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Association of Low Fasting Glucose and HbA1c With Cardiovascular Disease and Mortality: The MESA Study

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Trials of intensive glucose control have not improved cardiovascular disease (CVD) risk in populations with type 2 diabetes; however, in the general population, reports are inconsistent about the effects of maintaining lower glucose levels. Some speculate that low glycemic values are associated with increased glycemic variability, which is in turn associated with higher CVD risk. It has also been suggested that fasting glucose and hemoglobin A1c (HbA1c) in the lower ranges have a different relationship with CVD and mortality. In 4990 participants from the Multi-Ethnic Study of Atherosclerosis, we used logistic regression to investigate associations of low fasting glucose (<80 mg/dL) and HbA1c (<5.0%) from baseline and averaged across follow-up with incident CVD and mortality over 13 years. We used normal glycemic ranges (80 to <100 mg/dL and 5.0 to <5.7%) as references and analyzed glycemic levels with visit-matched covariates. We adjusted for potential confounding by age, sex, race/ethnicity, education, income, smoking status, body mass index, total cholesterol level, cholesterol medications, high-density lipoprotein cholesterol, and hypertension. Low baseline glucose and HbA1c were positively, but not significantly, associated with mortality, whereas low average fasting glucose and HbA1c were strongly and significantly associated with incident CVD [glucose OR, 2.04 (95% CI, 1.38-3.00); HbA1c OR, 2.01 (95% CI, 1.58-2.55)] and mortality [glucose OR, 1.93 (95% CI, 1.33-2.79); HbA1c OR, 2.51 (95% CI, 2.00-3.15)]. These results were not due to type 2 diabetes or medication use. Glucose variability did not explain CVD risk beyond average glucose levels. Chronic low fasting glucose and HbA1c may be better indicators of risk than a single low measurement.

Freeform/Key Words: cardiovascular disease, epidemiology, fasting glucose, HbA1c, mortality

Once questioned as an intermediate condition, impaired fasting glucose (100 to <125 mg/dL) has now been shown to confer cardiovascular disease (CVD) risk even though it is below the diabetic range (≥126 mg/dL) [1]. Similarly, there is now evidence that low blood glucose levels [<80 mg/dL fasting or hemoglobin A1c (HbA1c) <5.0%] without reported clinical hypoglycemia may also indicate metabolic dysregulation and confer increased risk for CVD or mortality [2–10]. It remains unknown whether low glucose itself places some individuals at risk or whether low glucose is a marker for glycemic variability, which has consistently been

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein.

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associated with CVD events and mortality in those with type 2 diabetes [11–14]. Research on hypoglycemia has predominantly been focused on iatrogenic hypoglycemia resulting from glucose-lowering therapy in type 2 diabetes. The unexpected findings about the failure of intensive glucose control interventions in type 2 diabetes to prevent CVD events and the possibility that such interventions may even increase mortality have heightened the uncertainty around lower glucose values in individuals without type 2 diabetes as well [15]. Few studies have investigated the relationship of low fasting glucose or HbA1c with CVD outcomes in the general population [6, 16, 17]. Similarly, few have investigated whether glucose variability is associated with CVD outcomes beyond a single measurement [11, 12, 14, 18].

Increasing evidence supports the need to study CVD outcomes in the population of individuals who consistently have fasting and/or average glucose levels in the lower ranges [2, 3, 6, 7, 16, 17]. Thus, we sought to determine whether low fasting glucose (<80 mg/dL), low HbA1c (<5.0%), or glycemic variability (coefficient of variation) are associated with incident CVD and all-cause mortality in individuals without type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Following up on prior work in MESA on fasting glucose at baseline and CVD [19] and based on previous evidence of a J-shaped association [2, 3, 20–22], we hypothesized that low HbA1c would be similarly associated with all-cause mortality. Extending this work, our primary hypothesis was that glycemic levels averaged over follow-up would be stronger predictors of CVD and mortality than baseline measurements alone. We further hypothesized that higher glycemic variability would be associated with increased risk for CVD and all-cause mortality, independent of fasting glucose or HbA1c level. Finally, we hypothesized that these associations would differ by age, sex, and race/ethnicity. Our interest in heterogeneity is based on prior literature suggesting that the relationship between other risk factors, mainly obesity, and CVD is stronger in younger individuals [23], and the knowledge that the distribution of glucose is generally lower in women than in men [24, 25], and the likelihood of hypoglycemia higher [26].

