Assessing Baseline and Temporal Changes in Cardiometabolic Risk Using Metabolic Syndrome Severity and Common Risk Scores

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Background—Type 2 diabetes mellitus (T2DM) is considered a cardiovascular disease (CVD) risk equivalent, thereby linking assessment of cardiometabolic risk with that of CVD risk over time. Our goal was to determine how commonly used CVD risk scores and metabolic syndrome (MetS) severity performed in predicting T2DM with and without ultimate CVD.

Methods and Results—We assessed data from 8273 participants of the ARIC (Atherosclerosis Risk in Communities) Study, using the pooled cohort atherosclerotic CVD risk score, the Framingham Risk Score, and a MetS severity *Z* score to assess their association with future risk for CVD alone, T2DM alone, or both over 20 years of follow-up. Baseline levels of all scores were significantly associated with isolated incident T2DM (odds ratios [ORs] for each 1-SD increase: atherosclerotic CVD=1.7, Framingham risk score=1.7, MetS *Z* score=5.1). All 3 baseline scores were also significantly associated with isolated incident CVD (atherosclerotic CVD OR=2.4, Framingham risk score OR=2.3, MetS *Z*-score OR=1.8), with the 2 CVD scores remaining significant independent of MetS severity. MetS severity was strongly associated with future T2DM leading to CVD (MetS *Z*-score OR=7.0, atherosclerotic CVD OR=3.9, Framingham risk score OR=3.5). Furthermore, changes in MetS severity were independently associated with future T2DM-CVD progression.

Conclusions—CVD risk scores are associated with risk for future isolated T2DM in addition to isolated CVD. However, MetS severity (both baseline and changes over time) was more strongly associated with T2DM, including T2DM ultimately leading to CVD. Following MetS severity within patients over time may identify those at greatest risk of combined cardiometabolic disease. (***J Am Heart Assoc***. 2018;7:e009754. DOI: 10.1161/JAHA.118.009754.)

Key Words: cardiovascular disease • metabolic syndrome • prediction • type 2 diabetes mellitus

T
he ongoing increase in prevalence of type 2 diabetes mellitus (T2DM), affecting 9% of US adults,[1,2] has impeded public health efforts to slow the incidence of cardiovascular disease (CVD).[3–5] Individuals with T2DM but without prior CVD are at similar risk for myocardial infarction as those with current CVD but without T2DM,[6] such that in prompting treatment with lipid-lowering agents, T2DM has been considered a coronary heart risk equivalent.[7] This

elevates the importance of simultaneously monitoring risk for both T2DM and CVD to identify individuals at a high likelihood for developing either or both of these diseases and to motivate those individuals toward lifestyle change and additional interventions.

Multiple scoring systems have been developed as tools to predict future CVD based on baseline risk factors, including the American Heart Association/American College of Cardiology pooled cohort atherosclerotic CVD (ASCVD) score[8] and the Framingham Risk Score (FRS).[9] Although these scores were derived specifically for prediction of CVD, they incorporate multiple measures that are also risk factors for T2DM, including obesity status,[10,11] smoking,[12] age,[10] high-density lipoprotein (HDL),[13] and (in the case of the ASCVD score) race/ethnicity,[13] emphasizing substantial overlap in cardiometabolic risk. Thus, there is a clear likelihood for these scores to also correlate with risk for future T2DM, either with or without ultimate CVD. Nevertheless, the ASCVD score incorporates T2DM in its CVD risk equation, potentially limiting its utility in identifying risk for both T2DM and CVD. Therefore, the role for these CVD risk scores in T2DM risk prediction remains unclear.

An additional assessment tool associated with cardiometabolic risk is the metabolic syndrome (MetS), a group of CVD risk factors, including central obesity, high blood pressure, high triglycerides, low HDL, and high fasting glucose, that cluster together, likely based on shared underlying pathophysiological features.[14] MetS is traditionally classified on the basis of criteria such as those of the Adult Treatment Panel III.[15] MetS can also be assessed using a MetS severity *Z* score, which was formulated according to how the 5 individual components correlate together on a sex and racial/ethnic basis.[16,17] Although the MetS severity score was not specifically derived to be a risk score, as an estimate of metabolic disarray, it is not surprising that this score is a predictor of T2DM[18–20] and CVD.[20–22]

