The Association Between A1C and Subclinical Cardiovascular Disease

The Multi-Ethnic Study of Atherosclerosis

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OBJECTIVE — To test the hypothesis that A1C is associated with subclinical cardiovascular disease (CVD) in a population without evident diabetes, after adjusting for traditional CVD risk factors and BMI.

RESEARCH DESIGN AND METHODS — This was a cross-sectional study of 5,121 participants without clinically evident CVD or diabetes (fasting glucose ≥ 7.0 mmol/l or use of diabetes medication), aged 47–86 years, enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Measurements included carotid intimal-medial wall thickness (CIMT) and coronary artery calcification (CAC). Results were adjusted for age, sex, ethnicity, smoking, systolic blood pressure, LDL cholesterol, HDL cholesterol, antihypertensive medication use, lipid-lowering medication use, and BMI.

RESULTS — Compared with those in the lowest quartile for A1C ([mean $\pm$ SD] $5.0 \pm 0.2\%$), participants in the highest quartile ($6.0 \pm 0.3\%$) had higher adjusted mean values for common CIMT (0.85 vs. 0.87 mm, $P = 0.003$) and internal CIMT (1.01 vs. 1.08 mm, $P = 0.003$). A1C quartile was not associated with prevalence of CAC in the entire cohort ($P = 0.27$); however, the association was statistically significant in women (adjusted prevalence of CAC in lowest and highest A1C quartiles 37.5 vs. 43.0%, $P = 0.01$). Among those with some CAC, higher A1C quartile tended to be associated with higher CAC score, but the results were not statistically significant (adjusted $P = 0.11$).

CONCLUSIONS — In this multiethnic cohort, there were small, positive associations between A1C, common CIMT, and internal CIMT in the absence of clinically evident diabetes. An association between higher A1C and CAC prevalence was evident only in women.

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Higher level of A1C, a measurement of recent glycemia status, has been associated with clinical cardiovascular disease (CVD) in both the diabetic and nondiabetic population (1–3), but little information is available on the association between A1C and subclinical CVD in nondiabetic populations. Studies of subclinical CVD, including coronary artery calcification (CAC) and carotid intimal-medial wall thickness (CIMT), can provide complementary information to studies of clinical CVD outcomes by providing a more focused understanding of the factors that contribute to atherosclerosis, whereas studies of clinical CVD events are also influenced by factors related to plaque rupture and thrombosis. CAC and CIMT are associated with future risk of CVD events (4,5) and offer an opportunity to better understand the factors that contribute to the development and natural progression of early stage CVD.

To date, the few studies that have examined the association between A1C and subclinical CVD in individuals without diabetes have shown mixed results. Sander et al. (6) found that A1C was associated with progression of common CIMT over 2 years, particularly when C-reactive protein (CRP) was also elevated. Doruk et al. (7) found no significant association between A1C and CIMT (mean of 12 common and internal CIMT measurements) in 78 elderly nondiabetic participants. Aihara et al. (8) showed that A1C was significantly associated with maximum plaque thickness (or CIMT if plaque was absent) in the internal or common carotid arteries in 306 Japanese participants; however, the association was not independent of diabetes status and was not described among nondiabetic participants. Temelkova-Kurktschiev et al. (9) showed that fasting glucose, glucose measured 2 h after an oral glucose load (2-h glucose), and A1C were each associated with common CIMT in 582 German participants without clinically diagnosed diabetes after adjusting for age and sex, but 30% of these participants had undiagnosed diabetes.

To our knowledge, there are no pub-

lished studies examining the association between A1C and CAC in participants without clinically evident diabetes and no large studies of A1C and CIMT in minority ethnic populations. The purpose of this study was to test the hypothesis that A1C within the range observed in subjects without clinically evident diabetes is associated with subclinical CVD after accounting for traditional CVD risk factors and that this association persists after further adjustment for BMI. Secondary aims of this study were to determine whether the association between A1C and subclinical CVD varied by sex or race/ethnicity and whether results were explained by differences in other nontraditional CVD risk factors (triglycerides, CRP, intentional exercise, and albuminuria).