1. Methods

A. Study Population

MESA includes 6809 participants without known CVD at baseline starting in 2000 with visits approximately every 2 years [27]. Participants from six sites around the United States were oversampled by four racial/ethnic groups and were aged 45 to 84 years at baseline. We excluded participants with type 1 diabetes (n = 10), resulting in a total of 6799 MESA participants for this analysis. Because HbA1c is measured at only two of the five study visits (visits 2 and 5), there were fewer participants available for analysis of HbA1c. After excluding eight participants who experienced a CVD event before visit 2 and 662 participants who did not return for these two visits or could not be followed for events, the analysis for HbA1c included 6129 participants.

Although the primary investigation of this study is of low glucose values, to investigate the shape of the relationships across the whole range of values while avoiding the known problems with hypoglycemia in those being treated for type 2 diabetes, we excluded measurements from the low, normal, and impaired ranges of glucose (20, 83, and 195 mg/dL, respectively) and HbA1c (6, 50, and 165%, respectively), separately, if participants had a diagnosis of type 2 diabetes. Cutpoints for fasting glucose and HbA1c categories are described in the following section. This resulted in 6501 participants with fasting glucose at baseline (916 low, 4074 normal, 937 impaired, and 574 with fasting glucose in the diabetic range) and 5908 participants with HbA1c at baseline (552 low, 3249 normal, 1416 impaired, and 691 with HbA1c in the diabetic range). For average glucose and average HbA1c, we similarly excluded observations from any visit with diagnosed type 2 diabetes from the low, normal, and impaired categories, and additionally excluded glycemic measurements that occurred after a CVD event. When calculating measures of variability, we also excluded measurements that occurred after a CVD event. All participants provided written informed consent and all MESA activities were approved by the institutional review boards from the participating institutions.

B. Measurement and Categorization of Glycemic Levels

Fasting glucose was measured at every visit using the glucose oxidase method and the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY). We categorized participants by fasting glucose level at baseline, averaged across follow-up, and variability across follow-up. Low fasting glucose was categorized as low (<80 mg/dL); normal (80 to <100 mg/dL); impaired (100 to <126 mg/dL); and diabetic (≥126 mg/dL). We chose this cut-point for low fasting glucose for consistency with prior research [4, 7, 28] and to avoid small numbers in the low group. We defined high fasting glucose variability as the highest quartile of glucose coefficient of variation across all fasting glucose measurements (from visits 1 through 5).

Similar to the approach for fasting glucose, we categorized participants by HbA1c level at baseline (visit 2), averaged across follow-up, and by variability across follow-up. HbA1c was categorized as low (<5.0%), normal (5 to <5.7%), impaired (5.7 to <6.5%), and diabetes (≥6.5%) based on the most common cutpoints used in prior research [2, 3, 20–22]. High HbA1c variability was defined as the highest quartile of HbA1c coefficient of variation across both HbA1c measurements (at visits 2 and 5).

C. Cardiovascular Events and All-Cause Mortality

MESA participants were followed for incident events of coronary artery disease, stroke, heart failure, combined CVD, and all-cause mortality through 2013. All events were adjudicated and median follow-up time was 12.2 years. A full description of follow-up and adjudication procedures for these events has been previously published [29]. A combined cardiovascular outcome was created and included coronary heart disease, stroke, heart failure, and CVD death. Events classified as hard clinical events included: myocardial infarction, resuscitated cardiac arrest, coronary heart disease death, stroke, and stroke death. The primary analysis includes all events, combining hard clinical events with definite or probable angina if followed by revascularization, other atherosclerotic death, and other CVD deaths.

D. Covariates

Age, sex, race/ethnicity, smoking status, education, and income were collected at the baseline interview by self-report. CVD risk factors were measured at the baseline clinic visit using a standardized protocol [27]. We defined high cholesterol as total cholesterol ≥200 mg/dL or use of lipid-lowering medications; low high-density lipoprotein (HDL) cholesterol as <50 mg/dL for women or <40 mg/dL for men; and hypertension as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or use of blood pressure–lowering medications. Body mass index (BMI) was calculated as measured weight (in kilograms) divided by the square of the measured height (square meters).