A strength of the CVD risk scores and the MetS severity score is their continuous nature, in contrast to dichotomous risk predictors, such as the Adult Treatment Panel III MetS criteria. Although not yet clear, these scores may be able to be used over time to track changes in risk, and to detect ominous increases that may prompt elevated concern. Because of the importance of T2DM as a CVD risk factor, our goal in the current study was to use CVD risk scores and the MetS severity *Z* score to assess a population that was disease free at baseline for risk for CVD and/or T2DM in a temporal manner, evaluating baseline risk scores and change in score over time. We hypothesized that each of these scores would be predictors of T2DM, with and without CVD, and that change in score would provide further predictive ability. This analysis may have importance for evaluation of not only CVD risk by itself, but of optimal tracking of combined cardiometabolic risk for T2DM and CVD over time.

Materials and Methods

The data use agreement in place with the ARIC (Atherosclerosis Risk in Communities) Study prevents us from directly sharing the data and study materials. However, statistical programs in SAS will be available to researchers on request to the first author for purposes of reproducing the results, for those with access to ARIC Study data.

Study Population

The ARIC Study is a large community-based epidemiological cohort study across 4 field centers in the United States, with timing as follows: visit 1 (1987–1989), visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998), and ongoing follow-up for adjudicated CVD outcomes thereafter. This study and/or its analysis was approved by the Institutional Review Boards of the University of Florida and the ARIC Study sites. Further details of the study design and objectives are published elsewhere.[23] A total of 15 397 participants, aged 45 to 64 years, provided informed consent to be included in the study. From this sample, we excluded participants other than blacks or whites (n=46), those with history of CVD at baseline (n=1008) or who developed CVD by visit 2 (n=191), those with diabetes mellitus at baseline or visit 2 (n=2578), those with reported nonfasting laboratory results at visit 1 or 2 (n=845), and those with missing MetS (n=1762) or CVD (n=1929) risk scores at visit 1 or 2. To be categorized into groups by progression to T2DM and CVD at or between visits 2 and 4, participants must have completed these follow-up visits; those without complete data or with incident coronary heart disease between visits 1 and 2 were excluded (n=6249). Participants could have been excluded on the basis of ≥1 of these criteria. In total, 7124 participants were excluded, leaving 8273 participants for the current analyses.

Measurement of MetS Components

Details have been reported previously on procedures for blood collection and analysis for lipids[24] and glucose.[25] Briefly, participants fasted overnight for 12 hours before the examination. Phlebotomy was performed, and serum and plasma samples were sent to a central laboratory for examination. Triglycerides were measured by enzymatic methods, and HDL was measured after dextran-magnesium precipitation. Low-density lipoprotein was calculated using the Friedewald equation. Serum glucose was measured by the hexokinase-6-phosphate dehydrogenase method.[26] Trained clinical staff measured waist circumference at the umbilical level to the nearest cm. Blood pressure was examined in sitting position, with 3 measurements performed and the average of the last 2 used for analysis. Smoking was classified by participant self-report of current smoking status at each visit.

Study Outcomes

Incident CVD

Incident CVD was determined from adjudicated outcomes using standard ARIC Study protocols and included fatal or nonfatal hospitalized myocardial infarction, fatal coronary heart disease, silent myocardial infarction identified by electrocardiography or coronary revascularization, and hospitalized and fatal stroke.[25,27] We excluded those who had an incident CVD event at or before visit 2.

Type 2 diabetes mellitus

Incident T2DM was determined if participants reported that a physician had told them they had diabetes mellitus, if they had a fasting glucose $\geq$126 mg/dL or a nonfasting glucose $\geq$200 mg/dL, or if they reported they were taking insulin or oral hypoglycemic medications.[10] Incident T2DM was dichotomized as being "yes" for either visit 3 or 4 (because we excluded those with T2DM at visit 1 or 2).

