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Hyperglycemia and Arterial Stiffness: the Atherosclerosis Risk in the Communities Study

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Abstract

Objectives—Hyperglycemia has been associated with an increased risk of cardiovascular morbidity and mortality. Although numerous studies have demonstrated that hyperglycemia is associated with the atherosis component of atherosclerosis, limited studies have addressed the independent role of hyperglycemia in the pathophysiology of sclerotic vascular disease. We hypothesized that hyperglycemia, as assessed by hemoglobin A1c (HbA1c), would be independently associated two common indices of arterial stiffness (pressure-strain elastic modulus (Ep) and Young's elastic modulus (YEM)).

Methods—We examined the cross-sectional association between HbA1c and arterial stiffness using B-mode ultrasound examination of the carotid artery in 9,050 participants from the community-based Atherosclerosis Risk in Communities (ARIC) Study. We used multivariable linear and logistic regression models to characterize the association between HbA1c and increased Ep and YEM.

Results—Higher values of HbA1c were associated in a graded fashion with increased arterial stiffness (P-trend <0.001 for both EP and YEM). After adjusting for traditional risk factors, increasing HbA1c deciles were significantly associated with elevated EP (OR for the highest decile of HbA1c compared to the lowest, 2.01, 95% CI 1.30, 3.11) and YEM (OR = 1.71, 95% CI 1.15, 2.55).

Conclusion—Elevated HbA1c is associated with measures of increased arterial stiffness, even after accounting for arterial wall thickness. This is consistent with the hypothesis that hyperglycemia contributes to arterial stiffness beyond its effects on atherosis and suggests that hyperglycemia is associated with altered material within the arterial wall.

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Keywords

atherosclerosis; distensibility; hyperglycemia; epidemiology

Introduction

In the United States an estimated 5.4 million individuals have been diagnosed with diabetes and around 2.4 million are undiagnosed [1]. Diabetes is associated with early and accelerated atherosclerosis, and heart disease death rates among adults with diabetes are 2 to 4 times higher than for those without diabetes. Diabetes affects the vasculature by various mechanisms; “atherosis” is a term which has been used to refer to lipid deposition in the vasculature to form intimal plaques while sclerosis refers to “vessel stiffening” [2]. Although most studies have shown positive associations between hyperglycemia and arterial stiffness among persons with diabetes [3–9], there is inconclusive evidence among persons with impaired fasting glucose or impaired glucose tolerance [8, 9]. Because atherosis and sclerosis typically coexist *in vivo*, the isolation of the arterial sclerotic component is difficult. Although numerous studies have demonstrated that hyperglycemia is associated with the atherosis (lipid) component of atherosclerosis, and have addressed the independent role of hyperglycemia in the pathophysiology of sclerotic vascular disease in diabetes, there are limited and conflicting data in the general population [2]

Although different methods exist for quantifying the elastic properties of arteries, pressure-strain elastic modulus (Ep) and Young’s elastic modulus (YEM) provide useful and complementary information [10]. While the two measures are similar, YEM incorporates the ratio of arterial wall thickness to radius and the circumferential arterial strain to estimate the degree of arterial wall stiffness [10, 11]

The objective of this study was to examine the relationship between hyperglycemia–as assessed by glycated hemoglobin (HbA1c)- and measures of increased arterial stiffness in diabetics and non-diabetics in the Atherosclerosis Risk in Communities (ARIC) cohort. Furthermore, we sought to determine the arterial wall thickness-independent association of hyperglycemia and arterial stiffness with the use of an index that does and one that does not adjust for arterial wall thickness (YEM and EP, respectively).

Methods

Study Population

The ARIC Study is a prospective, community-based study of the natural history of atherosclerotic disease. The initial sample consisted of 15,792 men and women aged 45 to 64 years from four US communities: Forsyth County, North Carolina; suburban Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi. Institutional review boards at participating institutions approved the study and informed consent was obtained from all subjects. Details of the study design and examination procedures have been previously described [12]. Briefly, the baseline visit took place between 1987–89 (visit 1) and the first follow up examination took place in 1990–1992 (visit 2). Arterial stiffness indexes were assessed during visit 2 in 10,187 participants (71% of those who attended visit 2). We excluded individuals with missing HbA1c values (n=198), less than 2 EKG cycles available at the time of the ultrasound exam (n=730), self-reported race other than black or white (n= 32), or missing covariate data (n=177) for a final study sample of 9,050 participants with complete data.

