Diabetes and Clinical and Subclinical CVD

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ABSTRACT

Diabetes mellitus is a major cardiovascular risk factor and its prevalence has been increasing globally. This review examines the contributions of the MESA (Multi-Ethnic Study of Atherosclerosis), a diverse American cohort (6,814 adults ages 45 to 84, recruited from 2000 to 2002, 50% female, 62% nonwhite) toward understanding the relationship between diabetes and clinical and subclinical cardiovascular disease. People with diabetes have a high burden of subclinical vascular disease as measured by coronary artery calcification (CAC), carotid artery intima-media thickness, valvular calcification, and alterations in left ventricular structure. CAC substantially improves cardiovascular risk prediction. Among adults with diabetes, 63% had CAC >0; above CAC >400 Agatston units the event rate was 4% annually, whereas an absence of CAC was a marker of a very low cardiovascular disease rate (0.4% to 0.1% annually). These stark differences in rates may have implications for screening and/or targeted prevention efforts based on CAC burden. MESA has also provided insight on diabetes epidemiology.

Diabetes mellitus was initially established as a cardiovascular disease (CVD) risk factor by the Framingham Heart Study in 1979 [1]. Clinically, the strong association of diabetes with CVD led diabetes to be labeled a coronary heart disease (CHD) "risk equivalent" in the Adult Treatment Panel III lipid management guidelines in 2002, suggesting the risk of a CHD event was approximately 2% per year (20% 10-year risk), equivalent to the rate of events in an adult with previous CHD but without diabetes, and thus recommending aggressive prevention via lifestyle modification and lipid-lowering drugs [2]. A meta-analysis of 102 prospective studies with 698,000 persons (including data from MESA [Multi-Ethnic Study of Atherosclerosis]) published in 2010 demonstrates that diabetes confers an approximately 2-fold increase in risk of coronary heart disease (hazard ratio [HR]: 2.00; 95% confidence interval [CI]: 1.83 to 2.19), ischemic stroke (HR: 2.27; 95% CI: 1.95 to 2.65), coronary death (HR: 2.31; 95% CI: 2.05 to 2.60), and other vascular deaths (HR: 1.73; 95% CI: 1.51 to 1.98) [3]. The impact of diabetes on CVD is particularly important given the current population burden of diabetes, which has approached 12% to 14% of U.S. adults, depending on criteria used [4]. Although there has been a significant decline in CVD mortality in the United States over the last 20 to 30 years, and declines in some risk factors (notably cigarette smoking) [5], the prevalence of diabetes has been increasing, largely secondary to the obesity epidemic. CVD rates have also declined among those with diabetes, although the rates remain higher for those with the disease (than those without diabetes) [6]. Also, heart failure remains a common and expensive health problem [5], for which diabetes has also been recognized as a major risk factor for heart failure [7,8].

Despite the recognition that diabetes is an important risk factor for all forms of CVD, there remains much to learn regarding which persons with diabetes are mostly likely to have events. Numerous papers have examined whether diabetes is a CHD risk equivalent and a systematic review suggest that there is not a uniformly elevated risk [9]. Furthermore, how best to prevent CVD in this population remains unclear. The effects of intensive glucose control on CVD event rates in randomized clinical trials appear to be modest [10] and ≥1 major trial found an increase in mortality with aggressive glucose control (target hemoglobin A1c <6%) [11]. Uncertainty also surrounds potential mechanisms that underlie the propensity to develop CVD. Finally, diabetes is more common among American racial/ethnic minorities than among whites, and thus is an important contributor to health disparities [12]. Within this context, MESA has made important contributions to understanding the impact of diabetes on CVD risk in early 21st-century America.

MESA is a population-based cohort of 6,814 men and women (38% white, 28% black, 22% Hispanic, and 12% Chinese) ages 45 to 84 years without clinical CVD at baseline (2000 to 2002); its detailed design and objectives have been published [13]. Informed consent was obtained from each participant, and Institutional Review Board approval was granted at each site. As of January 2016, there have been a total of 5 in-person examinations; at each visit, medication use and fasting glucose values were ascertained, allowing for the determination of existing and new (incident) diabetes in this cohort.