E. Statistical Analysis

We described the study population by low and normal fasting glucose and HbA1c at baseline using t tests and χ^2 tests for continuous and categorical variables respectively. We used Cox proportional hazards models to assess the association between HbA1c categories at baseline with incident CVD and all-cause mortality. We then used multivariable logistic regression models to determine the association of fasting glucose and HbA1c categories at baseline (visit 1 and visit 2, respectively) and averaged across follow-up with incident CVD and mortality, using the normal range (80 to <100 mg/dL and 5.0 to <5.7% for fasting glucose and HbA1c, respectively) as reference categories throughout the analysis. We chose logistic regression to account for the cumulative exposure across the study period and adjusted for covariates matched to the initial visit of glycemic data collection (visit 1 for fasting glucose and visit 2 for HbA1c). This approach is also accessible for use in a clinical context, making use of easily available summary measures when complex repeated measures analysis would infeasible. We adjusted these models for confounders in a series of nested models, including age, sex,

race/ethnicity, socioeconomic status, and other CVD risk factors including high total cholesterol, low HDL cholesterol, BMI, and hypertension. We formally tested these associations for heterogeneity by age, sex, and race/ethnicity by including a multiplicative interaction term in the model. We conducted sensitivity analyses to assess whether the association with combined CVD was the same when using hard clinical CVD events compared with all CVD events and whether adjusting for glucose variability explained the results for average fasting glucose and HbA1c. We also assessed the most extreme scenario by comparing participants in the low glycemic categories at every visit to those who had normal levels at every visit. We investigated the robustness of results in specified subgroups. Finally, we evaluated the association between glycemic variability and CVD outcomes, using likelihood ratio tests to formally test whether variability improved the model fit.

2. Results

Unadjusted baseline characteristics of study participants are displayed in Table 1. MESA participants with low fasting glucose or HbA1c at baseline were younger, had higher education and income, and lower levels of CVD risk factors compared with those with normal glucose or HbA1c. Participants with average low fasting glucose and HbA1c had higher incident CVD [fasting glucose: low 11.86% (SD, 1.83) vs normal 9.80% (SD, 0.44); HbA1c: low 12.86% (SD, 1.13) vs normal 9.16% (SD, 0.51)] and mortality [fasting glucose: low 17.63% (SD, 2.16) vs normal 12.39% (SD, 0.49); HbA1c: low 26.96% (SD, 1.50) vs normal 10.96% (SD, 0.55)] compared with participants with average values in the normal range.

There was little evidence from logistic regression that low fasting glucose or low HbA1c at baseline were significantly associated with CVD or all-cause mortality (Fig. 1). HbA1c in the impaired and diabetes ranges at baseline was significantly associated with increased risk for CVD and mortality after adjustment for age, sex, race/ethnicity, income, and education (Table 2). These estimates were attenuated by adjustment for other CVD risk factors (Fig. 1 and Table 2). Similar results for fasting glucose have been previously reported [19].

In contrast to baseline values, low average fasting glucose and low average HbA1c were strongly and significantly associated with CVD and mortality (Fig. 1). Estimates for impaired and diabetes categories were generally similar for average glycemic values compared with baseline. There appeared to be a J-shaped relationship of average fasting glucose and HbA1c with CVD and mortality. Despite slightly stronger low fasting glucose associations for women, white and Hispanics, nonsmokers, and participants older than 70, there was no significant heterogeneity by age, sex, or race/ethnicity; results were generally robust to other subgroup stratification (Table 3). Being in the low glycemic category at every visit (fasting glucose <80 mg/dL or HbA1c $<5.0\%$ at every visit) had similar results to having low average values (average fasting glucose <80 mg/dL or average HbA1c $<5.0\%$) when compared with having normal values at every visit [fasting glucose and CVD OR = 1.45 (95% CI, 0.74-2.85); fasting glucose and mortality OR = 3.40 (95% CI, 1.93-6.02); HbA1c and CVD OR = 0.94 (95% CI, 0.58-1.52); HbA1c and mortality OR = 1.53 (95% CI, 1.04-2.24)] (data not shown).