RESEARCH DESIGN AND METHODS

— Details about the study design of the Multi-Ethnic Study of Atherosclerosis (MESA) have been previously published (10). Briefly, 6,814 participants, aged 45–84 years, who identified themselves as white, African American, Hispanic, or Asian (predominantly of Chinese ancestry), were recruited from six U.S. communities between July 2000 and August 2002. All participants were free of clinically apparent CVD at enrollment. Each study site recruited an approximately equal number of men and women, according to prespecified age and race/ethnicity proportions. All participants gave informed consent, and the study protocol was approved by the institutional review board of each center. A1C was measured at exam 2 in MESA, which was conducted ~16 months after the baseline study exam. Of 6,233 participants attending exam 2, 1,112 were excluded because of missing A1C ($n = 96$) or fasting glucose ($n = 4$) data, diabetes based on fasting glucose ≥7.0 mmol/l (11) or reported use of oral hypoglycemic medication or insulin ($n = 962$), or prevalent CVD at exam 2 ($n = 50$), leaving 5,121 participants for this cross-sectional analysis.

All measurements were obtained at exam 2, unless otherwise specified. Medication use and smoking status were ascertained by questionnaire. Smoking status was coded as current, quit <1 year ago, quit ≥1 year ago, and never smoked. Physical activity was measured by questionnaire. Participants reported the average time spent doing intentional exercise activities per week during the past month, and the total estimated metabolic energy expenditure (in MET units per minute)

for each activity was summed (12). The summary scores were categorized as no intentional exercise, ≤735 MET min/week, 736–1,785 MET min/week, and >1,785 MET min/week. Fasting blood samples were obtained for measurements of lipids, glucose, A1C, and highly sensitive CRP. CRP was not measured at exam 2, so baseline measurements were used in the analysis. A morning urine sample was obtained to measure urine albumin-to-creatinine ratio, which was categorized as normal (<30 mg/g), microalbuminuric (30–299 mg/g), or macroalbuminuric (≥300 mg/g).

Common and internal CIMTs were measured by ultrasound on all participants at baseline, as previously described (13). CIMT was measured on the right and left side, and the maximum value was used for analysis. CIMT is expected to change only ~0.008–0.012 mm per year (14), hence we assumed that baseline CIMT measurements were a reasonable approximation of CIMT at exam 2.

CAC was measured using either electron-beam computed tomography at three field centers or multidetector computed tomography at three field centers. Each participant was scanned twice consecutively, and these scans were read independently at a centralized reading center, as previously reported (15). All participants had CAC measured at baseline. Follow-up CAC measurements were performed on about half the cohort (2,438 randomly selected participants) at exam 2 (~16 months after baseline) and the other half of the cohort ($n = 2,246$) at exam 3 (~39 months [range 23–59] after baseline). For 2,246 participants who did not have CAC measured concurrently with A1C at exam 2, we used a linear interpolation of their CAC scores from baseline and exam 3 as an estimate of their exam 2 CAC. Either measured or interpolated CAC data for exam 2 were available for 4,684 participants, and 437 participants had missing CAC data.

Participants who had CAC measured at exam 2 were similar to those with interpolated CAC with regard to age, sex, smoking status, BMI, A1C, fasting glucose, systolic blood pressure, LDL cholesterol, HDL cholesterol, common CIMT, and internal CIMT (all $P > 0.08$). Compared with participants with CAC measured at exam 2, participants with interpolated CAC had higher prevalence of detectable CAC (57 vs. 50%, χ^2 test $P < 0.001$), lower median CAC score if CAC >0 (66.6 vs. 85.1 Agatston units,

Wilcoxon rank sum test $P < 0.001$), and lower mean natural logarithm (ln) CAC score if CAC was more than zero (3.93 vs. 4.36 ln Agatston units, Student's t test $P < 0.001$). Differences in CAC measurements by interpolated status were not accounted for by adjustment for age, sex, race, smoking status, BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, antihypertensive medication use, or lipid-lowering medication use (all $P < 0.001$).

Statistical analysis

For CIMT, associations with A1C were analyzed using linear regression. In the MESA, about half of the participants had a CAC score of zero, with the positive scores being highly skewed. We modeled this using a two-stage approach. The association between presence or absence of detectable CAC and A1C was analyzed using relative risk regression (16). Specifically, we used generalized linear models with log link, Gaussian error structure and used a Huber-White sandwich (robust) estimator of variance to calculate the prevalence ratio (PR). Logistic regression was not used because the presence of CAC is not a rare outcome, and the odds ratio would overestimate the PR. Among those with positive CAC scores, we modeled ln of the value as a function of A1C using linear regression. Interactions between A1C and sex or A1C and race/ethnicity were considered. To confirm that results were not dependent on A1C outliers, we repeated all analyses excluding values >6.1% (95th percentile); results were similar, so the findings presented in this report are based on all available A1C data. We also modeled results using all A1C quartiles entered as dummy variables with quartile 1 as the reference group. These models were used to calculate adjusted means or prevalences of CVD measurements by A1C quartile using the mean value for each covariate. To confirm that the linear interpolation of CAC values did not alter the findings, we repeated all CAC analyses using only the participants with a CAC measurement at exam 2. Because multiple comparisons were made, P values near 0.05 should be interpreted with caution. All statistics were calculated using Stata/SE software (version 8.0 for Windows; Stata, College Station, TX).