Classification of disease progression

We categorized individuals based on their progression of disease (incident T2DM and CVD) and how visit 1 CVD risk scores and MetS Z, as well as their changes from visit 1 to 2, were associated with these disease progression classifications. We created 6 categories of development of disease after visit 2 (Figure 1). T2DM was formally assessed only at the main study visits (through visit 4; mean follow-up after visit 2=6.0 years), whereas CVD was assessed throughout the adjudicated follow-up period (maximum=21.9 years of follow-up after visit 2; mean=17.8 years). We classified both incident disease events into "early" and "late" periods, with early incident events occurring between visits 2 and 4, and late (CVD only) events occurring after visit 4. This created a classification that captured temporality of events, except for

those individuals (n=33) categorized as having developed both T2DM and CVD in the early period. Given the lack of a precise date of T2DM development, we did not exclude individuals who experienced a CVD event before official T2DM classification. However, in this group of 33 individuals, these 2 diagnosis events occurred $\pm$3 years of one another.

Predictors: Risk Scores

Existing CVD risk scores

Using data from the FHS (Framingham Heart Study), D'Agostino et al derived the FRS as a sex-specific multivariable risk factor algorithm for assessing 10-year general CVD risk.[9,28] The 2013 ASCVD score[8] is a sex- and race-specific 10-year ASCVD risk estimation algorithm derived using extensive data from several large racially and geographically diverse cohort studies, including the FHS, the ARIC Study, the CHS (Cardiovascular Health Study), and the CARDIA (Coronary Artery Risk Development in Young Adults) study.

MetS severity score

We calculated MetS severity Z scores for study participants.[16] The MetS severity score was derived from the 5 traditional MetS components (waist circumference, triglycerides, HDL cholesterol, systolic blood pressure, and fasting glucose) using a factor analysis approach. Because of differences in traditional MetS criteria by race/ethnicity,[29,30] confirmatory factor analysis was performed, as previously described,[16] to determine the weighted contribution of each component to a latent MetS factor on a sex- and race/ethnicity-specific basis, using the National Health and Nutrition Examination Survey data for adults aged 20 to 64 years. For each of the subgroups defined by sex and race/ethnicity, factor loadings from the 5 MetS components were determined and used to generate equations for computing a standardized MetS severity score (http://mets.health-outcomes-policy.ufl.edu/calculator/). The MetS severity score was shown to correlate with other MetS risk markers, such as insulin[20] and adiponectin,[20] and is predictive of long-term risk of T2DM[18–20] and CVD.[20–22] We recently demonstrated that the MetS severity score was predictive of future coronary heart disease and T2DM events above and beyond the individual MetS components alone.[22]

Statistical Analysis

For each of the progression categories (Figure 1) and for each CVD risk score and MetS Z score, we calculated means (95% confidence intervals) at baseline (visit 1) and changes between visits 1 and 2 (adjusted for visit 1 scores). We used multinomial logistic regression to estimate odds of each disease progression category (relative to no disease). Separate models were fit for each of ASCVD, FRS, and MetS
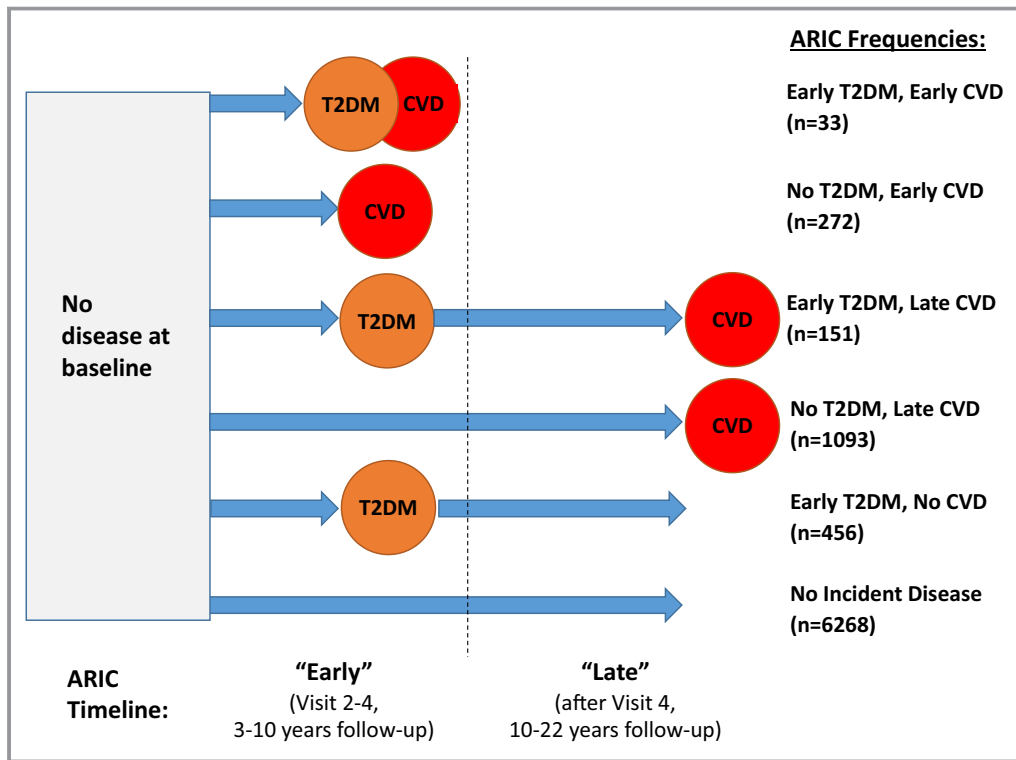
Figure 1. Incident disease progression classifications (after visit 2). Participants were categorized by timing of diagnosis of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), with "early" diagnosis corresponding to that found during visits 2 to 4 (3–10 years of follow-up) and "late" diagnosis occurring after visit 4 (10–22 years of follow-up). T2DM ascertainment was only available through the early period of the ARIC (Atherosclerosis Risk in Communities) Study.