There was modest evidence of an association between the variability in fasting glucose and CVD or mortality in participants without type 2 diabetes (Table 4). HbA1c variability was significantly and monotonically associated with odds of CVD and mortality. There was little evidence that glycemic variability is independently associated with CVD or mortality once average glycemic levels were included in the model (Table 3; likelihood ratio tests for inclusion of variability in the model for fasting glucose and CVD, $P = 0.17$; fasting glucose and mortality, $P = 0.053$; HbA1c and CVD, $P = 0.25$; and average HbA1c and mortality, $P = 0.38$).

3. Discussion

Low fasting glucose and low HbA1c at baseline were not significantly associated with increased risk for CVD or mortality in MESA participants without diabetes. In contrast, low average fasting glucose and low average HbA1c levels across follow-up were strongly and

Table 1. Mean (SD) Baseline Characteristics of 4990 MESA Participants Without Diabetes for Low and Normal Range Fasting Glucose and HbA1c

	Fasting Glucose			HbA1c[a]		
Model	Low (<80 mg/dL)	Normal (80 to <100 mg/dL)	*P* for Difference[a]	Low (<5.0%)	Normal (5.0 to <5.7%)	*P* for Difference[b]
N	916	4074		552	3249	
Fasting glucose, mg/dL	75.8 (0.11)	88.5 (0.08)	–	85.3 (0.53)	87.8 (0.19)	–
HbA1c, %	5.23 (0.01)	5.43 (0.01)	–	4.73 (0.86)	5.33 (0.32)	–
Age, y	58.5 (0.34)	62.0 (0.16)	<0.001	58.4 (0.43)	61.2 (0.18)	<0.001
Sex, % female	69.4 (0.02)	52.2 (0.01)	<0.001	49.3 (2.12)	52.5 (0.87)	0.19
Race, %						
White	53.3 (1.65)	41.1 (0.78)		53.6 (2.11)	48.0 (0.87)	
Asian	6.22 (0.80)	12.3 (0.52)	<0.001	6.27 (1.03)	12.1 (0.57)	<0.001
African American	23.9 (1.41)	25.8 (0.69)		23.5 (1.80)	20.3 (0.70)	
Hispanic	16.6 (1.23)	20.8 (0.64)		16.7 (1.58)	19.5 (0.69)	
Education, % ≥high school	89.6 (1.01)	84.0 (0.58)	<0.001	88.5 (1.35)	86.7 (0.59)	0.20
Income, % ≥$35,000	63.5 (1.59)	55.1 (0.78)	<0.001	67.6 (1.98)	59.9 (0.85)	<0.001
Current smoking, %	15.7 (1.20)	12.6 (0.52)	0.011	10.9 (1.32)	11.0(0.54)	0.92
Total intentional exercise, METS	1573 (67.5)	1625 (38.8)	0.56	1723 (97.3)	1627 (39.8)	0.42
BMI, kg/m^2	26.3 (0.15)	27.9 (0.08)	<0.001	27.2 (0.20)	27.4 (0.09)	0.36
High cholesterol, %[c]	47.4 (1.65)	53.0 (0.78)	0.0026	43.7 (2.10)	54.5 (0.870)	<0.001
LDL cholesterol, mg/dL	113.3 (1.04)	118.9 (0.49)	<0.001	108.2 (1.330)	115.4 (0.56)	<0.001
HDL cholesterol, mg/dL	57.2 (0.53)	51.5 (0.23)	<0.001	54.5 (0.76)	53.4 (0.27)	0.15
Triglycerides, mg/dL	109.2 (2.11)	126.4 (1.17)	<0.001	121.5 (2.99)	125.4 (1.29)	0.24
Hypertension, %	30.3 (1.52)	41.0 (0.77)	<0.001	35.9 (2.04)	38.8 (0.85)	0.19
Systolic BP, mm Hg	119.5 (0.70)	125.6 (0.33)	<0.001	121.8 (0.35)	120.3 (0.85)	0.11
Kidney disease, %	1.82 (0.13)	2.22 (0.15)	0.13	2.51 (0.16)	1.76 (0.13)	0.57
Across follow-up						
Cardiovascular disease, %	8.52 (0.92)	9.97 (0.47)	0.21	8.15 (1.17)	9.26 (0.51)	0.40
Mortality, %	10.9 (1.03)	12.4 (0.51)	0.21	10.4 (0.54)	10.5 (1.31)	0.92