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Covariates

Age, sex, race, alcohol use and smoking status were ascertained from interviews during visit 2. History of diabetes was defined as a self-reported physician diagnosis of diabetes or use of glucose lowering medication at either the first or second ARIC examination. Trained examiners measured weight and height. Serum creatinine concentration was measured using a modified kinetic Jaffe method. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study equation. Serum glucose was measured by the hexokinase method and HbA1c was measured from frozen whole blood samples from ARIC visit 2 using a high performance liquid chromatography instrument (Tosoh Corporation, Tokyo, Japan).

Ultrasound exam

Data from the visit 2 ultrasound examination was collected as previously described [10]. Briefly, after participants rested in the supine position for 20 minutes, a centrally trained and certified sonographer used non-invasive B-mode ultrasound to collect arterial diameter data from the left common carotid artery. Data was digitized by an analog to digital converter and then sent to an ultrasound-reading center where arterial diameter data was estimated as the average over the cardiac cycles available (average = 5.6 cycles). The diastolic arterial diameter (DAD) and the arterial diameter change (ADC) between systole and diastole from the left carotid artery during cardiac cycles were used for this analysis. Pulse Pressure (PP) was calculated as the systolic blood pressure – diastolic blood pressure. Concurrent resting brachial blood pressure was measured every 5 minutes with an automated oscillometric device (1846SX Dinamap), and the mean of 2 BP measures before the completion of ultrasound examination was used in calculating arterial stiffness indices. From these diameter and BP data, the following parameters were estimated:

Peterson's elastic modulus [13] (Ep) = (PP × DAD)/ADC (kPa)

Young's elastic modulus (YEM) [10] = (Ep × DAD)/(2 × IMT)] (kPa)

Higher values of both Ep and YEM indicate greater arterial stiffness [10, 13]. The reliability coefficient was 0.66 for EP [14] and 0.38 for YEM.

Statistical Analysis

HbA1c was modeled continuously and by deciles. The characteristics of the study population were compared across HbA1c deciles. We conducted analyses using multivariable logistic regression to assess the association between increasing deciles of HbA1c and arterial stiffness (highest decile of EP and YEM) with adjustment for covariates. We implemented three models for the adjustment of covariates. Model 1 was adjusted for age, gender, center and race; Model 2 was further adjusted for height, weight, education, smoking, LDL and HDL-cholesterol and diabetes history; Model 3 was further adjusted for mean arterial pressure measured at the time of the ultrasound exam. We tested for interaction by age, race, and sex. We also performed analysis restricted to persons without a history of diabetes. All analyses were conducted using STATA 11.1 (Stata Corp, College Station, TX) and a P-value of <0.05 was considered statistically significant.

Results

Baseline characteristics according to HbA1c deciles are listed in Table 1. Mean age was 56.7 years and 57% of participants were female. Participants with higher HbA1c were more likely to be African American, have hypertension, have higher BMI and LDL-cholesterol levels and lower HDL-cholesterol levels. Participants in the higher deciles of HbA1c were also more likely to have increased arterial stiffness parameters (Ep and YEM). Ep and YEM

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were highly correlated (Spearman's correlation coefficient=0.86). There were 788 participants with diabetes.

Table 2 shows the characteristics of participants with increasing quartiles of EP. Most notably, participants with the highest stiffness indexes (highest EP quartile) were more likely to be hypertensive and non-smokers. They also had higher HbA1c and BMI and were more likely to be African Americans and older.

The continuous association between HbA1c and arterial stiffness measures is shown in Table 3. Baseline HbA1c was positively associated with arterial stiffness measures. In the analysis adjusted for age, gender, race and field center, every 1-percentage point higher HbA1c value was associated with higher value of EP (β=7.89; 95% CI=6.74, 9.03) and YEM (β=37.33; 95% CI=27.54, 44.01). This association remained significant after additional adjustment for other cardiovascular risk factors (Model 2) and concurrently-measured mean arterial pressure (β for EP=3.91; 95% CI=2.57, 5.26 and β for YEM=13.50; 95% CI=3.10, 23.90).