MESA inquired regarding having diabetes, using oral medications or insulin, age at which diabetes medication were first taken, and whether insulin was the first medication used. A medication inventory was also taken. MESA

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has defined diabetes as fasting glucose ≥126 mg/dl or use of glucose-lowering medications. At study baseline, 10% of the cohort had treated diabetes, and an additional 2.6% had untreated or previously undiagnosed diabetes. Only 16 participants reported using insulin as their first diabetes medication prior to age 30; thus it is assumed that most diabetes in this study are type 2 diabetes mellitus (T2DM). Another 12.4% had impaired fasting glucose (IFG) (defined as glucose ≥100 mg/dl and without T2DM by previous definition). The prevalence of total (treated and untreated) diabetes at study baseline varied significantly by race/ethnicity (Table 1).

DIABETES, SUBCLINICAL DISEASE, AND CVD EVENTS

MESA has contributed to the elucidation of the association of T2DM with subclinical CVD among middle- and older-aged adults, specifically arterial calcification, and has provided evidence that these relationships differ by race/ethnicity. At baseline, 63% of those with diabetes had a CAC >0, compared with 48% of those without diabetes. This finding is somewhat lower than in some other studies: 85% CAC >0 in a German sample of 716 with diabetes [14]; and 84% of participants in a subset of the VADT (Veterans Affairs Diabetes Trial) [15]. However, the VADT sample was 95% male and 38% of the participants had previous CVD. The highest prevalence of measurable CAC in MESA was in whites, followed by Chinese, Hispanics, and blacks (Table 1) [16]. The prevalence of any CAC and CAC burden compared with their counterparts without diabetes is presented in the Figure 1. When adjusting for traditional risk factors, body mass index, education, and use of cholesterol-lowering medication, diabetes was only marginally associated with the presence of any CAC in each of the racial/ethnic groups (relative risk [RR] of 1.07 to 1.10) but was strongly associated with the amount of CAC in each ethnic group. The relative difference in coronary calcification associated with diabetes ranged from 1.37 (95% CI: 1.03 to 1.81) in whites, 1.38 (95% CI: 1.02 to 1.87) in Hispanics, 1.58 (95% CI: 1.20 to 2.09) in blacks, and 2.37 (95% CI: 1.59 to 3.53) in Chinese [17]. To put this in context, a relative difference of 1.50 represents a 50% increase in the amount of CAC.

The notable difference between blacks and whites in CAC prevalence was further explored in subsequent reports that pooled data from MESA, the Family Heart Study, and the Diabetes Heart Study, which yielded a sample of 835 black and 1,122 white adults with diabetes [18,19]. In this combined cohort, the prevalence of CAC >0 was lower in both black men and women, compared with white men and women. However the relationship between risk factors and CAC did not differ between races. Thus, racial differences in CAC prevalence among adults with diabetes are likely due to unmeasured risk factors and/or genetic susceptibility [18,19].

Diabetes was associated with an increased risk of incident CAC: RR for treated diabetes 1.37 (95% CI: 1.05 to 1.79) after adjusting for lipids, body mass index, race, age, sex, and family history of heart attack. MESA also found that T2DM was the strongest risk factor for CAC progression even with adjustment for baseline CAC scores [20]. There was also evidence of a racial/ethnic difference in the effect of diabetes. Treated diabetes was associated with an estimated 48 more units of CAC progression in blacks, 28 more units in whites, 19 in Chinese, and 7 units among Hispanics [20].