Abbreviations: BP, blood pressure; LDL, low-density lipoprotein; METS, metabolic equivalents.
[a]Baseline for HbA1c is visit 2.
[b]Based on *t* tests for continuous variables and χ^2 tests for categorical variables.
[c]High cholesterol >200 mg/dL or medication use.

significantly associated with higher odds of CVD and mortality. Although higher HbA1c variability was associated with CVD, HbA1c variability did not provide additional explanation of CVD risk beyond average HbA1c.

In assessing the associations of fasting glucose and HbA1c with CVD and mortality in individuals without diabetes, prior studies found that the shape of the relationships was inconsistent and varied from linear [4, 20, 22, 28, 30, 31], mildly but not significantly J-shaped [21], or fully J-shaped even after adjustment [2–4, 6, 7, 11], with stronger associations between low HbA1c and mortality [2, 3, 20–22]. Potential mechanisms for this J-shaped association remain speculative, although suggestions that these results are due to bias have not been supported by the literature. The association between fasting glucose and CVD has been reported before in MESA with no substantial increase in risk from impaired fasting glucose compared with the normal range after adjustment [19]. Our results follow and support that work showing similar results for impaired HbA1c and adding a focus on the lower range. Our results align with the findings and summarization of the literature in The Emerging Risk Factor Collaboration meta-analysis, which reported a weak J-shaped association between baseline fasting glucose and coronary heart disease in those without type 2 diabetes, with a more pronounced J-shape for average fasting glucose [4]. Contrary to the idea that associations would be stronger for HbA1c because of its known advantages measuring glucose exposure across a longer time frame (reflecting ~3 months of average daily glucose concentration), we found similar results for fasting glucose and HbA1c using either baseline or average values. This suggests that a single measurement of even HbA1c may not

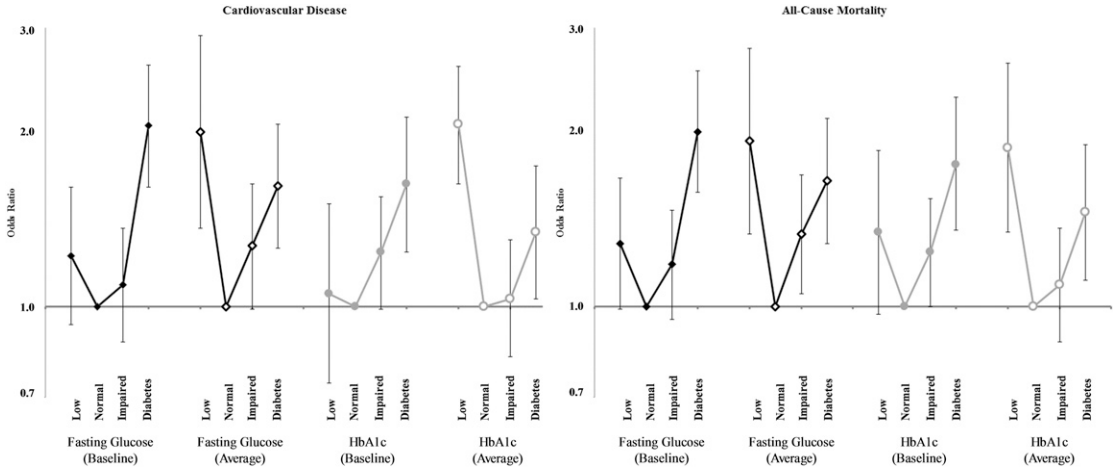

Figure 1. Association of fasting glucose and HbA1c with cardiovascular disease and all-cause mortality (OR and 95% CI) in 6483 MESA participants. Fasting glucose categories: low (<80 mg/dL), normal (80 to <100 mg/dL), impaired (100 to <126 mg/dL), and diabetes (≥126 mg/dL). HbA1c categories: low (<5.0%), normal (5.0 to <5.7%), impaired (5.7 to <6.5%), and diabetes (≥6.5%). All measurements from participants with diagnosed type 2 diabetes have been removed from the low, normal, and impaired categories. All models adjusted for age, sex, race/ethnicity, education, income, smoking status, BMI, total cholesterol level and medication use, HDL cholesterol, and hypertension status.

sufficiently classify those with low average glucose for CVD risk stratification, and that CVD risk is impacted more by chronic (>3 months) patterns of low glucose.