Table 4 shows the odds ratios (ORs) for the highest EP and YEM decile in relation to HbA1c deciles. In age, gender, race, and field center adjusted analyses, increasing HbA1c deciles were significantly associated with elevated EP (OR for the highest decile of HbA1c compared to the lowest, 3.11; 95% CI 2.17, 4.48). The association remained significant after adjusting for other cardiovascular risk factors (Model 2, OR= 1.93, 95% CI 1.29, 2.89) and after further adjustment for mean arterial pressure (Model 3, OR 2.01, 95% CI 1.30, 3.11). Adjustment for SBP rather than MAP did not appreciably alter our results (results not shown).

In age, gender, race, and field center adjusted analyses, increasing HbA1c deciles were also associated with elevated YEM (OR for the highest decile of HbA1c compared to the lowest =2.34; 95% CI 1.67, 3.28) (Table 4). The association remained significant after adjustment for cardiovascular risk factors (OR = 1.70, 95% CI 1.16, 2.49) and further adjustment for mean arterial pressure (Model 3, OR 1.71 1.15, 2.55).

The results were consistent when analysis was restricted to persons without a history of diabetes (online appendix). There was no evidence that gender, race, age or history of diabetes, modified the association between HbA1c and elevated EP and YEM (P>0.20 for all interactions).

Discussion

In a community-based study of 9,050 individuals without clinically evident coronary heart disease, we found that hyperglycemia was independently associated with measures of increased arterial wall stiffness. Our results also demonstrate that hyperglycemia is associated with a measure of arterial stiffness that incorporates arterial wall thickness, which may suggest that hyperglycemia is associated with altered material within the arterial wall.

Stiffness measures adjusted for blood pressure, particularly when measured concurrently with the stiffness assessment as done here, may relate more closely to inherent characteristics of the arterial wall. Our models adjusted for blood pressure and furthermore pulse pressure is used for the estimation of both EP and YEM. Despite these adjustments, hyperglycemia remained associated with stiffness. This, together with the fact that the hyperglycemia associations were found with both Ep and YEM contribute to evidence that the effect glycemia on stiffness is due in large part to altered material within the arterial wall, not to wall thickness or its reaction to increased blood pressure.

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Cardiovascular disease is the leading cause of morbidity and mortality in persons with diabetes mellitus. Although risk factors present in persons with diabetes (e.g. obesity, hypertension) partially explain the increased cardiovascular risk observed among persons with diabetes, hyperglycemia remains an independent risk factor for cardiovascular disease morbidity and mortality [15]. Arterial stiffness has been associated with adverse cardiovascular events in the general population as well. In a meta-analysis of 17 studies [16] Vlachopoulos et al have demonstrated that regional arterial stiffness (i.e. pulse wave velocity) is associated with cardiovascular events, and, cardiovascular and all-cause mortality. In the ARIC study [17] local arterial stiffness (measured through carotid ultrasound as in the current analysis) has been shown to be associated with stroke but not coronary heart disease. Our study by demonstrating an association between hyperglycemia and arterial stiffness suggests that hyperglycemia-associated arterial stiffness may partially contribute to the increased cardiovascular risk observed among persons chronically exposed to elevated glucose levels.

Our data are consistent with previous studies demonstrating that elevated fasting glucose concentrations are positively associated with arterial stiffness measures [3, 9, 18]. Using biomechanical techniques to estimate arterial stiffness parameters from pathological specimens from 27 subjects, Oxlund et al showed that those with diabetes had decreased vessel wall distensibility in areas without atherosclerotic plaque [18]. Interestingly, they suggested that this was due to changes in the connective tissue of arteries that was independent of atherosclerosis and suggested that this may be due to non-enzymatic glycation of proteins. Because they only excluded atherosclerotic plaques visually they were unable to provide a reliable estimate of the atherosis-independent stiffness association.