RESULTS

— Table 1 shows the characteristics of the 5,121 MESA participants at exam 2, stratified by A1C quartile. A1C

Table 1—*Characteristics of nondiabetic MESA participants without clinical CVD at exam 2 by A1C quartile*

	Overall	A1C quartile 1	A1C quartile 2	A1C quartile 3	A1C quartile 4	Crude P
A1C range (%)		(3.5–5.2)	(5.3–5.4)	(5.5–5.7)	(5.8–8.6)	
Sample size (n)	5,121	1,668	1,051	1,411	991	
Age (years)	63.2 ± 10.2	60.9 ± 10.0	62.9 ± 9.9	64.2 ± 10.2	65.9 ± 9.7	<0.0001
Male sex [n (column %)]	2,391 (46.7)	813 (48.7)	489 (46.5)	666 (47.2)	423 (42.7)	0.03
Race/ethnicity [n (column %)]						<0.0001
White	2,190 (42.8)	926 (55.5)	511 (48.6)	525 (37.2)	228 (23.0)	
Asian American	594 (11.6)	139 (8.3)	138 (13.1)	203 (14.4)	114 (11.5)	
African American	1,298 (25.4)	302 (18.1)	201 (19.1)	380 (26.9)	415 (41.9)	
Hispanic	1,039 (20.3)	301 (18.1)	201 (19.1)	303 (21.5)	234 (23.6)	
Smoking status [n (column %)]						0.85
Current	593 (11.6)	177 (10.7)	123 (11.7)	170 (12.1)	123 (12.5)	
Never	2,534 (49.7)	825 (49.7)	526 (50.1)	702 (49.9)	481 (49.0)	
Intentional exercise [n (column %)]						0.003
None	1,217 (23.8)	370 (22.2)	238 (22.7)	341 (24.2)	268 (27.1)	
<735 MET min/week	1,269 (24.8)	387 (23.2)	262 (25.0)	363 (25.7)	258 (26.1)	
736–1785 MET min/week	1,275 (24.9)	411 (24.7)	277 (26.4)	356 (25.3)	231 (23.4)	
>1,785 MET min/week	1,351 (26.4)	499 (29.9)	273 (26.0)	348 (24.7)	231 (23.4)	
BMI (kg/m^2)	27.9 ± 5.2	26.9 ± 4.8	27.2 ± 4.9	28.2 ± 5.3	30.0 ± 5.6	<0.0001
Systolic blood pressure (mmHg)	123 ± 20	120 ± 20	122 ± 21	123 ± 20	127 ± 21	<0.0001
LDL cholesterol (mmol/l)	2.98 ± 0.82	2.89 ± 0.82	3.02 ± 0.80	3.01 ± 0.80	3.05 ± 0.87	<0.0001
HDL cholesterol (mmol/l)	1.37 ± 0.39	1.41 ± 0.43	1.38 ± 0.38	1.34 ± 0.36	1.30 ± 0.37	<0.0001
Triglycerides (mmol/l) [median (interquartile range)]	1.22 (0.87)	1.17 (0.82)	1.19 (0.83)	1.24 (0.88)	1.29 (0.89)	<0.001
CRP (mg/l) [median (interquartile range)]	1.75 (3.21)	1.38 (2.66)	1.53 (3.04)	1.86 (3.30)	2.61 (3.98)	<0.0001
A1C (%)	5.4 ± 0.4	5.0 ± 0.2	5.3 ± 0.1	5.6 ± 0.1	6.0 ± 0.3	<0.0001
Glucose (mmol/l)	5.4 ± 0.5	5.1 ± 0.5	5.3 ± 0.5	5.4 ± 0.5	5.8 ± 0.6	<0.0001
Albuminuria [n (column %)]						0.001
None	4,734 (93.2)	1,562 (94.3)	972 (93.0)	1,309 (93.9)	891 (90.6)	
Microalbuminuria	311 (6.1)	87 (5.3)	62 (5.9)	74 (5.3)	88 (9.0)	
Macroalbuminuria	33 (0.7)	7 (0.4)	11 (1.05)	11 (0.8)	4 (0.4)	
Antihypertensive medication use [n (column %)]	1,859 (36.3)	518 (31.1)	352 (33.5)	505 (35.8)	484 (48.8)	<0.0001
Hypertension [n (column %)]	2,320 (45.3)	646 (38.8)	458 (43.6)	623 (44.2)	593 (59.8)	<0.0001
Lipid-lowering medication use [n (column %)]	983 (19.2)	240 (14.4)	185 (17.6)	300 (21.3)	258 (26.0)	<0.0001
Common CIMT (mm)	0.85 ± 0.19	0.82 ± 0.18	0.84 ± 0.18	0.87 ± 0.19	0.91 ± 0.19	<0.0001
Internal CIMT (mm)	1.03 ± 0.56	0.97 ± 0.51	1.02 ± 0.53	1.04 ± 0.57	1.14 ± 0.65	<0.0001
Prevalence of CAC >0 [n (column %)]	2,504 (53.5)	724 (47.4)	520 (54.1)	719 (55.4)	541 (60.3)	<0.0001
CAC score (if >0) (Agatston units) [median (interquartile range)]	77.4 (254.2)	62.1 (217.4)	73.3 (233.2)	86.9 (273.9)	84.1 (310.7)	0.06