Glucose variability is increasingly considered to be a risk factor for CVD independent of hyperglycemia [32]. Our results are generally consistent with prior research, showing that glycemic variability is associated with CVD and mortality [11–14], although our results for mortality were weaker. Bouchi *et al.* and Takao *et al.* showed that HbA1c variability is associated with incident CVD, independent of mean HbA1c in those with type 2 diabetes [11, 13]. In contrast, in those without type 2 diabetes, we found that variability is not an independent determinant of CVD once average fasting glucose or HbA1c are accounted for. Our result is consistent with findings from Borg *et al.* in the premise that excursions into the lower glucose range may be a marker for high glycemic variability [33]. It is also possible that the CVD association of variability independent of mean value may hold only for those with type 2 diabetes or taking glucose-lowering medication. More generally, our results and those of

Table 2. Cox Proportional HRs and 95% CIs for CVD and All-Cause Mortality by Baseline HbA1c Category in 6775 MESA Participants

		Baseline HbA1c Categories			
Model	**Events**	**Low (<5.0%)**	**Normal (5.0 to <5.7%)**	**Impaired (5.7 to <6.5%)**	**Diabetic (≥6.5%)**
CVD					
1	621	1.08 (0.79-1.49)	1.00 (ref)	**1.30 (1.08-1.56)**	**1.83 (1.46-2.28)**
2	620	1.04 (0.76-1.44)	1.00 (ref)	**1.33 (1.10-1.61)**	**1.82 (1.45-2.30)**
3	620	1.08 (0.79-1.49)	1.00 (ref)	1.21 (1.00-1.47)	**1.53 (1.21-1.95)**
All-cause mortality					
1	781	1.29 (0.98-1.71)	1.00 (ref)	**1.26 (1.07-1.49)**	**1.61 (1.32-1.97)**
2	779	1.21 (0.92-1.60)	1.00 (ref)	**1.22 (1.03-1.45)**	**1.55 (1.25-1.91)**
3	779	1.24 (0.94-1.63)	1.00 (ref)	**1.21 (1.02-1.44)**	**1.51 (1.22-1.88)**

Bold indicates where estimates are significantly different from the normal category at the $P < 0.05$ level. All HbA1c measurements from participants with diagnosed type 2 diabetes have been removed from the low, normal, and impaired categories. Model 1, adjusted for age; model 2, model 1 + sex, race, income, and education; model 3, model 2 + current smoking, BMI, total cholesterol and lipid medications, HDL cholesterol, and hypertension.
Abbreviation: HR, hazard ratio.

Table 3. Sensitivity Analyses for Low Average Fasting Glucose and HbA1c Compared With the Normal Category With CVD and All-Cause Mortality in MESA Participants Without Diabetes, Stratified by Selected Factors (OR and 95% CI)