Consistent with previous studies [3,21], Yeboah et al. [22] found that after a 7.5-year median follow-up in MESA participants, T2DM was associated with incident CVD (adjusted HR: 1.87; 95% CI: 1.47 to 2.37), which included myocardial infarction, angina, cardiac arrest, stroke, and fatal cardiovascular events. McClelland et al. [23] published a 10-year CHD risk calculator that demonstrates that adding CAC substantially improved risk prediction in MESA: the area under the curve of the traditional risk factor model was 0.760 and adding CAC raised it to 0.814. In a model adjusted for demographics and standard risk factors, the adjusted HR associated with T2DM was 1.68 ($p < 0.001$). In a model adjusting for those variables plus coronary artery calcium, the HR associated with T2DM was 1.48 ($p = 0.002$) [23]. These previous studies examining the association between T2DM and CVD did not include heart failure as a clinical event. However,

TABLE 1. Characteristics of MESA participants 2000 to 2002

Characteristic	White	Black	Hispanic	Chinese
Diabetes prevalence, %	6.0	17.6	17.7	13.1
Prevalence of CAC >0% among participants with diabetes	78	54	58	68
Geometric mean CAC score for participants with diabetes	145.5	106.7	95.6	120.3
RR for prevalence of CAC >0* (95% CI)	1.07 (0.99–1.17)	1.10 (1.00–1.21)	1.08 (0.97–1.19)	1.09 (0.94–1.27)
Relative difference in amount of CAC, if CAC >0†	1.37 (1.03–1.81)	1.58 (1.20–2.09)	1.38 (1.02–1.87)	2.37 (1.59–3.53)

CAC, coronary artery calcification; RR, relative risk.
*Relative risk associated with diabetes.
†Relative difference in burden of CAC associated with diabetes.