In a study of 747 older and predominately white persons, Henry et al. evaluated the association between impaired glucose metabolism, diabetes and increased arterial stiffness [9]. Although Henry et al. demonstrated an association between hyperglycemia and most stiffness measures among persons with diabetes, they did not observe any associations among participants with impaired glucose metabolism (composite of IFG and IGT). By contrast, we found that hyperglycemia was significantly associated with YEM, even below threshold for diagnosis of diabetes (i.e. HbA1c <6.5%).

Using data from the first ARIC examination, Salomaa et al. showed using models adjusted for age, smoking and total cholesterol, that persons with non-insulin dependent diabetes or impaired fasting glucose had stiffer arteries than persons with fasting glucose values in the normal range [3]. In models further adjusted for other cardiovascular risk factors this association was no longer significant in most subgroups. After further adjusting for other cardiovascular risk factors, EP and YEM only remained significant in some gender-race subgroups.

Although we did not formally perform test to identify a HbA1c threshold for stiffness, it is worth noting that our study showed that hyperglycemia was associated with increased arterial stiffness as assessed by EP from the eighth decile of glycated hemoglobin (HbA1c = 5.7–5.8%) and by YEM from the highest decile (HbA1c ≥6.3%). These values are below the current diagnosis threshold for diabetes [19], and our findings accord with other studies that have demonstrated that hyperglycemia, even below the diagnosis threshold for diabetes, is associated to increased cardiovascular risk [20].

Advanced glycation endproducts (AGEs) are a mechanism by which chronic hyperglycemia may contribute to arterial stiffness. Thirty years ago Monnier et al. postulated that non-enzymatic glycation (Maillard reaction) was associated with protein aging [21]. Numerous studies have since demonstrated associations between measures of glycation products and

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complications of diabetes mellitus. Chronic hyperglycemia enhances the reaction between glucose and proteins and facilitates cross-linking of collagen, elastin and other molecules commonly referred to as advanced glycation end products [22]. Similar to their effect on glycated hemoglobin (HbA1c), elevated levels of glucose are associated with the non-enzymatic glycation of other proteins in skin, vasculature and lens collagen, and have also been demonstrated to promote collagen deposition, tissue inflammation and fibrosis. Although we are unable to establish temporality in our study, we can speculate that the observed association between hyperglycemia and arterial stiffness is causal, mediated by advanced glycation end products.

In vitro studies have suggested that hyperglycemia affects the arterial wall by stimulating the proliferation of smooth muscle cells [23] and the non-enzymatic glycosylation of proteins [24]. Advanced glycation end products are associated with arterial stiffness and hypertension in humans [25]. The administration of a chemical that break advanced glycation end product cross-links has been shown to reverse arterial and myocardial stiffness in rhesus monkeys [26]. In a recent study of older individuals with vascular stiffening, Kass et al. showed that using an advanced glycation end-product crosslink breaker improved arterial compliance in humans with vascular stiffening [27]. However recent evidence suggests that there is no relationship between crosslink breaks and arterial stiffness [28].

B-mode ultrasound assessment of the arterial wall thickness has been used as a surrogate marker of atherosclerosis and has also been associated to future cardiovascular events [29, 30]. It is important to point out that because atherosis and sclerosis typically coexist in vivo, there is no way to reliably obtain a measure of stiffness that is entirely independent of atherosis. Furthermore, some have questioned the accuracy of arterial wall thickness as a reliable measure of atherosis [31] as clearly several other factors contribute to the thickening of the intima-medial complex. However, atherosis is a sub-intimal process and therefore accounting for the arterial wall thickness (as done for YEM), while imperfect, may represent one of the best surrogate approaches to account for local atherosis in a large population-based study.

We found that elevated HbA1c was associated with increased arterial stiffness using two different measures: YEM and Ep. Prior evidence suggests that YEM is less precise the Ep due to added variability from inclusion of wall thickness [32]. This was also observed in our study in that the reliability coefficient of YEM was less than Ep. Despite YEM's decreased precision, we found that Hba1c was much more strongly associated with YEM than Ep (Table 3), which may suggest an even stronger link between hyperglycemia and arterial wall thickness than frequently observed by measures that do not incorporate wall thickness.