	Average Fasting Glucose (<80 vs 80 to <100 mg/dL)		Average HbA1c (<5.0% vs 5.0 to <5.7%)	
Subgroup	**Cardiovascular Disease**	**All-Cause Mortality**	**Cardiovascular Disease**	**All-Cause Mortality**
Primary analysis (n = 4544)[a]	**2.04 (1.38-3.00)**	**1.93 (1.33-2.79)**	**2.01 (1.58-2.55)**	**2.51 (2.00-3.15)**
Adjusted for variability (n = 4113)[b]	**1.85 (1.15-2.99)**	**1.81 (1.15-2.86)**	**3.09 (1.59-6.02)**	2.05 (0.93-4.53)
Hard CVD events only (n = 4544)	**2.23 (1.46-3.40)**	–	**1.84 (1.41-2.41)**	–
Sex				
Women (n = 2523)	**2.23 (1.37-3.64)**	**2.21 (1.39-3.50)**	**1.59 (1.10-2.32)**	**2.44 (1.76-3.39)**
Men (n = 2021)	1.77 (0.93-3.39)	1.73 (0.91-3.30)	**2.37 (1.74-3.24)**	**2.64 (1.93-3.62)**
P for difference	0.67	0.75	0.18	0.80
Age				
<70 y (n = 3374)	1.47 (0.85-2.53)	1.56 (0.93-2.61)	**2.26 (1.66-3.09)**	**3.07 (2.25-4.19)**
≥70 y (n = 1170)	**2.57 (1.47-4.50)**	**1.90 (1.14-3.18)**	**1.96 (1.29-2.66)**	**2.08 (1.52-2.84)**
P for difference	0.096	0.79	0.38	0.21
Race/ethnicity				
White (n = 2001)	**2.06 (1.23-3.45)**	**2.65 (1.61-4.36)**	**2.39 (1.70-3.35)**	**2.96 (2.11-4.17)**
Asian (n = 528)	2.46 (0.27-22.4)	1.21 (0.13-11.4)	**6.96 (2.64-18.3)**	1.44 (0.66-3.12)
African American (n = 1152)	1.66 (0.74-3.71)	1.21 (0.60-2.45)	**1.78 (1.11-2.85)**	**2.26 (1.50-3.40)**
Hispanic (n = 863)	**2.94 (1.10-7.85)**	**1.95 (0.67-5.63)**	1.13 (0.62-2.08)	**2.58 (1.45-4.59)**
P for difference	0.70	0.35	0.89	0.15
Current smoking				
No (n = 3928)	**2.22 (1.45-3.39)**	**1.94 (1.28-2.94)**	**2.09 (1.60-2.72)**	**2.62 (2.04-3.37)**
Yes (n = 616)	1.34 (0.51-3.53)	2.11 (0.91-4.91)	**1.89 (1.07-3.35)**	**2.08 (1.22-3.55)**
P for difference	0.33	0.87	0.76	0.44
Cancer				
No (n = 4151)	**1.55 (1.01-2.40)**	**1.85 (1.27-2.68)**	1.00 (0.67-1.50)	**1.86 (1.29-2.70)**
Yes (n = 350)	1.00 (0.26-3.80)	1.38 (0.48-4.06)	2.07 (0.79-5.42)	2.15 (0.90-5.14)
P for difference	0.56	0.62	0.18	0.76
Hormone therapy use[c]				
No (n = 1478)	1.52 (0.72-3.19)	1.81 (0.99-3.31)	0.74 (0.43-2.06)	1.46 (0.77-2.77)
Yes (n = 768)	**2.64 (1.22-5.71)**	**2.84 (1.30-6.21)**	0.56 (0.13-2.47)	1.01 (0.33-3.14)
P for difference	0.31	0.36	0.76	0.73

Bold for the subgroups indicates a significant difference from primary model results at $P < 0.05$ level.
[a]Primary analysis is model 3 from Table 2. Paired subgroups are mutually exclusive. For example, the cancer analysis includes only participants with a diagnosis of cancer. Sample size differs by group with smaller sample sizes for HbA1c compared with fasting glucose and for additional exclusions.
[b]*P* values from likelihood ratio tests for the inclusion of variability in the model with average glucose values were: fasting glucose and CVD, $P = 0.17$; HbA1c and CVD, $P = 0.25$; fasting glucose and mortality, $P = 0.053$; and HbA1c and mortality, $P = 0.38$.
[c]Hormone therapy is for women only.

Bouchi *et al.* support the need for measurement of glycemic markers at multiple time points. Coutinho *et al.* specify in their analysis that a single measurement of fasting glucose may lead to underestimates of the association between glucose levels and CVD [32]. Although additional measurements generally increase precision and should thus improve the performance of the average over a single measurement, it is rare that such improvement leads to a different inference. Our results support the notion that a single measurement of fasting glucose or even HbA1c is not representative of chronic exposure to hypoglycemia; however, what this means for clinical care remains uncertain.