Z, including both their visit 1 scores and changes in scores between visit 1 and visit 2. Because the ASCVD and FRS scores are risk estimates between 0 and 1, to compare odds ratios (ORs) across the 3 scores, we created "*Z* scores" for both ASCVD and FRS, based on mean and SD values of ln-transformed scores at visit 1. ORs were then calculated for a 1-unit increase in these *Z* scores (ie, a 1-SD increase). For our primary analysis, we further categorized disease progression (no disease, incident CVD but no T2DM, incident T2DM but no CVD, and incident T2DM and CVD) comparing ORs across the 3 scores. We also included MetS *Z* and each of ASCVD/FRS *Z* scores in the same models to measure independent associations with these disease progression categories. As a supplementary analysis, we also examined fasting glucose (standardized) as a standalone predictor in place of and alongside MetS *Z*. Lack of collinearity was verified when including MetS *Z* and either of the CVD risk scores in the same model, as well as supplementary models that included MetS *Z* and fasting glucose. Because of collinearity, we were unable to include both ASCVD and FRS in the same model. Because age, sex, and race were each included in multiple risk scores that we assessed, these factors were not included in any of the models. Given our exclusion of incident disease by

visit 2 to assess the predictive ability of changes in scores, we did a supplementary analysis of baseline scores only (and thus including those individuals who developed disease after visit 1 but before visit 2).

Results

Participant Characteristics

Table 1 displays the cardiometabolic characteristics of the 8273 participants who met inclusion/exclusion criteria. In comparison, individuals who developed DM and CVD before visit 2 (who were thus excluded from the central analysis) were slightly older (mean [SD] age, 54.1 [5.9] years), with slightly higher baseline scores for MetS *Z* (mean [SD], 0.21 [0.80]), ASCVD (mean [SD], 0.07 [0.06]), and FRS (mean [SD], 0.13 [0.10]). Compared with those who never developed either disease, those who developed T2DM after visit 1 had at baseline greater abnormalities in MetS components, a higher prevalence of Adult Treatment Panel III MetS, and a higher proportion of male sex and black race. These same differences (compared with the disease-free group) were also present at baseline among those who developed isolated

Table 1. Descriptive Statistics at Baseline of Analytic Sample (n=8273)