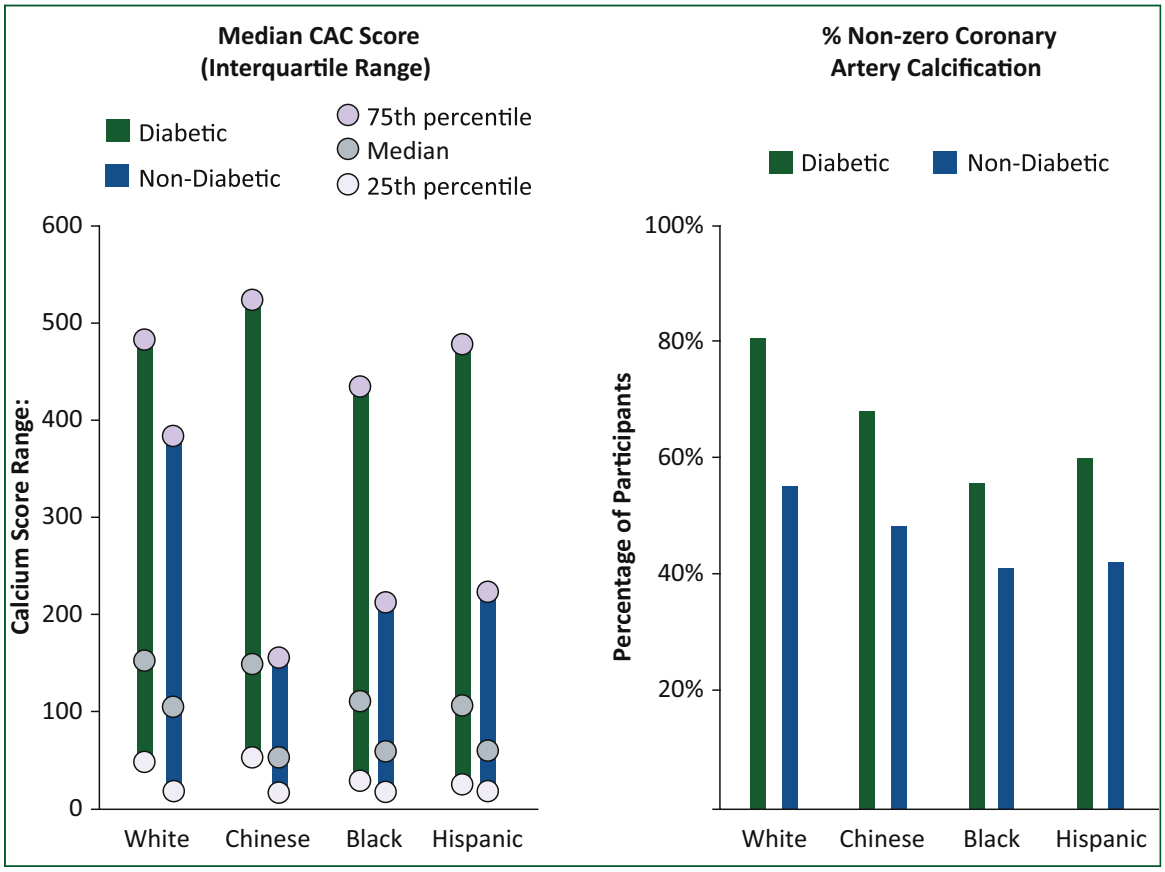

FIGURE 1. Prevalence of a nonzero CAC score (right) by diabetes status and the median and interquartile range of the CAC scores (left) among participants with a nonzero CAC score by race/ethnicity group in the MESA (Multi-Ethnic Study of Atherosclerosis). Prevalence (unadjusted $p < 0.001$) and amount (unadjusted $p < 0.001$) of CAC significantly higher for those with diabetes compared with those without diabetes in each ethnic group. Adjusted comparisons detailed in the text. CAC, coronary artery calcification.

T2DM has also been associated with a heightened risk for incident heart failure in MESA (RR: 2.06 (95% CI: 1.25 to 3.39) [24]).

MESA has demonstrated that CAC predicts incident CVD events [25] better than other subclinical atherosclerosis measures in adults with diabetes. Using data from MESA and the Heinz-Nixdorf study (a German cohort with subclinical atherosclerosis measures) Yeboah et al. [26] assessed whether CAC, ankle-brachial index, or carotid intima-media thickness when added to traditional risk factors, predicted incident CHD better than other risk estimators specifically for those with diabetes (Framingham, and the diabetes-specific UKPDS [U.K. Prospective Diabetes Study] risk score). There are several notable findings. First, CAC was a better predictor of incident events in adults with diabetes than either ankle-brachial index or carotid intima-media thickness. Second, a novel scoring algorithm derived from this sample had a high area under the curve (AUC) (0.76) and outperformed the Framingham Risk Score (AUC: 0.70) and UKPDS (AUC: 0.69). The 8-year MESA-HNR (Heinz Nixdorf Recall) Diabetes CHD risk score used age (above or below age 65), sex, systolic blood pressure, duration of diabetes, and CAC in the categories of 0 to 24, 25 to 124, 125 to 399, and 400+. A final notable result from this paper is that the lowest category (0 to 24) CAC score was associated with a lower risk of CHD. In fact, the absence of CAC or a low CAC score (<25) was protective—it was a "negative" factor in the points-based system.

Malik et al. [27] highlights the heterogeneity of event rates by diabetes and CAC status. Among those with diabetes and CAC ≥400, the annual rate of incident CHD and CVD was 4% and 5.1%, respectively. However event rates were very low in the absence of CAC: CHD 0.4%; and CVD 0.8% [27]. Clearly, T2DM does not necessarily confer a uniformly high absolute risk of CVD, even if it there is still an increased risk on the relative scale (event rates for those without T2DM and no CAC are in the 0.1% to 0.2% range for CHD and CVD). Reasons for this were explored by Yeboah et al. [28], which demonstrated that the

relationship between diabetes and CVD is only partially mediated (19.4%, 95% CI: 12.8 to 40.0) by CAC burden. One possible explanation for these finding is that MESA did not ascertain noncalcified coronary artery plaque. Another interpretation is that diabetes promotes CVD events via other, non-atherosclerosis-related mechanisms.