The primary limitation of this study is that HbA1c was only measured at two time points in MESA, limiting investigation of average HbA1c and HbA1c variability; however, even a single additional measurement changed the inference for low HbA1c. Similarly, HbA1c measurement began at visit 2, limiting the follow-up time for analysis of HbA1c with events and restricting comparability with fasting glucose measurement at baseline. The small number of participants in the low fasting glucose category precludes investigation of further

Table 4. Association of Variation in Fasting Glucose and HbA1c With CVD and Mortality in MESA Participants Without Diabetes (OR and 95% CI)

	CVD		All-Cause Mortality	
	Variation	Adjusted for Average	Variation	Adjusted for Average
Fasting glucose variability, mg/dL[a]				
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	0.91 (0.72-1.17)	0.93 (0.72-1.20)	**0.77 (0.61-0.98)**	0.79 (0.61-1.01)
Quartile 3	0.91 (0.71-1.16)	0.87 (0.67-1.13)	0.85 (0.67-1.08)	0.87 (0.67-1.12)
Quartile 4	**1.31 (1.04-1.65)**	0.97 (0.68-1.39)	1.20 (0.95-1.51)	1.12 (0.80-1.56)
P for linear trend	**0.022**	0.48	0.096	0.50
HbA1c variability, %[b]				
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	1.07 (0.77-1.49)	0.95 (0.66-1.38)	0.89 (0.54-1.47)	0.81 (0.45-1.45)
Quartile 3	1.28 (0.93-1.77)	1.15 (0.80-1.65)	1.20 (0.74-1.96)	1.05 (0.59-1.87)
Quartile 4	**1.63 (1.20-2.23)**	1.10 (0.73-1.67)	**1.65 (1.03-2.65)**	1.65 (0.89-3.04)
P for linear trend	**0.001**	0.80	**0.017**	0.067

Bold indicates significance at the $P < 0.05$ level. All models are adjusted for age, sex, race/ethnicity, education, income, smoking, BMI, high total cholesterol, low HDL cholesterol, statin use, and hypertension.
Abbreviation: ref, reference.
[a]Variability cutpoints for fasting glucose: quartile 1 (<4.579706), quartile 2 (4.579706 to <6.485385), quartile 3 (6.485385 to <9.60496), and quartile 4 (>9.60496).
[b]Variability cutpoints for HbA1c: quartile 1 (<2.481076), quartile 2 (2.481076 to <4.04061), quartile 3 (4.04061 to <6.640249), and quartile 4 (>6.640249).

stratification in this range; however, even if risk increases toward the extreme values the inclusion of fasting glucose from 70 to 80 mg/dL would likely bias our estimates toward a null result. We could not rule out all known causes of nondiabetic hypoglycemia, but doubt that excluding these rare conditions would change our results. Some differential loss to follow-up is possible, but would also likely bias our results toward the null. Last, availability of information on potential sources of error in measuring HbA1c, such as hemoglobinopathy, anemia, and hemolytic disorders, is limited and residual confounding remains a possibility.

Strengths of this study include our ability to do a more comprehensive investigation into the relationship of glycemia with CVD risk and mortality, and this study adds multiple elements to the current literature. First, by including both CVD and mortality end points, we assessed whether the etiology of glycemia in the lower range differs for CVD and mortality. Second, by using MESA, we could investigate whether these associations differ by age, sex, and race/ethnicity. Third, we investigated whether the relationship with CVD and mortality differed between fasting glucose and HbA1c in the same population in an attempt to reconcile discrepancies in the literature. Finally, we used the approach of including average low fasting glucose, average low HbA1c, and glycemic variability in our investigation of the relationship between glycemia and cardiovascular risk.

In conclusion, low fasting glucose and HbA1c averages were more strongly associated with CVD and all-cause mortality than a single measurement of low glycemia at baseline. Higher HbA1c variability was also significantly associated with incident CVD, but variability did not explain the association for low average HbA1c. In individuals without type 2 diabetes, chronic glycemia lower than the normal range may be a better indicator of risk than a single low glycemic measurement, but more information is needed about the mechanisms connecting low fasting glucose and HbA1c with outcomes.

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