Variable	Overall	No Incident T2DM			Incident T2DM		
		No CVD	Late CVD	Early CVD	No CVD	Late CVD	Early CVD
N (%)	8273	6268 (75.8)	1093 (13.2)	272 (3.3)	456 (5.5)	151 (1.8)	33 (0.4)
Sex (male), N (%)	3528 (42.6)	2380 (38.0)	632 (57.8)	201 (73.9)	209 (45.8)	87 (57.6)	19 (57.6)
Race (black), N (%)	1401 (16.9)	1021 (16.3)	169 (15.5)	34 (12.5)	131 (28.7)	34 (22.5)	12 (36.4)
Age, y	53.8±5.6	53.4±5.6	55.5±5.5	55.6±5.4	53.1±5.4	55.0±5.3	55.1±6.1
Visit 1: current smoker, N (%)	1728 (20.9)	1210 (19.3)	282 (25.8)	84 (30.9)	98 (21.5)	38 (25.2)	16 (48.5)
Visit 2: current smoker, N (%)	1572 (19.0)	1092 (17.4)	266 (24.3)	77 (28.3)	88 (19.3)	33 (21.9)	16 (48.5)
BMI, kg/m^2	27.0±4.8	26.6±4.7	27.0±4.4	27.5±3.9	30.5±6.0	30.6±5.4	29.7±4.9
Waist circumference, cm	95.0±13.0	93.7±12.8	96.1±11.7	98.2±10.4	104.3±14.1	105.3±12.1	104.1±11.0
HDL, mg/dL	53.3±16.8	55.1±17.1	49.3±15.2	44.4±12.3	47.4±14.5	43.2±11.9	39.9±11.2
LDL, mg/dL	136.0±37.7	133.4±36.8	144.1±39.3	152.4±40.7	137.7±38.1	147.9±35.3	154.9±45.5
SBP, mm Hg	118.2±16.7	116.7±16.2	121.4±16.8	124.3±18.1	123.0±15.5	128.3±18.2	131.4±26.0
Triglycerides, mg/dL	121.7±73.3	115.8±70.9	132.1±71.2	141.0±78.3	148.1±80.1	165.7±103.4	154.5±76.7
Glucose, mg/dL	97.6±8.6	96.7±8.2	98.0±8.3	98.7±8.4	105.4±9.3	105.5±9.3	104.9±10.2
ATP-III MetS, N (%)	2546 (30.8)	1610 (25.7)	391 (35.8)	119 (43.8)	294 (64.5)	109 (72.2)	23 (69.7)
MetS severity score	0.03±0.75	−0.07±0.73	0.18±0.69	0.34±0.66	0.64±0.66	0.78±0.64	0.80±0.64
FRS (2008)	0.10±0.08	0.08±0.07	0.13±0.09	0.17±0.10	0.11±0.08	0.16±0.10	0.20±0.11
ASCVD (2013)	0.05±0.05	0.04±0.04	0.07±0.05	0.09±0.06	0.06±0.05	0.09±0.06	0.13±0.09
Follow-up time to CVD (years)	20.7±4.8	22.3±2.9	16.0±4.1	6.2±1.7	21.4±3.9	15.9±4.6	6.6±1.6

Unless noted, mean±SD values are provided. ASCVD indicates atherosclerotic cardiovascular disease; ATP-III, Adult Treatment Panel III; BMI, body mass index; CVD, cardiovascular disease; FRS, Framingham risk score; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

incident CVD, with these individuals also having higher levels of low-density lipoprotein. Those who developed both T2DM and early CVD had the highest proportion of smokers of any group (48.5%).

Visit 1 Risk Score Level and Changes in Risk Score Level (Visit 2-Visit 1), by Diagnosis Group

Figure 2A provides mean CVD risk scores and MetS *Z* scores at visit 1 by disease diagnosis group. Baseline levels of all scores were gradually higher in groups that experienced no CVD, late CVD, and early CVD, respectively, regardless of T2DM status. In each case, scores were highest for those who developed T2DM. Seen in Table S1, the OR for late CVD for the ASCVD score was 2.2 for those without T2DM, compared with an OR of 3.4 for those who developed T2DM first; these results were nearly identical for FRS. The difference in risk for late CVD between the T2DM groups was particularly striking for MetS *Z*, with an OR for late CVD of 1.6 without T2DM compared with an OR of 6.9 for those who developed T2DM first. For each diagnosis category, MetS *Z* had higher ORs than a *Z* score of fasting glucose values alone (Table S1).

