). The equivalent HRs per SD increase in the VIM of FPG were 1.13 (95% CI 0.99 to 1.29, p=0.073), 1.28 (95% CI 0.99 to 1.66, p=0.059), 1.00 (95% CI 0.89 to 1.11, p=0.940), and 1.10 (95% CI 0.89 to 1.37, p=0.386 (online supplemental table S5). The multivariable-adjusted HRs per SD increment in the CV and ASV are shown in online supplemental tables S6 and S7).

The adjusted HRs of the highest (vs lowest) quartile of SD of FPG were 1.66 (95% CI 0.96 to 2.85), 2.20 (95% CI 0.67 to 7.25), 0.94 (95% CI 0.65 to 1.35), and 2.05 (95% CI 0.80 to 5.31) for all-cause mortality, cardiovascular mortality, CVD composite and incident HF, respectively (table 3). The HRs for the highest quartile (vs lowest quartile) of VIM of FPG were 1.53 (95% CI 0.96 to 2.43), 1.25 (95% CI 0.52 to 2.99), 1.02 (95% CI 0.75 to 1.39), and 1.61 (95% CI 0.81 to 3.23) for all-cause mortality, cardiovascular mortality, CVD composite and incident HF, respectively (online supplemental table S5). The HRs by quartiles of CV and ASV of FPG are displayed in online supplemental tables S6 and 7).

DISCUSSION

We evaluated the associations of visit-to-visit variability of two glycemic markers (HbA_{1C} and FPG) with clinical outcomes in a large sample of individuals with type 2 diabetes. We observed that higher variability of HbA_{1C} was associated with increased mortality independently of the key relevant CVD risk factors and the average of HbA_{1C} over follow-up. The associations between measures of HbA_{1C} variability and outcomes tended to be stronger

Table 1 Characteristics of participants by quartiles of SD of hemoglobin A_{1C} in the Look AHEAD study

		Quartiles of SD of hemoglobin A_{1C}, %				
	Entire sample, N=3560	Q1 (<0.259), n=900	Q2 (0.259–0.430), n=884	Q3 (0.430–0.697), n=887	Q4 (>0.697), n=889	P value
At baseline						
Age, years	58.4 (6.7)	59.5 (6.7)	59.2 (6.6)	58.3 (6.6)	56.6 (6.4)	<0.001
Women, %	62.1	66.3	60.3	59.0	62.7	0.008
Randomization arm, %						0.632
Diabetes support and education	48.9	49.8	49.3	49.5	47.0	
Intensive lifestyle intervention	51.1	50.2	50.7	50.5	53.0	
Race/ethnicity, %						0.001
Caucasian	67.0	70.2	69.1	66.4	62.2	
Non-Hispanic black	17.1	16.0	16.2	17.3	18.8	
Hispanic	12.6	10.4	10.4	13.1	16.3	
Body mass index, kg/m^2	36.0 (5.9)	35.2 (5.9)	35.6 (6.0)	36.3 (5.7)	36.9 (6.0)	<0.001
Current smoking, %	3.7	3.2	2.7	4.0	4.7	0.122
Alcohol drinking, %	33.4	34.9	33.4	33.6	31.6	0.533
Use of antihypertensive medication, %	70.9	70.9	70.4	71.7	70.8	0.938
Duration of diabetes, years	5.0 (2.0–9.0)	4.0 (1.0–7.0)	4.0 (2.0–8.0)	5.0 (2.0–10.0)	6.0 (3.0–10.0)	<0.001
eGFR, mL/min/1.73 m^2	90.9 (15.7)	89.2 (15.6)	89.5 (15.5)	91.0 (15.8)	93.9 (15.6)	<0.001
During follow-up						
Average systolic blood pressure, mm Hg	125.6 (13.9)	123.9 (13.7)	124.7 (12.8)	126.3 (14.2)	127.5 (14.5)	<0.001
Average diastolic blood pressure, mm Hg	68.4 (8.0)	67.2 (7.8)	68.5 (7.8)	68.5 (8.2)	69.5 (8.0)	<0.001
Average total-to-HDL cholesterol ratio	4.2 (1.2)	4.1 (1.2)	4.1 (1.1)	4.3 (1.2)	4.5 (1.2)	<0.001
Fasting plasma glucose, mg/dL						
Baseline fasting plasma glucose, mg/dL	151.4 (44.5)	127.8 (26.1)	140.0 (32.4)	156.6 (39.4)	181.5 (55.0)	<0.001
12-month fasting plasma glucose, mg/dL	136.4 (41.7)	122.3 (26.7)	128.4 (32.0)	139.7 (39.9)	155.2 (54.8)	<0.001
24-month fasting plasma glucose, mg/dL	140.0 (45.0)	122.8 (25.5)	131.0 (32.8)	142.4 (41.6)	164.0 (60.9)	<0.001
36-month fasting plasma glucose, mg/dL	142.3 (45.6)	124.7 (25.7)	133.9 (32.6)	144.7 (40.4)	166.0 (63.4)	<0.001
Average fasting plasma glucose, mg/dL	142.5 (33.9)	124.4 (21.8)	133.4 (26.1)	145.8 (31.2)	166.6 (38.3)	<0.001
Hemoglobin A_{1C}, %						
Baseline hemoglobin A_{1C}, %	7.2 (1.1)	6.4 (0.7)	6.8 (0.7)	7.4 (0.9)	8.2 (1.3)	<0.001
12-month hemoglobin A_{1C}, %	6.8 (1.1)	6.3 (0.7)	6.5 (0.8)	6.9 (1.0)	7.5 (1.5)	<0.001
24-month hemoglobin A_{1C}, %	6.9 (1.3)	6.4 (0.7)	6.6 (0.8)	7.0 (1.1)	7.8 (1.7)	<0.001
36-month hemoglobin A_{1C}, %	7.0 (1.3)	6.4 (0.7)	6.7 (0.8)	7.1 (1.1)	7.9 (1.8)	<0.001
Average hemoglobin A_{1C}, %	7.0 (1.0)	6.4 (0.7)	6.7 (0.7)	7.1 (0.9)	7.8 (1.1)	<0.001

