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Diabetes: Insights from the Multi-Ethnic Study of Atherosclerosis

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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 Multi-Ethnic Study of Atherosclerosis, a diverse American cohort (6814 adults aged 45-84, recruited 2000-2002, 50% female, 62% non-white) towards 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 Agatson units the event rate was 4% annually, whereas an absence of CAC was a marker of a very low CVD rate (0.4-0.1% 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 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 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% ten-year risk), equivalent to the rate of events in an adult with prior 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

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(including data from MESA) published in 2010 demonstrates that diabetes confers an approximately two-fold increase in risk of coronary heart disease (HR 2.00, 95% CI 1.83-2.19), ischemic stroke (HR 2.27, 95%CI 1.95-2.65), coronary death (HR 2.31, 95%CI 2.05-2.60), and other vascular deaths (HR 1.73, 95%CI 1.51-1.98) [3]. The impact of diabetes on CVD is particularly important given the current population burden of diabetes, which has approached 12-14% of U.S. adults, depending on criteria used [4]. While there has been a significant decline in CVD mortality in the United States over the last 20-30 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 if diabetes is a CHD risk equivalent and a systematic review suggest that there is not a uniformly elevated risk [9]. Further, 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 at least one major trial found an increase in mortality with aggressive glucose control (target HbA1c<6%) [11]. Uncertainty also surrounds potential mechanisms which 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% African American, 22% Hispanic, and 12% Chinese) aged 45–84 years without clinical CVD at baseline (2000-2002); 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 utilized. A medication inventory was also taken. MESA 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 reported using insulin as their first diabetes medication prior to age 30; thus it is assumed that most diabetes in this study is T2DM. Another 12.4% had impaired fasting glucose (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).

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 provided evidence that these relationships differ by race/ethnicity. At baseline, 63% of those with diabetes had a CAC>0, compared to 48% of those without diabetes. This finding is somewhat lower than some studies; 85% CAC>0 in a German sample of 716 with diabetes [14] and 84% of participants in a subset of the Veterans Affairs Diabetes Trial (VADT) [15]. However the VADT sample was 95% male and included 38% with prior 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 their counterparts without diabetes is presented in the Figure. When adjusting for traditional risk factors, BMI, 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 (RRs of 1.07-1.10) 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 1.03-1.81) in whites, 1.38 (1.02-1.87) in Hispanics, 1.58 (1.20-2.09) in AAs and 2.37 (1.59-3.53) 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 AAs and whites in CAC prevalence was further explored in subsequent reports which pooled data from MESA, the Family Heart Study, and the Diabetes Heart Study, which yielded a sample of 835 AAs and 1122 white adults with diabetes [18,19]. In this combined cohort, the prevalence of CAC>0 was lower in both AA men and women, compared to 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 1.05-1.79) after adjusting for lipids, BMI, race, age, gender, 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 prior studies [3,21], Yeboah et al found that after a 7.5 year median follow-up in MESA participants, T2DM was associated with incident CVD (adjusted HR of 1.87 (95%CI 1.47-2.37), which included myocardial infarction, angina, cardiac arrest, stroke, and fatal cardiovascular events [22]. McClellan et al published a 10-year CHD risk calculator which demonstrates that adding CAC substantially improved risk prediction in MESA – the area under the curve of the traditional risk factor model was 0.760, adding CAC raised it to 0.814. In a model adjusted for demographics and standard risk factors, the adjusted hazards ratio associated with T2DM was 1.68 (p-value <0.001). In a model adjusting for those variables plus coronary artery calcium the HR associated with T2DM was 1.48 (p-value