Data are means ± SD, unless otherwise indicated. Sample size varies across A1C quartiles because of tied values. All measurements were obtained at exam 2, except for CRP and CIMT, which were measured 16 months prior to exam 2 at baseline, and CAC, which was measured either at exam 2 (n = 2,438) or interpolated from measurements made at baseline and 39 months later at exam 3 (n = 2,246). Data were missing for smoking status (n = 25), intentional exercise (n = 9), systolic blood pressure (n = 3), LDL cholesterol (n = 42), HDL cholesterol (n = 4), triglycerides (n = 2), CRP (n = 33), albuminuria (n = 43), common CIMT (n = 57), internal CIMT (n = 120), and CAC (n = 437). P values for comparisons among A1C quartiles are based on χ^2 or one-way ANOVA (3 degrees of freedom). For CRP, triglycerides, and CAC score, P values were calculated using ln.

values ranged from 3.5 to 8.6%, with 95th percentile of 6.1% and 99th percentile of 6.6%. A1C was significantly associated with all characteristics except smoking status and CAC score.

Associations of A1C and subclinical CVD by sex and race/ethnicity
Table 2 shows the associations between A1C (modeled as a continuous variable) and measures of subclinical CVD, stratified by sex and race/ethnicity, and adjusted for smoking status, systolic blood pressure, LDL cholesterol, HDL cholesterol, antihypertensive medication use, and lipid-lowering medication use. Results were similar after adjustment for study site (data not shown). Higher A1C was significantly associated with greater common CIMT, and there were no significant interactions by sex or race/ethnicity. Higher A1C was significantly associated with greater internal CIMT, and the magnitude of this association varied by race/ethnicity but not by sex. The magnitude of the association between A1C and internal CIMT was significantly larger in whites than in Asians ($P = 0.02$) and Hispanics ($P = 0.02$) but not in African Americans ($P = 0.20$), ($P = 0.04$ for all

Table 2—*Associations between A1C and subclinical CVD adjusted for traditional CVD risk factors*