Data are mean (SD), median (IQR), or proportion as appropriate.
AHEAD, Action for Health in Diabetes; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hemoglobin A_{1C}, glycosylated hemoglobin; Q, quartile.

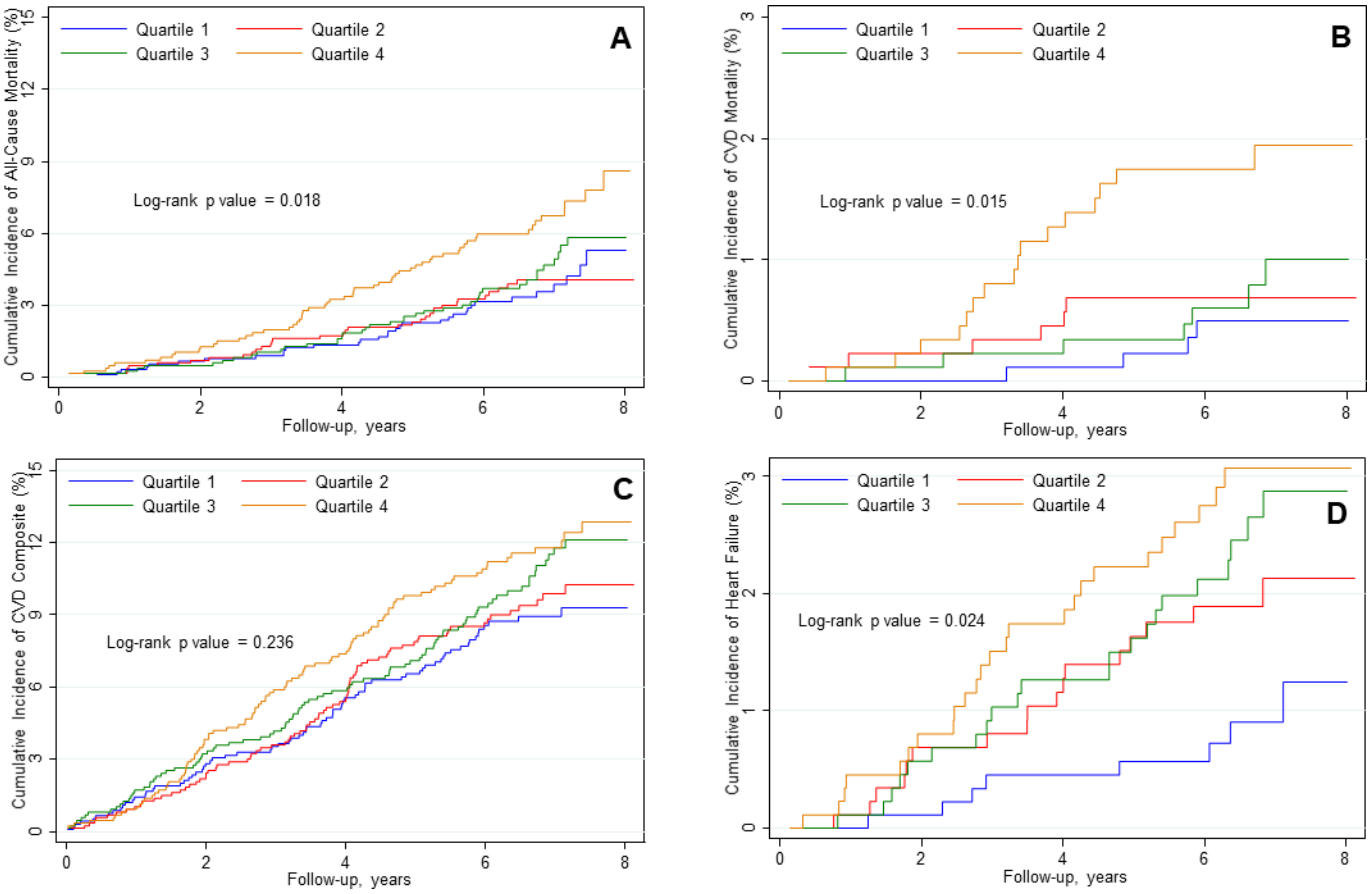

Figure 1 Cumulative hazard of all-cause mortality (A), cardiovascular mortality (B), cardiovascular disease (CVD) composite (C), and incident heart failure (D) by quartile of SD of hemoglobin A_{1C}. CVD composite was a composite of myocardial infarction, stroke, hospitalization for angina, and death for cardiovascular causes. hemoglobin A1C, glycosylated hemoglobin.

than those with FPG variability. The lack of homogeneity in the magnitude and significance of the associations with outcomes across variability indices suggest that they possibly represent different aspects of variability.

Our findings underscore the need of a consistent and less variable glycemic control over time and indicate that HbA_{1C} variability is potentially a better marker of long-term glycemic variability than FPG variability. Our results also suggest that long-term glycemic variability, especially that measured by HbA_{1C} may capture the metabolic memory effect, which has been shown to be detrimental in terms of outcomes in diabetes.[7–9]

To our knowledge, our study is unique in its kind to include in its assessment of long-term glycemic variability of two glycemic markers, as well as the assessment of incident HF as a separate outcome.[12–19 24] A prior systematic review of adverse events associated with glycemic variability in people with diabetes showed that prior studies limited by their retrospective design, a small sample size, the lack of racially diverse samples, and the focus on single glycemic markers.