Our study contributes to the field by providing evidence in a large well characterized population that hyperglycemia (as measured by HbA1C) is associated with arterial stiffness. A major strength of our study was the assessment of hyperglycemia by HbA1c, a marker of long-term glycemic exposure that has recently been recommended as a diagnostic test for diabetes mellitus [19]. Additionally we tried to account for the arterial thickness (and hence partially the atherosis component) which is factored in the determination of YEM [10], Therefore our results suggest that hyperglycemia leads to increased arterial stiffness even after accounting for blood pressure and arterial thickness.

Limitations

Arterial stiffness parameters used for the calculation of EP and YEM were measured at the carotid artery but blood pressure used in the calculations was measured from the brachial artery, and this may result in the overestimation of the central blood pressure. However, studies have shown an excellent correlation between central and brachial blood pressure

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measurements [33] and most epidemiological studies use brachial artery blood pressures in the estimation of carotid artery stiffness measures. Additionally, the low reliability coefficient for YEM suggest that our estimates of the association are conservative and thus emphasizes our findings regarding the association of measures of glycemia to alteration in the material of the arterial wall. Although we adjusted for known risk factors for cardiovascular disease, we cannot exclude the possibility of residual confounding in this observational study. These data were collected approximately 20 years ago (1990–1992), prior to the widespread use of statins. This likely eliminates any potential confounding effect of statins on the association between hyperglycemia and arterial stiffness. Our study represents one of the largest community-based studies of HbA1c and arterial stiffness measures. Additional strengths of this study include the large sample of persons with and without diabetes, including a large number of African Americans and the rigorous measurement of major cardiovascular risk factors.

In conclusion, in this community-based study, HbA1c was significantly and independently associated with measures of increased arterial stiffness. Our findings suggest that hyperglycemia contributes to arterial stiffness beyond its effects on atherosis and provide new evidence that hyperglycemia is associated with altered material within the arterial wall.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Elevated HbA1c is associated with measures of increased arterial stiffness
- This association persisted even after accounting for arterial wall thickness.
- Hyperglycemia may contribute to arterial stiffness beyond its effects on atherosis