	Overall		Women		Men	
	Coefficient or PR (95% CI)	*P*	Coefficient or PR (95% CI)	*P*	Coefficient or PR (95% CI)	*P*
Common CIMT (mm)						
Overall	0.02 (0.01–0.04)	<0.001	0.02 (0.00–0.03)	0.04	0.03 (0.01–0.05)	<0.001
White	0.03 (0.01–0.05)	0.01	0.03 (0.00–0.05)	0.03	0.03 (−0.01 to 0.06)	0.14
Asian American	0.04 (0.00–0.07)	0.04	0.05 (0.00–0.10)	0.04	0.02 (−0.02 to 0.07)	0.33
African American	0.01 (−0.01 to 0.03)	0.24	−0.01 (−0.04 to 0.02)	0.54	0.03 (0.00–0.06)	0.03
Hispanic	0.03 (0.01–0.06)	0.009	0.02 (−0.01 to 0.05)	0.22	0.04 (0.01–0.08)	0.03
Internal CIMT (mm)						
Overall	0.05 (0.01–0.09)*	0.01*	0.04 (−0.01 to 0.09)	0.14	0.06 (0.01–0.12)	0.03
White	0.09 (0.02–0.16)	0.01	0.09 (−0.00 to 0.18)	0.05	0.09 (−0.01 to 0.20)	0.09
Asian American	0.04 (−0.05 to 0.13)	0.38	0.06 (−0.06 to 0.19)	0.32	0.00 (−0.13 to 0.13)	0.99
African American	0.04 (−0.02 to 0.11)	0.20	0.03 (−0.07 to 0.12)	0.62	0.06 (−0.03 to 0.16)	0.18
Hispanic	0.00 (−0.07 to 0.08)	0.91	−0.03 (−0.13 to 0.06)	0.51	0.05 (−0.06 to 0.17)	0.36
Prevalence of CAC >0 (%)						
Overall	1.05 (0.99–1.11)†	0.10†	1.14 (1.03–1.26)	0.01	1.01 (0.95–1.08)	0.71
White	1.06 (0.98–1.16)	0.14	1.20 (1.03–1.40)	0.02	1.01 (0.92–1.11)	0.79
Asian American	1.22 (1.01–1.48)	0.04	1.31 (0.94–1.82)	0.11	1.21 (0.97–1.52)	0.09
African American	1.01 (0.90–1.13)	0.93	1.16 (0.94–1.43)	0.16	0.93 (0.80–1.06)	0.28
Hispanic	1.06 (0.93–1.20)	0.39	1.02 (0.83–1.24)	0.88	1.07 (0.91–1.26)	0.38
CAC score if >0 (ln Agatston units)						
Overall	0.15 (−0.03 to 0.33)	0.10	0.06 (−0.22 to 0.33)	0.70	0.22 (−0.02 to 0.45)	0.08
White	0.36 (0.07–0.65)	0.02	0.19 (−0.26 to 0.63)	0.41	0.48 (0.09–0.87)	0.02
Asian American	0.02 (−0.52 to 0.57)	0.93	−0.33 (−1.16 to 0.50)	0.43	0.31 (−0.46 to 1.08)	0.42
African American	0.01 (−0.32 to 0.34)	0.96	−0.07 (−0.61 to 0.47)	0.81	0.14 (−0.28 to 0.57)	0.51
Hispanic	0.08 (−0.33 to 0.48)	0.71	0.34 (−0.28 to 0.95)	0.28	0.04 (−0.51 to 0.59)	0.90

Partial regression coefficients and PRs are for a 1% increment in A1C in separate models. Results are adjusted for age, smoking status, systolic blood pressure, LDL cholesterol, HDL cholesterol, antihypertensive medication use, and lipid-lowering medication use. Overall models are also adjusted for sex and race/ethnicity. Overall models were tested for interactions by race/ethnicity or sex; there were no significant interactions except as noted. *Significant interaction present for association between A1C and subclinical CVD measure by race/ethnicity, *P* < 0.05. †Significant interaction present for the association between A1C and subclinical CVD measure by sex, *P* < 0.05.

race interaction terms combined). The magnitude of the association between A1C and prevalence of CAC score more than zero was significantly larger in women than in men (*P* < 0.001 for sex interaction term), but there were no significant differences by race/ethnicity. For women overall, the relative prevalence of CAC more than zero increased by 14% for every one-unit (1%) increase in A1C (PR = 1.14 [1.03–1.26], *P* = 0.01). Analyses restricted to the 2,438 participants with exam 2 CAC measurements (excluding those with extrapolated CAC measurements) showed adjusted PRs of similar magnitude to those shown in Table 2 (for all women, adjusted PR 1.12, *P* = 0.12; for all participants, adjusted PR 1.06, *P* = 0.15). Among participants with CAC more than zero, there was no significant association between A1C and CAC score in the cohort overall and no significant interactions by sex or race/ethnicity.

Effect of excluding participants with A1C >95th percentile

When participants with A1C >95th percentile (>6.1%) were excluded, the magnitude of the regression coefficients or PR were not substantially different from those shown in Table 2 for analysis of common CIMT in all participants (coefficient 0.02 [95% CI 0.01–0.03], *P* = 0.005), internal CIMT in all participants (coefficient 0.05 [95% CI 0.00–0.09], *P* = 0.03), or prevalent CAC in all women (PR 1.14 [95% CI 1.02–1.27], *P* = 0.02).