We next assessed whether changes in score values over time were associated with additional increase in cardiometabolic disease risk, supporting the utility in tracking scores within individuals. Figure 2B provides mean changes in scores between visits 1 and 2, adjusted for visit 1 score, by disease diagnosis group. Similar patterns emerged to what was observed with baseline scores. Among those who did not develop T2DM, there were higher degrees of change in CVD risk scores among those with isolated incident CVD. The degree of change in MetS severity *Z* scores between visits 1 and 2 was much more striking before incident T2DM, although there was no significant difference in the degree of change between those with or without additional CVD diagnosis. In logistic regression models, each SD change in MetS *Z* score (relative to the change in nondiseased individuals) carried an OR of 3.6 in isolated incident T2DM and 3.5 and 5.2 in those with T2DM and late and early CVD, respectively (Table S1).

Primary Analysis: Odds of Disease Progression

Because of relatively small frequencies when breaking down CVD by time period, our primary analysis used multinomial logistic regression to assess the relationship between the
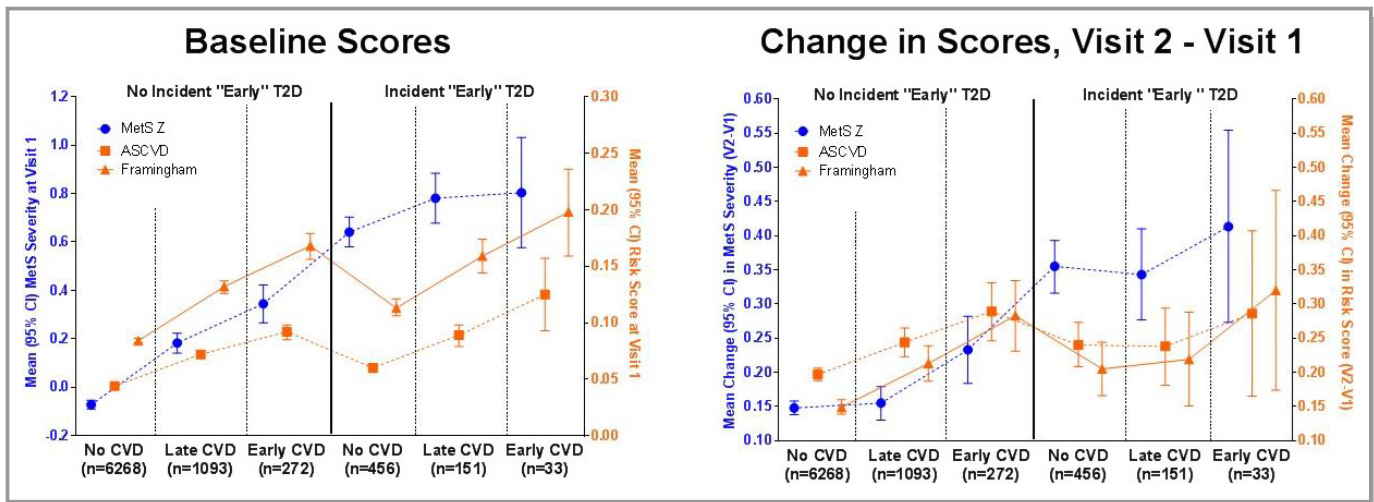
Figure 2. Mean baseline scores and change in scores between visit 1 and visit 2 by disease category. Scores (mean [95% confidence interval {CI}]) for metabolic syndrome (MetS) severity *Z* score, atherosclerotic cardiovascular disease (ASCVD) pooled cohort score, and Framingham risk score by ultimate disease diagnosis category are shown for baseline visit and changes in scores from visit 2 to visit 1 (V2–V1), adjusted for visit 1. Early CVD=incident disease between visit 2 and visit 4 (between ≈3 and ≈9 years after visit 1); late CVD=incident adjudicated CVD event after visit 4 (>≈9 years after visit 1). T2DM indicates type 2 diabetes mellitus.

scores and odds of each of three different categories of disease progression (compared with no disease): (1) isolated CVD (no T2DM), (2) isolated T2DM (no CVD), and (3) T2DM followed by CVD. We fit separate models for each individual score (as *Z* scores within the analytic cohort), as well as models with the combination of a CVD risk score and MetS severity (Table 2). When assessed in individual models, both ASCVD and FRS (baseline and change in scores) were associated with increased odds of each type of disease progression. These 2 scores were associated with isolated T2DM, and unsurprisingly they were more strongly associated with isolated CVD. Likewise, MetS severity by itself was associated with all 3 types of disease progression, but was more strongly associated with T2DM-related progression (with and without eventual CVD).