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Table 1

Baseline characteristics by category of glycated hemoglobin

	Deciles									
HbA1c Range (%) Characteristic	**≤4.9 n=750**	**5 n=477**	**5.1 n=678**	**5.2 n=791**	**5.3 n=1,003**	**5.4–5.5 n=1,604**	**5.6 n=734**	**5.7–5.8 n=1,073**	**5.9–6.2 n=964**	**≥6.3 n=976**
Glycated hemoglobin - %	4.8 ± 0.2	5.0 ± 0.0	5.1 ± 0.0	5.2 ± 0.0	5.3 ± 0.0	5.4 ± 0.05	5.6 ± 0.0	5.7 ± 0.5	6.0 ± 0.01	8.1 ± 2.0
Fasting glucose (mg/dl)	90.0 ± 8.8	98.1 ± 8.8	98.9 ± 0.5	98.5 ± 8.4	100.1 ± 9.0	101.2 ± 9.4	103.7 ± 10.6	105.4 ± 11.3	110.8 ± 15.0	189.1 ± 86.3
Age (yr)	55.3 ± 5.4	55.2 ± 5.7	55.3 ± 5.5	56.0 ± 5.6	56.7 ± 5.5	56.6 ± 5.5	57.2 ± 5.7	57.3 ± 5.7	57.8 ± 5.7	57.8 ± 5.7
Female (%)	53.5	59.5	58.1	61.1	56.8	57.9	55.3	54.2	55.1	55.5
African American (%)	15.7	10.1	13	10.4	12	17	23.7	32	43.7	52.6
LDL-cholesterol (mg/dl)	123.3 ± 34.6	124.5 ± 35.7	127 ± 34.3	130.3 ± 36.4	131.5 ± 34.4	133.5 ± 34.5	134.6 ± 33.4	138.4 ± 40.0	138.8 ± 36.9	139.2 ± 40.3
HDL-cholesterol (mg/dl)	53.1 ± 18.0	53.6 ± 17.5	53.3 ± 17.9	53.7 ± 16.9	52.2 ± 16.9	51.7 ± 16.6	50.7 ± 16.8	49.6 ± 16.3	48.1 ± 14.8	44.6 ± 13.9
Body-mass index [a]	26.1 ± 4.3	26.1 ± 4.0	26.3 ± 4.2	26.0 ± 4.3	26.2 ± 4.2	26.8 ± 4.4	26.9 ± 4.5	27.7 ± 5.0	28.5 ± 5.0	30.1 ± 5.2
Hypertension (%)	25.1	24.4	22.9	24.6	28.3	25.3	31.1	35.9	44.6	54.2
Education (%)										
Less than high school	13.9	12.4	14	13.3	14.2	16	21.3	24.8	28.7	35.5
High School or equivalent	40.7	42.1	42.3	47.3	47.3	41.9	40.1	40.6	40.8	37.1
College or above	45.5	45.5	43.7	39.4	38.6	42.1	38.7	34.6	30.5	27.5
Smoking status (%):										
Current	12.1	13.2	17.8	16.8	18.7	23.2	27	30	27.6	18.9
Former	43.9	42.6	39.5	37.8	38.4	37.4	32.7	33.4	36.2	38
Never	44	44.2	42.6	45.4	42.9	39.4	40.3	36.6	36.2	43.1
Ep (kPa)	127 ± 53	127 ± 58	127 ± 53	124 ± 54	131 ± 58	132 ± 56	137 ± 61	145 ± 64	151 ± 66	172 ± 77
Yem (kPa)	786 ± 394	782 ± 395	799 ± 391	769 ± 358	820 ± 410	815 ± 402	848 ± 439	870 ± 438	918 ± 478	998 ± 505
Mean arterial pressure (mmHg)	87.9 ± 11.3	87.2 ± 10.2	87.6 ± 11.2	86.7 ± 11.3	88.5 ± 11.4	87.7 ± 11.0	88.7 ± 11.7	90.1 ± 11.4	91.9 ± 12.1	94.3 ± 11.5
Diabetes, %	0.8	0.6	0.6	1.6	1.6	0.8	3.3	3.8	8.8	59.7
Glucose medication use, %	0.4	0.2	0	0.4	0.2	0.1	0.5	0.7	2	43.7
Blood pressure-lower medication use, %	23.1	22.9	19.5	22.4	23.8	22.9	26.6	32.2	40.1	53.3
Lipid-lowering medication use, %	4	5.5	4.7	4.6	6.3	6.4	6.5	5.5	6.5	8.7

[a] The body-mass index is the weight in kilograms divided by the square of the height in meters.

LDL = low density lipoprotein, HDL = high density lipoprotein

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Values are means ± standard deviation and percentage

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Table 2

Baseline characteristics by quartiles of EP

Characteristic	Total n=9,050	Ep Quartiles 1 n=2,261	2 n=2,260	3 n=2,266	4 n=2,263
Ep (kPa)	136	79	111	143	222
YEM (kPa)	846	483	684	884	1332
Glycated hemoglobin - %	5.7	5.5	5.6	5.7	6
Fasting glucose (mg/dl)	111.5	103.5	106.9	113.3	122.1
Age (yr)	56.7	54.2	55.8	57.3	59.4
Female (%)	56.6	59.1	56.5	54.2	56.6
African American (%)	24.1	17.1	21.2	26.1	31.9
LDL-cholesterol (mg/dl)	133	129.7	131.4	134	137.1
HDL-cholesterol (mg/dl)	50.8	52.2	51	50.2	49.7
Body-mass index [a]	27.2	25.7	26.8	27.8	28.4
Hypertension (%)	32.2	14.3	23.8	36.7	54.1
Education (%)					
Less than high school	20	13.6	16.4	21	28.8
High School or equivalent	42	42.9	43.5	42.5	39
College or above	38	43.5	40.1	36.5	32.2
Smoking status (%):					
Current	21.4	28.3	21.6	19.8	16
Former	37.6	34.9	37	38.4	40.1
Never	41	36.8	41.4	41.8	44

[a] The body-mass index is the weight in kilograms divided by the square of the height in meters.