Effect of further adjustment for BMI plus other nontraditional CVD risk factors

Compared with results shown in Table 2, results were similar when models were further adjusted for traditional CVD risk factors plus BMI and one of the following variables per model: ln(triglycerides), ln-(CRP), intentional exercise, or albuminuria (data not shown).

Results by quartile of A1C adjusted for traditional CVD risk factors and CVD risk factors plus BMI

To better demonstrate the magnitude of the difference in subclinical CVD measures between participants across the A1C range, adjusted means are presented by A1C quartile in Table 3, adjusted for traditional CVD risk factors and adjusted for traditional CVD risk factors plus BMI. Subgroup analyses are presented if indicated by the presence of statistically significant interactions by ethnicity or sex in Table 2. Compared with those in the lowest quartile for A1C, participants in the highest quartile had higher adjusted mean values for common CIMT (0.85 vs. 0.87 mm, *P* < 0.001) and internal CIMT (1.01 vs. 1.08 mm, *P* = 0.001) after adjustment for traditional CVD risk factors (Table 3). For comparison, results for lowest versus highest LDL cholesterol quartile showed lower mean common CIMT (0.84 vs. 0.87 mm, coefficient 0.03 [95% CI 0.02–0.04], *P* < 0.001) and

Table 3—A1C and subclinical CVD by quartile of A1C with adjustment for CVD risk factors and CVD risk factors plus BMI

	A1C quartile 1	A1C quartile 2	A1C quartile 3	A1C quartile 4	Quartile 4 versus quartile 1	
	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)	Coefficient or PR (95% CI)	P*
Adjusted for CVD risk factors						
Common CIMT (mm)						
Overall	0.85 (0.84–0.85)	0.85 (0.84–0.86)	0.86 (0.85–0.87)	0.87 (0.86–0.89)	0.03 (0.01–0.04)	<0.001
Internal CIMT (mm)						
Overall	1.01 (0.98–1.03)	1.02 (0.99–1.06)	1.02 (1.00–1.05)	1.08 (1.05–1.11)	0.07 (0.03–0.12)	0.001
White	1.08 (1.05–1.12)	1.06 (1.02–1.11)	1.11 (1.07–1.16)	1.21 (1.14–1.28)	0.13 (0.05–0.21)	0.002
Asian American	0.79 (0.73–0.85)	0.83 (0.77–0.89)	0.79 (0.73–0.84)	0.86 (0.79–0.93)	0.07 (−0.03 to 0.17)	0.17
African American	1.02 (0.96–1.09)	1.08 (1.00–1.16)	1.04 (0.99–1.10)	1.10 (1.04–1.15)	0.08 (−0.01 to 0.16)	0.08
Hispanic	0.96 (0.90–1.01)	1.00 (0.93–1.06)	0.94 (0.89–1.00)	0.97 (0.91–1.04)	0.02 (−0.07 to 0.10)	0.72
Prevalence of CAC >0 (%)						
Overall	49.0 (47.0–51.1)	50.9 (48.1–53.1)	50.9 (48.8–53.0)	51.7 (49.2–54.4)	1.06 (0.99–1.12)	0.09
Women	37.3 (34.4–40.3)	40.1 (36.8–43.7)	40.6 (37.7–43.7)	43.5 (40.3–47.1)	1.17 (1.05–1.30)	0.003
Men	62.1 (59.1–65.1)	62.5 (59.0–66.2)	62.4 (59.4–65.5)	62.3 (58.5–66.5)	1.00 (0.93–1.08)	0.92
CAC score if >0 (ln Agatston units)						
Overall	4.04 (3.90–4.17)	4.05 (3.90–4.21)	4.21 (4.08–4.34)	4.25 (4.09–4.41)	0.21 (−0.00 to 0.42)	0.05
Adjusted for CVD risk factors and BMI						
Common CIMT (mm)						
Overall	0.85 (0.84–0.86)	0.85 (0.84–0.86)	0.86 (0.85–0.87)	0.87 (0.86–0.88)	0.02 (0.01–0.02)	0.003
Internal CIMT (mm)						
Overall	1.01 (0.98–1.03)	1.03 (0.99–1.06)	1.02 (0.99–1.05)	1.08 (1.04–1.11)	0.07 (0.02–0.11)	0.003
White	1.08 (1.05–1.12)	1.06 (1.02–1.11)	1.11 (1.07–1.16)	1.21 (1.14–1.28)	0.13 (0.04–0.21)	0.003
Asian American	0.79 (0.73–0.85)	0.83 (0.77–0.89)	0.79 (0.73–0.84)	0.86 (0.78–0.93)	0.07 (−0.03 to 0.12)	0.18
African American	1.02 (0.95–1.08)	1.08 (1.00–1.16)	1.05 (0.99–1.10)	1.10 (1.05–1.16)	0.08 (−0.01 to 0.17)	0.07
Hispanic	0.96 (0.91–1.02)	1.00 (0.94–1.07)	0.94 (0.89–0.99)	0.96 (0.90–1.03)	0.00 (−0.09 to 0.09)	0.36
Prevalence of CAC >0 (%)						
Overall	49.3 (47.2–51.4)	50.6 (48.3–53.2)	50.7 (48.6–52.9)	51.0 (48.5–53.7)	1.04 (0.97–1.10)	0.27
Women	37.5 (34.7–40.5)	40.3 (36.7–43.9)	40.5 (37.6–43.5)	43.0 (39.7–46.5)	1.15 (1.03–1.30)	0.01
Men	62.4 (59.4–65.4)	62.6 (59.2–66.4)	62.2 (59.2–65.3)	61.6 (57.8–65.7)	0.99 (0.92–1.07)	0.77
CAC score if >0 (ln Agatston units)						
Overall	4.05 (3.92–4.19)	4.06 (3.91–4.22)	4.21 (4.08–4.34)	4.23 (4.07–4.39)	0.18 (−0.04 to 0.39)	0.11