0.002) [23]. These previous studies examining the association between T2DM and CVD did not include heart failure as a clinical event. However, T2DM has also been associated with a heightened risk for incident heart failure in MESA (Relative risk 2.06 (1.25-3.39) [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. assessed whether CAC, ankle-brachial index (ABI), or carotid IMT 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 risk score) [26]. There are several notable findings. First, CAC was a better predictor of incident events in adults with diabetes than either ABI or carotid IMT. Second, a novel scoring algorithm derived from this sample had a high AUC (0.76) and outperformed FRS (0.70) and UKPDS (AUC 0.69). The 8-year MESA-HNR Diabetes CHD risk score used age (above or below age 65), gender, systolic BP, duration of diabetes, and CAC in the categories of 0-24, 25-124, 125-399, and 400+. A final notable result from this paper is that the lowest category (0-24) 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 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 0.1-0.2% range for CHD and CVD). Reasons for this were explored by Yeboah et al, which demonstrated that the relationship between diabetes and CVD is only partially mediated (19.4%, 95%CI 12.8-40.0) by CAC burden [28]. One possible explanation for these finding is that MESA did not ascertain non-calcified 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 (AVC) (Relative risk 2.1 for diabetes in women and 1.7 for men) [29] as well as associated with an increased risk of incident AVC (adjusted OR 2.1; 95%CI 1.4-3.1) [30]. Diabetes is also associated with an increased prevalence of thoracic aortic calcification (38%) compared to 24% of those with neither diabetes nor metabolic syndrome [31]. Diabetes was also found to be associated with reduced aortic distensibility, as assessed by cardiac MRI, particularly in participants under age 65 [32]. Finally, diabetes is postulated to affect cardiac structure/function and thus predispose to heart failure abnormalities [33]. The effect of diabetes on left-ventricular mass, end diastolic volume, and ejection fraction (as measured by cardiac MRI) [34] was assessed, and determined if any differences were independent of subclinical atherosclerosis. Bertoni et al 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 (34).

Prediabetes 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 HOMA-IR) was associated with prevalent CAC, but this association did not remain after adjustment for metabolic syndrome variables [35]. Another analysis which utilized 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 found a graded increase in CAC incidence and progression with increasing HOMA-IR.. However, HOMA-IR was not predictive after adjustment for non-glucose 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 normals [3.5% vs 1.4%,] the association remained after adjustment for multiple risk factors (odds ratio 1.60; 95%CI 1.0-2.5, $p=0.048$) [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 1.26-2.14), but after adjusting for traditional risk factors the HR was 1.16 (95%CI 0.88-1.52) [22].

Insights on Diabetes Epidemiology

Consistent with population prevalence estimates showing excess diabetes in racial/ethnic minorities compared to whites, the incidence rate in MESA was 21.9/1000 for Hispanic, 21.6/1000 for blacks, 16.2/1000 for Chinese and 11.1/1000 for whites [39]. MESA has investigated the utility of previous diabetes risk equations at predicting incident T2DM in a more modern and multi-ethnic cohort [40], and also has investigated non-traditional risk factors for T2DM such as inflammation [39] and depression [41]. Lutsey et al showed that the relationship between obesity measures (BMI 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 (<85cm/33.5 inches), the risk of incident diabetes was <1/100 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 type 2 diabetes [43,44]. The physical activity environment was assessed by two independent metrics; first the density of commercial recreational establishments (e.g. gyms) surrounding participants, and also a survey of participants perception of the walking environment). The healthy food environment was similarly assessed; one measure of the density of supermarkets and other fruit and vegetable outlets, and the other survey based 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 20.5/1000 person-years, while the highest tertile rate was 11.8/1000 person years. The association between diabetes and a healthier food environment followed a similar but not as robust pattern [44].

Conclusions

The association between diabetes and CVD is well established. MESA has confirmed that in a multi-ethnic 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 5-10 year horizon. These findings refute the notion that diabetes is a “CVD risk equivalent”, that is, that all adults with diabetes have a high absolute rate of incident CVD in the short term. It remains to be seen if CAC screening will become a routine part of clinical practice, or if 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 which 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 U.S. and many other nations are battling.

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Abbreviations

AA	African American
BMI	Body Mass Index
CHD	Coronary Heart Disease

CVD	Cardiovascular Disease
HbA1c	Hemoglobin A1c
HR	Hazard Ratio
IMT	Intima Media Thickness
MESA	Multi-Ethnic Study of Atherosclerosis
T2DM	Type 2 diabetes mellitus
HOMA-IR	homeostatic model assessment of insulin resistance