LDL = low density lipoprotein, HDL = high density lipoprotein

Values are means ± standard deviation and percentages

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Table 3

Adjusted regression coefficients for EP and YEM with increasing HbA1c

	Model 1		Model 2		Model 3	
HbA1c Category	**β**	**(95% CI)**	**β**	**(95% CI)**	**β**	**(95% CI)**
EP	7.89	6.74, 9.03	4.70	3.10, 6.30	3.91	2.57, 5.26
YEM	35.77	27.54, 44.01	18.10	6.51, 29.69	13.50	3.10, 23.90

β represents the linear regression coefficient (difference per 1.0 -% change in HbA1c).

Model 1: Adjusted for age, gender, race and center

Model 2: Model 1 + height, weight, education, smoking, LDL, HDL-cholesterol HDL-cholesterol, diabetes history, blood pressure lowering medication use, cholesterol lowering medication use, glucose lowering medication use

Model 3: Model 2 + mean arterial pressure

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Table 4

Odds Ratio for Highest Decile of EP and YEM across deciles of HbA1c

	Model 1			Model 2			Model 3		
HbA1c Category (HbA1c%)	**OR**	**(95% CI)**		**OR**	**(95% CI)**		**OR**	**(95% CI)**	
EP									
Decile 1 (≤4.9%)	1	(Reference)		1	(Reference)		1	(Reference)	
Decile 2 (5.0%)	1.28	0.79	2.09	1.32	0.81	2.15	1.53	0.91	2.57
Decile 3 (5.1%)	1.17	0.75	1.84	1.20	0.76	1.89	1.22	0.75	1.98
Decile 4 (5.2%)	0.86	0.54	1.35	0.85	0.54	1.34	0.92	0.56	1.51
Decile 5 (5.3%)	1.20	0.80	1.79	1.19	0.80	1.79	1.08	0.70	1.67
Decile 6 (5.4–5.5%)	1.18	0.81	1.72	1.16	0.80	1.69	1.30	0.87	1.94
Decile 7 (5.6%)	1.46	0.97	2.18	1.38	0.91	2.08	1.51	0.97	2.35
Decile 8 (5.7–5.8%)	**1.89**	**1.31**	**2.75**	**1.70**	**1.16**	**2.47**	**1.88**	**1.25**	**2.81**
Decile 9 (5.9–6.2%)	**1.91**	**1.31**	**2.78**	**1.60**	**1.09**	**2.35**	**1.59**	**1.05**	**2.39**
Decile 10 (≥6.3)	**3.11**	**2.17**	**4.48**	**1.93**	**1.29**	**2.89**	**2.01**	**1.30**	**3.11**
P-trend	<0.001			0.001			0.001		
YEM									
Decile 1 (≤4.9%)	1	(Reference)		1	(Reference)		1	(Reference)	
Decile 2 (5.0%)	0.97	0.61	1.54	0.98	0.61	1.55	1.05	0.65	1.69
Decile 3 (5.1%)	1.06	0.70	1.60	1.08	0.72	1.63	1.07	0.70	1.65
Decile 4 (5.2%)	0.89	0.59	1.33	0.89	0.59	1.33	0.95	0.62	1.45
Decile 5 (5.3%)	0.92	0.63	1.34	0.93	0.64	1.35	0.85	0.57	1.26
Decile 6 (5.4–5.5%)	1.02	0.73	1.43	1.02	0.72	1.43	1.08	0.76	1.54
Decile 7 (5.6%)	**1.46**	**1.01**	**2.10**	1.41	0.97	2.04	**1.50**	**1.02**	**2.22**
Decile 8 (5.7–5.8%)	1.31	0.93	1.86	1.21	0.85	1.73	1.24	0.86	1.80
Decile 9 (5.9–6.2%)	**1.73**	**1.23**	**2.44**	**1.55**	**1.09**	**2.19**	**1.51**	**1.04**	**2.17**
Decile 10 (≥6.3)	**2.34**	**1.67**	**3.28**	**1.70**	**1.16**	**2.49**	**1.71**	**1.15**	**2.55**
P-trend	<0.001		<0.001	0.012			0.012		

Bolded results represent P<0.05

Model 1: Adjusted for age, gender, race and center

Model 2: Model 1 + height, weight, education, smoking, LDL, HDL-cholesterol HDL-cholesterol, diabetes history, blood pressure lowering medication use, cholesterol lowering medication use, glucose lowering medication use

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Model 3: Model 2 + mean arterial pressure