CVD risk factors: age, sex, smoking status, systolic blood pressure, LDL cholesterol, HDL cholesterol, antihypertensive medication use, and lipid-lowering medication use. In addition to overall results for the entire cohort, subgroup analyses based on separate models are presented if indicated by the presence of statistically significant interactions by race/ethnicity or sex as shown in Table 2. *P values compare fourth and first quartiles.

mean internal CIMT (0.98 vs. 1.06 mm, 0.08 [0.04–0.13], $P < 0.001$) after adjustment for traditional CVD risk factors and A1C (continuous variable). A1C was not significantly associated with prevalence of detectable CAC in the cohort overall, but women in the highest quartile for A1C had a higher adjusted prevalence for detectable CAC compared with women in the lowest quartile ($P = 0.003$). Among participants with detectable CAC, A1C was not significantly associated with CAC score after adjustment for covariates. Analyses adjusted for CVD risk factors plus BMI yielded very similar results (Table 3).

CONCLUSIONS — In individuals without clinically evident diabetes, higher A1C level was associated with common and internal CIMT after adjustment for CVD risk factors and BMI. For analyses performed on the entire cohort, A1C was not significantly associated with the prevalence of detectable CAC or with CAC score after adjustment for covariates. However, the association between A1C and prevalence of detectable CAC varied by sex: higher A1C was associated with higher prevalence of detectable CAC in women but not in men. Our data suggest that glycemia within the range observed in subjects without clinically evident dia-

betes is associated with some measures of subclinical CVD. These findings are consistent with those reported by Sander et al. (6) for common CIMT.

To our knowledge, this is the first study to report on the association between A1C and CAC in people without clinically evident diabetes. Previous results from MESA showed that the prevalence of detectable CAC was higher in whites than in other ethnic groups after adjustment for age, education, lipid levels, BMI, smoking status, diabetes, hypertension, treatment for hypercholesterolemia, sex, and scanning center (17). The results of this study build on those findings, pro-

viding evidence that in individuals without clinically evident diabetes who have detectable CAC the magnitude of the correlation between A1C and CAC score tended to be larger in whites than Asians, African Americans, and Hispanics; however, the analysis for interaction by race did not reach statistical significance. We are not aware of other studies that examined whether the association between A1C and clinical CVD risk in people without clinically evident diabetes varied by race/ethnicity. However other studies have shown that whites with diabetes have higher CVD incidence than Asian Americans, African Americans, and Latinos (18). Thus, it is possible that glycemia is a stronger clinical CVD risk factor in whites than in other ethnic/racial groups, but further study is needed in populations without clinically evident diabetes.