[12–19 24] Nonetheless, our findings corroborate previous reports that have shown a positive relation between glycemic variability and mortality rates.[13 14] The positive association will all-cause mortality (but not CVD events) supports the previously reported links between glycemic variability and other drivers of mortality in type 2 diabetes including microvascular complications,[25–27] as well as malignancies.[28] The lack of association between glycemic variability and CVD events is consistent with data from previous studies of patients with type 2 diabetes.[13 29 30] As type 2 diabetes is independently associated with an excess risk of HF, we evaluated the association of glycemic variability with incident HF as a separate outcome. Indeed, it has been suggested that mechanisms through which diabetes increase atherosclerotic CVD (including oxidative stress, non-enzymatic glycation, endothelial dysfunction) likely extend to the myocardium and contribute to myocardial fibrosis is remodeling.[31] The absence of association with HF in observed our study suggests that the increased risk of HF in people with diabetes may be related to other mechanisms including cardiac autonomic neuropathy.[31]

The mechanisms relating glycemic variability to adverse outcomes are incompletely understood, but a few hypotheses have been suggested. Blood glucose fluctuations may worsen oxidative stress, which induces endothelial dysfunction and ultimately atherosclerosis.[32–34] Glycemic fluctuations could foster the release of inflammatory cytokines, the adhesion of monocytes to endothelial cells, and endothelial cell apoptosis, which all drive diabetes-related complications.[34 35] Additionally, glycemic alterations significantly attenuate the response

Table 2 HRs for clinical outcomes by intraindividual SD of HbA_{1C} in the Look AHEAD study