Diabetes and non-CAC subclinical CVD measures

Diabetes affects the entire vascular system; thus, it is perhaps not surprising that MESA has demonstrated that T2DM is also associated with other *subclinical* vascular disease measures. For example, diabetes is associated with an increased prevalence of aortic valve calcium (RR: 2.1 for diabetes in women and 1.7 for men) [29] as well as associated with an increased risk of incident aortic valve calcium (adjusted odds ratio [OR]: 2.1; 95% CI: 1.4 to 3.1) [30]. Diabetes is also associated with an increased prevalence of thoracic aortic calcification (38%) compared with those with neither diabetes nor metabolic syndrome (24%) [31]. Diabetes was also found to be associated with reduced aortic distensibility, as assessed by cardiac magnetic resonance imaging, particularly in participants younger than age 65 [32]. Finally, diabetes is postulated to affect cardiac structure/function and thus to predispose to heart failure abnormalities [33]. The effect of diabetes on left ventricular mass, end-diastolic volume, and ejection fraction (as measured by cardiac magnetic resonance imaging) [34] was assessed and determined whether any differences were independent of subclinical atherosclerosis. Bertoni et al. [34] found small but significant differences in left ventricular parameters among those with IFG and diabetes compared with those with normal fasting glucose even after adjusting for subclinical atherosclerosis; however, the pattern of abnormality and the degree to which risk factors and subclinical atherosclerosis modified the association differed by race/ethnicity.

Pre-diabetes and CVD

MESA has provided evidence that the association between glucose metabolism and subclinical atherosclerosis may begin before the onset of clinical diabetes. For example, insulin resistance (estimated by homeostatic model assessment of insulin resistance [HOMA-IR]) was associated with prevalent CAC, but this association did not remain after adjustment for metabolic syndrome variables [35]. Another analysis that used a smaller sample of MESA participants, but took into account adipokines, inflammatory markers, and body fat composition, found a modest independent association between insulin resistance and the prevalence of CAC, but not with the amount of CAC [36]. Blaha et al. [37] found a graded increase in CAC incidence and progression with increasing HOMA-IR. However, HOMA-IR was not predictive after adjustment for nonglucose metabolic syndrome components [37]. The conclusion from these papers, taken together, is that the independent association between insulin resistance and vascular calcification is likely at best very modest and confounded by metabolic syndrome components.

Finally, MESA data suggest that IFG is associated with heightened risk for silent (or unrecognized) myocardial infarction. There was a higher prevalence of unrecognized myocardial infarction at baseline in those with IFG compared with those with normal glucose levels (3.5% vs. 1.4%), the association remained after adjustment for multiple risk factors (OR: 1.60; 95% CI: 1.0 to 2.5; $p = 0.048$) [38]. A similar magnitude of risk was found for the association between IFG and incident CV events (at 7.5 years follow-up): unadjusted HR 1.64 (95% CI: 1.26 to 2.14), but after adjusting for traditional risk factors, the HR was 1.16 (95% CI: 0.88 to 1.52) [22].

INSIGHTS ON DIABETES EPIDEMIOLOGY

Consistent with population prevalence estimates showing excess diabetes in racial/ethnic minorities compared with whites, the incidence rate in MESA was 21.9 per 1,000 for Hispanic, 21.6 per 1,000 for blacks, 16.2 per 1,000 for Chinese, and 11.1 per 1,000 for whites [39]. MESA has investigated the utility of previous diabetes risk equations at predicting incident T2DM in a more modern and multiethnic cohort [40] and also has investigated nontraditional risk factors for T2DM such as inflammation [39] and depression [41]. Lutsey et al. [42] showed that the relationship between obesity measures (body mass index and waist circumference) and incident diabetes varies by race/ethnic group. The slope of incident diabetes per anthropometric unit was greatest for Chinese, less for whites and Hispanics, and still less for blacks. At a small waist circumference (<85 cm/33.5 inches), the risk of incident diabetes was <1 per 100 person-years for all racial/ethnic groups. At intermediate waist levels, Chinese had the highest and whites the lowest rates of incident diabetes. Adiposity influenced relative diabetes occurrence across racial/ethnic groups, in that Chinese had a steeper diabetes risk per unit of adiposity [42].