We found that the prevalence of detectable CAC was associated with A1C in women but not in men. The explanation for this observation remains unclear. However, our results are consistent with those from the Framingham Study, where impaired fasting glucose was associated with 4-year CVD incidence in women but not in men (19). Thus, mild hyperglycemia (associated with fasting glucose <7.0 mmol/l) may increase the relative risk of CVD to a greater extent in women than men.

CAC and CIMT are two distinct markers of subclinical CVD. The association between A1C and subclinical CVD varied in our data depending on whether CIMT or CAC was used as the outcome. These differences might be due to differences in measurement accuracy between CIMT and CAC or differences in the association between A1C and subclinical CVD by anatomic site of atherosclerosis. It should also be noted that there was less statistical power to detect associations with CAC score because only about half the participants had detectable CAC.

The current use of a fasting glucose level ≥7.0 mmol/l to define diabetes is based largely on data that support the concept of a hyperglycemic threshold below which microvascular diabetic complications are unlikely to occur (11). However, others have concluded that this concept of a hyperglycemic threshold does not appear to apply to CVD (macrovascular disease) risk (20). The results of this study were limited to participants without clinically diagnosed diabetes whose fasting glucose was less than the value used to define diabetes. Thus, our

findings suggest either that the association between hyperglycemia as measured by A1C and subclinical macrovascular disease is continuous (i.e., no threshold effect) or that the A1C threshold for macrovascular disease complications of hyperglycemia is within the range of values observed in people whose fasting glucose level is below the diagnostic threshold for diabetes. We obtained similar results even when we excluded participants whose A1C was >95th percentile (>6.1%), so if there is a threshold it appears to occur at lower values of A1C. The magnitude of the differences in CIMT across quartiles of A1C was similar to that of the differences in CIMT across quartiles of LDL cholesterol.

While we did not find any evidence to support a diagnosis of diabetes in the 5% of participants with A1C >6.1% based on fasting glucose level or medication use, it is likely that some participants in this study may have met criteria for diabetes by an oral glucose tolerance test. About 2.6% of adults ≥20 years of age with fasting glucose in the nondiabetic range have undiagnosed diabetes based on 2-h glucose (21). However, the diagnostic criteria used in our study are those most commonly used in clinical practice in the U.S. (11). Furthermore, because results were similar when participants with A1C >6.1% were excluded, it is unlikely that our results were due to misclassification of diabetes status. We did not screen participants for genetic hemoglobin variants, which may be another potential explanation for A1C levels that did not correlate as expected with fasting blood glucose levels.

Our results are consistent with the results of other studies that showed an association between glucose and subclinical CVD in nondiabetic populations. Zhang et al. (22) found that 2-h glucose was associated with common CIMT after adjustment for age, LDL cholesterol, and insulin sensitivity. The RIAD (Risk Factors in IGT for Atherosclerosis and Diabetes) study showed that 2-h glucose was associated with common CIMT in nondiabetic subjects after adjustment for age, sex, total cholesterol, HDL cholesterol, triglycerides, and C-peptide (23). Our study advances the understanding of the association between glycemia and subclinical CVD by demonstrating that A1C was associated with common CIMT and internal CIMT in participants from four racial/ethnic groups. Also, we used A1C, a measure of overall glycemia, not just fasting or postprandial glycemia (20).

There are several limitations to this study. CIMT measures were obtained ~16 months prior to the A1C measurements. Others (14) have demonstrated that little change in CIMT is expected over this interval. Any change in A1C values between baseline and exam 2 might weaken the correlation between A1C measured at visit 2 and CIMT measured at baseline, but we know of no reason to expect that this would increase the chance of a spurious association. CAC measurements were obtained at exam 2 (simultaneous with the A1C measurement) in 52% of participants, and missing CAC data for exam 2 were interpolated from baseline and exam 3 CAC measurements. This approach is unlikely to have introduced systematic bias, as shown by the similar results obtained from analyses restricted to the subset of participants with exam 2 CAC data.

In summary, in this multiethnic cohort, there were small, positive associations between A1C, common CIMT, and internal CIMT in the absence of clinically evident diabetes. The associations between A1C and CIMT were not fully explained by adjustment for traditional CVD risk factors or BMI. An association between increased A1C and CAC prevalence was evident only in women. These findings suggest that a clinical definition of diabetes based on fasting glucose does not completely capture the CVD risk that is associated with variation in glycemia as measured by A1C.

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