	Quartiles of SD of hemoglobin A_{1C}, %					
Outcome	**Q1 (<0.259)**	**Q2 (0.259–0.430)**	**Q3 (0.430–0.697)**	**Q4 (>0.697)**	**P_{trend}**	**Per SD**
All-cause mortality						
Model 1	Reference	1.04 (0.64 to 1.69)	1.35 (0.85 to 2.15)	2.47 (1.60 to 3.83)***	<0.001	1.38 (1.22 to 1.56)***
Model 2	Reference	1.04 (0.64 to 1.70)	1.24 (0.77 to 1.99)	2.19 (1.39 to 3.44)**	<0.001	1.34 (1.17 to 1.52)***
Model 3	Reference	1.03 (0.63 to 1.69)	1.22 (0.75 to 1.98)	2.10 (1.26 to 3.51)**	0.005	1.34 (1.14 to 1.57)***
Cardiovascular mortality						
Model 1	Reference	1.49 (0.42 to 5.30)	1.86 (0.54 to 6.37)	5.25 (1.73 to 15.97)**	0.001	1.53 (1.20 to 1.96)**
Model 2	Reference	1.38 (0.38 to 4.99)	1.64 (0.47 to 5.72)	3.64 (1.14 to 11.66)*	0.018	1.46 (1.10 to 1.93)**
Model 3	Reference	1.36 (0.37 to 4.95)	1.60 (0.45 to 5.70)	3.43 (0.95 to 12.38)	0.050	1.44 (1.01 to 2.05)*
CVD composite†						
Model 1	Reference	1.07 (0.78 to 1.47)	1.27 (0.93 to 1.73)	1.55 (1.14 to 2.11)**	0.003	1.14 (1.03 to 1.26)*
Model 2	Reference	1.10 (0.80 to 1.52)	1.15 (0.84 to 1.58)	1.29 (0.94 to 1.78)	0.119	1.06 (0.95 to 1.18)
Model 3	Reference	1.05 (0.76 to 1.45)	1.02 (0.73 to 1.42)	1.01 (0.69 to 1.46)	0.994	0.95 (0.83 to 1.08)
Heart failureevent						
Model 1	Reference	2.20 (0.95 to 5.11)	2.96 (1.31 to 6.66)**	3.87 (1.73 to 8.66)**	<0.001	1.33 (1.11 to 1.60)**
Model 2	Reference	2.17 (0.93 to 5.04)	2.29 (1.00 to 5.23)*	2.64 (1.16 to 6.01)*	0.030	1.21 (1.00 to 1.47)
Model 3	Reference	2.00 (0.86 to 4.66)	1.90 (0.82 to 4.40)	1.71 (0.69 to 4.24)	0.372	1.03 (0.80 to 1.31)

Data are HRs (95% CIs) unless otherwise indicated.
Model 1 adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in model 1 with further adjustment for body mass index, current smoking, alcohol drinking, use of antihypertensive medications, average ratio of total to high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, and average systolic blood pressure. Model 3 includes model 2 plus further adjustment for average HbA_{1C}.
*P<0.05, **p<0.01, ***p<0.001.
†CVD composite was a composite of myocardial infarction, hospitalization for angina, stroke, and death for cardiovascular causes.
AHEAD, Action for Health in Diabetes; CVD, cardiovascular disease; HbA_{1C}, glycosylated hemoglobin; Q, quartile.

Table 3 HRs for clinical outcomes by intraindividual SD of fasting plasma glucose in the Look AHEAD study