MESA has also provided evidence regarding how neighborhood factors influence the incidence of T2DM [43,44]. The physical activity environment was assessed by 2 independent metrics: the density of commercial recreational establishments (e.g., gyms) surrounding participants; and a survey of participants' perceptions of the walking environment. The healthy food environment was similarly assessed: 1 survey measured the density of supermarkets and other fruit and vegetable outlets; and the other survey was based on perception of availability of healthier foods in the neighborhood. Long-term exposure to residential environments with greater resources to support physical activity was associated with a lower incidence of T2DM over a 10-year period. Participants in the lowest tertile of neighborhood physical activity resources had an incidence rate of 20.5 per 1,000 person-years, whereas the highest tertile rate was 11.8 per 1,000 person-years. The

association between diabetes and a healthier food environment followed a similar but not as robust pattern [44].

SUMMARY

The association between diabetes and CVD is well established. MESA has confirmed that in a multiethnic sample reflective of Americans living in the 21st century, diabetes remains an important risk factor for incident CVD including heart failure. MESA provided new insights regarding the relationship between diabetes and subclinical CVD, including vascular calcification and heart structure and function. Among subclinical CVD markers, CAC can substantially improve risk prediction in adults with diabetes. Furthermore, MESA has shown that those with diabetes with a low burden of CAC are much less likely to have events within a 5- to 10-year horizon. These findings refute the notion that diabetes is a "CVD risk equivalent," in other words, that all adults with diabetes have a high absolute rate of incident CVD in the short term. It remains to be seen whether CAC screening will become a routine part of clinical practice, or whether guiding preventive therapies by the presence or burden of CAC would yield benefits. Finally, the data from MESA regarding the incidence of diabetes are consistent with existing knowledge regarding diabetes prevention, that is, healthier lifestyle choices are paramount. The excess risk of diabetes among ethnic minorities has substantial implications for the increasingly diverse United States. The findings regarding neighborhood-level factors that influence diabetes risk are intriguing and suggest that intervening at the community level may be a promising way to address the ongoing diabetes epidemic that the United States and many other nations are battling.

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REFERENCES

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. JAMA 1979;241:2035–8.
2. NCEP Adult Treatment Panel III. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
3. Sarwar N, Gao P, Seshasai SR, et al., for the Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.
4. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988—2012. JAMA 2015;314:1021–9.
5. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133:e38–60.
6. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990—2010. N Engl J Med 2014;370:1514–23.
7. Kannel WB. Vital epidemiologic clues in heart failure. J Clin Epidemiol 2000;53:229–35.
8. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. Diabetes Care 2003;26:2433–41.
9. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med 2009;26:142–8.
10. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373:1765–72.
11. Gerstein HC, Miller ME, Genuth S, et al., ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–28.
12. Centers for Disease Control and Prevention. CDC Health Disparities and Inequalities Report—United States, 2011. MMWR Suppl 2011;60:1–113.
13. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
14. Becker A, Leber AW, Becker C, et al. Predictive value of coronary calcifications for future cardiac events in asymptomatic patients with diabetes mellitus: a prospective study in 716 patients over 8 years. BMC Cardiovasc Disord 2008;8:27.
15. Reaven PD, Moritz TE, Schwenke DC, et al., for the Veterans Affairs Diabetes Trial. Intensive glucose-lowering therapy reduces cardiovascular disease events in Veterans Affairs Diabetes Trial participants with lower calcified coronary atherosclerosis. Diabetes 2009;58:2642–8.
16. Carnethon MR, Bertoni AG, Shea S, et al. Racial/ethnic differences in subclinical atherosclerosis among adults with diabetes: the Multi-ethnic Study of Atherosclerosis. Diabetes Care 2005;28:2768–70.
17. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2005;111:1313–20.
18. Wagenknecht LE, Divers J, Bertoni AG, et al. Correlates of coronary artery calcified plaque in blacks and whites with type 2 diabetes. Ann Epidemiol 2011;21:34–41.
19. Divers J, Palmer ND, Lu L, et al. Admixture mapping of coronary artery calcified plaque in African Americans with type 2 diabetes mellitus. Circ Cardiovasc Genet 2013;6:97–105.
20. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–30.
21. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–8.
22. Yeboah J, Bertoni AG, Herrington DM, Post WS, Burke GL. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2011;58:140–6.
23. McClelland RL, Jorgensen NW, Budoff M, et al. 10-Year coronary heart disease risk-prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol 2015;66:1643–53.
24. Bahrami H, Bluemke DA, Kronmal R, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;51:1775–83.
25. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
26. Yeboah J, Erbel R, Delaney JC, et al. Development of a new diabetes risk prediction tool for incident coronary heart disease events: the

Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study. Atherosclerosis 2014;236:411–7.
27. Malik S, Buduff MJ, Katz R, et al. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. Diabetes Care 2011;34:2285–90.
28. Yeboah J, Delaney JA, Nance R, et al. Mediation of cardiovascular risk factor effects through subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2014;34:1778–83.
29. Katz R, Wong ND, Kronmal R, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. Circulation 2006;113:2113–9.
30. Katz R, Budoff MJ, Takasu J, et al. Relationship of metabolic syndrome with incident aortic valve calcium and aortic valve calcium progression: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes 2009;58:813–9.
31. Katz R, Budoff MJ, O'Brien KD, Wong ND, Nasir K. The metabolic syndrome and diabetes mellitus as predictors of thoracic aortic calcification as detected by non-contrast computed tomography in the Multi-Ethnic Study of Atherosclerosis. Diabet Med 2016;33:912–9.
32. Stacey RB, Bertoni AG, Eng J, Bluemke DA, Hundley WG, Herrington D. Modification of the effect of glycemic status on aortic distensibility by age in the Multi-Ethnic Study of Atherosclerosis. Hypertension 2010;55:26–32.
33. Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. Eur Heart J 2015;36:1718–27.
34. Bertoni AG, Goff DC Jr, D'Agostino RB Jr, et al. Diabetic cardiomyopathy and subclinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2006;29:588–94.
35. Bertoni AG, Wong ND, Shea S, et al. Insulin resistance, metabolic syndrome, and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2007;30:2951–6.
36. Ong KL, McClelland RL, Rye KA, et al. The relationship between insulin resistance and vascular calcification in coronary arteries, and the thoracic and abdominal aorta: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2014;236:257–62.
37. Blaha MJ, DeFilippis AP, Rivera JJ, et al. The relationship between insulin resistance and incidence and progression of coronary artery calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2011;34:749–51.
38. Stacey RB, Leaverton PE, Schocken DD, Peregoy JA, Bertoni AG. Prediabetes and the association with unrecognized myocardial infarction in the Multi-Ethnic Study of Atherosclerosis. Am Heart J 2015;170:923–8.
39. Bertoni AG, Burke GL, Owusu JA, et al. Inflammation and the incidence of type 2 diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2010;33:804–10.
40. Mann DM, Bertoni AG, Shimbo D, et al. Comparative validity of 3 diabetes mellitus risk prediction scoring models in a multiethnic US cohort: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2010;171:980–8.
41. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008;299:2751–9.
42. Lutsey PL, Pereira MA, Bertoni AG, Kandula NR, Jacobs DR Jr. Interactions between race/ethnicity and anthropometry in risk of incident diabetes: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2010;172:197–204.
43. Auchincloss AH, Diez-Roux AV, Mujahid MS, Shen M, Bertoni AG, Carnethon MR. Neighborhood resources for physical activity and healthy foods and incidence of type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. Arch Intern Med 2009;169:1698–704.
44. Christine PJ, Auchincloss AH, Bertoni AG, et al. Longitudinal associations between neighborhood physical and social environments and incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis (MESA). JAMA Intern Med 2015;175:1311–20.