When the MetS severity *Z* score was included in models with ASCVD (Table 2, model 4), only MetS *Z* was associated with isolated T2DM (OR=5.0). Both scores remained independently associated with isolated CVD, with ASCVD being the stronger predictor (OR of 2.3 for ASCVD and 1.1 for MetS *Z*). With respect to T2DM that progressed to CVD, both scores were associated with this outcome, but it appears the association with ASCVD is attributable to the associated CVD outcome (OR=2.4, compared with OR=2.3 for isolated CVD), whereas the association with MetS severity is attributable to its association with T2DM (OR=4.9, versus OR=5.0 for isolated T2DM). For change in score, changes in ASCVD (OR=1.7) but not MetS *Z* were associated with impending isolated CVD, whereas only changes in MetS *Z* were associated with T2DM, both isolated (OR=3.9) and with progression to CVD (OR=4.1). Similar results were observed in the model that included FRS and MetS *Z*.

When combined with CVD risk scores, MetS *Z* had consistently higher ORs for future disease than did a *Z* score of fasting glucose values alone (Table S2). A baseline-only analysis (thus including those individuals who developed disease after visit 1 but before visit 2) revealed similar results for baseline scores (examined individually and jointly) (Table S3).

Discussion

The dramatic increase in CVD risk associated with development of T2DM, both because of shared cardiometabolic risk factors[31] and additional effects of glycosylation,[32] makes prediction of T2DM a relevant factor to consider for the clinical utility of cardiovascular risk scores. We found that both the ASCVD and FRS scores were associated with future T2DM, as evidenced by higher baseline scores and elevated ORs among those who went on to develop T2DM, whether they developed CVD afterward. These data both highlight T2DM as a stage toward development of CVD and emphasize that CVD risk scores could be used to identify those at high risk not only for CVD but also T2DM. Although current American Diabetes Association guidelines recommend diabetes mellitus screening every 3 years,[33] individuals with particularly high baseline risk scores could receive additional emphasis to watch for symptoms of new T2DM, prompting earlier follow-up screening, as well as enroll in prevention therapies, such as the National Diabetes Prevention Program.

Elevated cardiometabolic risk was also seen using a MetS severity *Z* score. MetS *Z* significantly predicted those who developed T2DM (with or without CVD), with mean MetS severity scores at baseline (displayed in Figure 2) exhibiting a

Table 2. Multinomial Logistic Regression: Odds of Disease Progression*

Variable	Odds of CVD (No T2DM) (n=1365)		Odds of T2DM → No CVD (n=456)		Odds of T2DM → CVD (n=184)[†]	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Model 1: MetS *Z* only						
Visit 1	1.77 (1.63–1.93)	<0.0001	5.10 (4.37–5.95)	<0.0001	6.99 (5.51–8.88)	<0.0001
Change (visit 2-visit 1)	1.14 (0.99–1.32)	0.0663	3.55 (2.79–4.51)	<0.0001	3.71 (2.58–5.33)	<0.0001
Model 2: ASCVD *Z* only[‡]						
Visit 1	2.43 (2.25–2.62)	<0.0001	1.65 (1.47–1.84)	<0.0001	3.87 (3.12–4.81)	<0.0001
Change (visit 2-visit 1)	1.62 (1.36–1.94)	<0.0001	1.43 (1.08–1.88)	0.0122	1.60 (1.01–2.51)	0.0434
Model 3: FRS *Z* only[‡]						
Visit 1	2.33 (2.17–2.50)	<0.0001	1.67 (1.51–1.86)	<0.0001	3.45 (2.87–4.14)	<0.0001
Change (visit 2-visit 1)	1.53 (1.32–1.76)	<0.0001	1.35 (1.08–1.69)	0.0090	1.64 (1.15–2.34)	0.0065
Model 4: MetS and ASCVD[§]						
Visit 1						
MetS *Z*	1.12 (1.01–1.23)	0.0308	**4.99 (4.23–5.88)**	<0.0001	**4.92 (3.79–6.37)**	<0.0001
ASCVD *Z*[‡]	**2.34 (2.15–2.54)**	<0.0001	0.96 (0.85–1.09)	0.5406	2.36 (1.88–2.96)	<0.0001
Change (visit 2-visit 1)						
MetS *Z*	0.93 (0.79–1.10)	0.4018	**3.85 (2.95–5.03)**	<0.0001	**4.11 (2.74–6.17)**	<0.0001
ASCVD *Z*[‡]	**1.71 (1.39–2.09)**	<0.0001	0.77 (0.57–1.04)	0.0893	0.86 (0.54–1.38)	0.5333
Model 5: MetS and FRS[§]						
Visit 1						
MetS *Z*	1.00 (0.90–1.11)	0.9676	**5.10 (4.30–6.04)**	<0.0001	**4.72 (3.62–6.15)**	<0.0001
FRS *Z*[‡]	**2.31 (2.13–2.50)**	<0.0001	0.94 (0.83–1.06)	0.3055	2.11 (1.72–2.59)	<0.0001
Change (visit 2-visit 1)						
MetS *Z*	0.89 (0.76–1.06)	0.1873	**4.09 (3.11–5.37)**	<0.0001	**4.19 (2.76–6.38)**	<0.0001
FRS *Z*[‡]	**1.61 (1.36–1.90)**	<0.0001	0.72 (0.56–0.93)	0.0115	0.88 (0.59–1.32)	0.5387