	Quartiles of SD of fasting plasma glucose, mg/dL					
Outcome	**Q1 (<10.15)**	**Q2 (10.15–17.53)**	**Q3 (17.53–29.80)**	**Q4 (>29.80)**	**P_{trend}**	**Per SD**
All-cause mortality						
Model 1	Reference	1.37 (0.84 to 2.23)	1.94 (1.22 to 3.10)**	2.18 (1.37 to 3.48)**	<0.001	1.36 (1.19 to 1.55)***
Model 2	Reference	1.27 (0.78 to 2.08)	1.72 (1.07 to 2.78)*	1.83 (1.12 to 2.98)*	0.007	1.29 (1.12 to 1.48)***
Model 3	Reference	1.25 (0.76 to 2.05)	1.65 (1.02 to 2.69)*	1.66 (0.96 to 2.85)	0.039	1.29 (1.08 to 1.53)**
Cardiovascular mortality						
Model 1	Reference	0.98 (0.32 to 3.05)	1.28 (0.43 to 3.82)	2.78 (1.06 to 7.29)*	0.021	1.44 (1.10 to 1.90)**
Model 2	Reference	0.99 (0.31 to 3.15)	0.90 (0.26 to 3.06)	2.27 (0.79 to 6.51)	0.104	1.30 (0.95 to 1.78)
Model 3	Reference	0.98 (0.31 to 3.15)	0.89 (0.26 to 3.08)	2.20 (0.67 to 7.25)	0.210	1.25 (0.84 to 1.86)
CVD composite†						
Model 1	Reference	0.96 (0.70 to 1.31)	1.06 (0.78 to 1.45)	1.41 (1.05 to 1.89)*	0.018	1.20 (1.09 to 1.32)***
Model 2	Reference	0.93 (0.68 to 1.28)	0.90 (0.65 to 1.25)	1.16 (0.85 to 1.58)	0.384	1.11 (1.01 to 1.24)*
Model 3	Reference	0.89 (0.65 to 1.23)	0.83 (0.60 to 1.16)	0.94 (0.65 to 1.35)	0.620	1.03 (0.91 to 1.18)
Heart failureevent						
Model 1	Reference	2.89 (1.22 to 6.84)*	2.92 (1.23 to 6.96)*	4.23 (1.83 to 9.77)**	0.001	1.42 (1.19 to 1.69)***
Model 2	Reference	2.45 (1.03 to 5.85)*	2.44 (1.02 to 5.85)*	2.79 (1.17 to 6.63)*	0.039	1.28 (1.04 to 1.56)*
Model 3	Reference	2.33 (0.98 to 5.58)	2.17 (0.89 to 5.26)	2.05 (0.80 to 5.31)	0.256	1.17 (0.91 to 1.50)

Data are HRs (95% CIs) unless otherwise indicated.
Model 1 adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in model 1 with further adjustment for body mass index, current smoking, alcohol drinking, use of antihypertensive medications, average ratio of total to high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, and average systolic blood pressure. Model 3 includes model 2 plus further adjustment for average fasting plasma glucose.
*P<0.05, **p<0.01, ***p<0.001.
†CVD composite was a composite of myocardial infarction, hospitalization for angina, stroke, and death for cardiovascular causes.
AHEAD, Action for Health in Diabetes; CVD, cardiovascular disease; Q, quartile.

to oxidative stress by decreasing the induction of superoxidase dismutase activity.[36] Hyperglycemia has been proven to downregulate the genes involved in detoxication and free radical scavenging, further worsening the effects of oxidative stress.[37] Additionally, glycemic fluctuations have been associated to epigenetic changes in endothelial and mononuclear cells that contribute to endothelial dysfunction and inflammation.[32] Moreover, oscillating blood glucose has been shown in mechanistic studies to have stronger effects than constant hyperglycemia at inducing a metabolic memory.[11] Finally, fluctuating blood glucose has cytotoxic effects in the pancreas, leading to a significant reduction of glucose-mediated insulin secretion, beta cells' apoptosis, and mitochondrial alterations,[38] perpetuating the vicious cycle of worsening glycemic control and complications of diabetes.[39]

Our findings have potential implications, as these add to the growing body of evidence on the prognostic value of glycemic variability.[12–19 24]

A few limitations to this study should be acknowledged. First, although we evaluated two glycemic markers, we did not have data on the 2-hour post oral load glucose level. Second, our study was observational and there is a possibility of unmeasured, residual confounding.

Third, given that we excluded participants who died during the first 36 months of follow-up, it is likely that subjects at the high extreme of variability were not included in our analytical sample. This would suggest that the effects of glycemic variability on mortality are actually higher than those observed in this study. Finally, our estimation of variability relied on glycemic measures assessed at only four time points, which may be a limitation, as a higher number of visits may more reliably capture variability, as suggested by data from the BP literature.[40] This latter phenomenon may have affected the magnitude and significance of our effect estimates. Despite these limitations, our study has multiple strengths. First, we used a large multiracial/ethnic sample of participants. Second, our study is one of a few that evaluated variability of two glycemic markers, as opposed to prior studies which measured a single glycemic index.[12–17 19] Third, the outcomes (including HF, which had seldom been evaluated previously) were ascertained following a standardized process, and relevant confounders including the average of HbA_{1C} and FPG over the follow-up period were accounted for in the analyses.

In conclusion, in a large sample of adults with type 2 diabetes, a higher long-term variability of glycemic measures is associated with greater risks of mortality, above and beyond the degree of glycemic control. Further research is needed to elucidate the mechanisms underlying these associations and to evaluate the potential benefit of lowering glycemic variability in curbing the excess mortality in individuals with type 2 diabetes.

Correction notice This article has been corrected since it was published. Author notes have been added.

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