Reference List

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979; 241:2035–2038. [PubMed: 430798]
2. 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; 106:3143–3421. [PubMed: 12485966]
3. The Emerging Risk Factors Collaboration: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. The Lancet. 2010; 375:2215–2222.
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; 314:1021–1029. [PubMed: 26348752]
5. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics 2016 Update: A Report From the American Heart Association. Circulation. 2015
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; 370:1514–1523. [PubMed: 24738668]
7. Kannel WB. Vital epidemiologic clues in heart failure. J Clin Epidemiol. 2000; 53:229–235. [PubMed: 10760631]
8. Bell DS. Heart Failure: The frequent, forgotten, and often fatal complication of diabetes. Diabetes Care. 2003; 26:2433–2441. [PubMed: 12882875]
9. Bulughapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis.
10. Ray KK, Seshasai SRK, 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. The Lancet. 2013; 373:1765–1772.
11. Gerstein HC, Miller ME, Genuth S, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011; 364:818–828. [PubMed: 21366473]
12. Centers for Disease Control and Prevention. CDC Health Disparities and Inequalities Report--United States, 2011. MMWR Morb Mortal Wkly Rep. 2011; 60:S1–S113.
13. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–881. [PubMed: 12397006]
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. [PubMed: 18847481]
15. Reaven PD, Moritz TE, Schwenke DC, et al. Intensive Glucose-Lowering Therapy Reduces Cardiovascular Disease Events in Veterans Affairs Diabetes Trial Participants With Lower Calcified Coronary Atherosclerosis. Diabetes. 2009; 58:2642–2648. [PubMed: 19651816]
16. Carnethon MR, Bertoni AG, Shea S, et al. Racial/Ethnic differences in subclinical atherosclerosis among adults with diabetes: the multiethnic study of atherosclerosis. Diabetes Care. 2005; 28:2768–2770. [PubMed: 16249554]

17. Bild DE, Detrano R, Peterson D, et al. Ethnic Differences in Coronary Calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2005; 111:1313–1320. [PubMed: 15769774]
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. [PubMed: 21130367]
19. Divers J, Palmer ND, Lu L, et al. Admixture Mapping of Coronary Artery Calcified Plaque in African Americans With Type 2 Diabetes Mellitus. *Circulation: Cardiovascular Genetics*. 2013; 6:97–105. [PubMed: 23233742]
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; 115:2722–2730. [PubMed: 17502571]
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; 332:73–78. [PubMed: 16371403]
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; 58:140–146. [PubMed: 21718910]
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). *Journal of the American College of Cardiology*. 2015; 66:1643–1653. [PubMed: 26449133]
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; 51:1775–1783. [PubMed: 18452784]
25. Detrano R, Guerci AD, Carr JJ, et al. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. *New England Journal of Medicine*. 2008; 358:1336–1345. [PubMed: 18367736]
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; 236:411–417. [PubMed: 25150939]
27. Malik S, Budoff 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; 34:2285–2290. [PubMed: 21844289]
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. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2014
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
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; 58:813–819. [PubMed: 19136658]
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 Medn/a*. 2015
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. [PubMed: 19933927]
33. Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *European Heart Journal*. 2015; 36:1718–1727. [PubMed: 25888006]
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; 29:588–594. [PubMed: 16505511]

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; 30:2951–2956. [PubMed: 17704348]
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; 236:257–262. [PubMed: 25108074]
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; 34:749–751. [PubMed: 21292863]
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. *American Heart Journal*. 2015; 170:923–928. [PubMed: 26542500]
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; 33:804–810. [PubMed: 20097779]
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; 171:980–988. [PubMed: 20375194]
41. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. *JAMA*. 2008; 299:2751–2759. [PubMed: 18560002]
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. [PubMed: 20570825]
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; 169:1698–1704. [PubMed: 19822827]
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; 175:1311–1320. [PubMed: 26121402]

Highlights

Diabetes is strongly associated with incident coronary artery calcium and with progression in the amount of coronary artery calcium

Coronary artery calcium can be used to improve the prediction of incident cardiovascular disease among adults with diabetes

Diabetes remains an independent risk factor for incident cardiovascular disease, even after accounting for the increased burden of subclinical atherosclerosis

Inflammatory markers, ethnic-specific waist circumference thresholds, depression, and neighborhood characteristics are associated with incident diabetes.

Figure.

Prevalence of a non-zero coronary artery calcification (CAC) score (right) by diabetes status and the median and interquartile range of the coronary artery calcification scores (left) among participants with a non-zero coronary artery calcification score by race/ethnicity group in the 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 to without diabetes in each ethnic group. Adjusted comparisons detailed in the text.

Table

Characteristics of MESA Participants 2000-2002.

Characteristic	White	AA	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 [*]	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)

^{*} Relative risk associated with diabetes

^{**} Relative difference in burden of CAC associated with diabetes