ASCVD indicates atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; FRS, Framingham risk score; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus.

*Relative to no T2DM or CVD throughout study.

[†]Includes the 33 individuals who had incident T2DM and CVD between visits 2 and 4, with some of them having a CVD event before classification as T2DM.

[‡]*Z* scores were calculated for both ASCVD and FRS to allow for comparisons of odds ratios across the 3 scores. These *Z* scores were based on the visit 1 mean and SD. Odds ratios calculated for a 1-unit increase in *Z* score (ie, a 1-SD increase).

[§]For models 4 and 5 (that include MetS and 1 of each of the CVD risk scores).

Odds ratios are highlighted in bold for the score that significantly outperforms the other (evidenced by nonoverlapping 95% CIs). No collinearity was present when using both MetS *Z* and either of the CVD risk scores in the same model.

nearly linear increase going from the group who remained disease free in follow-up, to the group who had isolated incident CVD, next to the group with isolated T2DM, and finally to the group who developed both. When including both MetS severity and either CVD risk score in the same model, as may be done eventually in electronic health record systems to optimize risk prediction,[34] the CVD risk scores continued to be a better predictor of CVD (with or without T2DM) and MetS severity continued to be a stronger predictor of T2DM, both with and without eventual CVD. This makes sense in that although each of these prediction tools had substantial overlap in the components used to calculate the scores, with each assessment including inputs for sex, HDL cholesterol, and systolic blood pressure, there are multiple differences in

score calculation to drive variation in risk prediction. The CVD scores both use low-density lipoprotein and smoking, critical predictors of CVD. The MetS severity score, by contrast, does not include these and instead includes fasting lipids and glucose. Thus, these scores are likely measuring different aspects of risk, with MetS *Z* potentially estimating a component of cardiometabolic risk not captured by the traditional CVD scores.

Indeed, a key difference between these scores is in their formulation, in that although the ASCVD and FRS were formulated by modeling predictive factors associated with CVD outcomes observed within a 10-year period, the MetS severity *Z* score was formulated according to how the individual components of MetS correlate together, likely as

an estimate of the underlying processes that cause the abnormalities in the individual components to cluster together. This appears to contribute to disease development in that prior studies indicated that MetS severity confers additional disease risk, even in models that include the individual risk factors,[19,22] contrasting with past perceptions that MetS "was not worth more than the sum of its parts."[35] Also, although MetS severity increases with age, age itself is not a component of the score, as it is with the ASCVD and FRS scores, and the models we tested were not adjusted for age, highlighting the importance of MetS severity for disease risk irrespective of age.

One important feature of continuous scores is the potential to track risk in an individual over time, with dramatic interval changes in scores signifying a particular increase in risk. We found that a change in ASCVD and FRS over a 3-year period conferred an increased risk of CVD and T2DM, supporting potential utility in their use to monitor for cardiometabolic derangement over time. Changes in MetS severity Z score conferred an increase in risk for CVD that was much greater when associated with T2DM. This suggests that MetS Z is a more specific assessment of underlying cardiometabolic factors, of potential importance given that T2DM is a common prequel to CVD.

Although these findings reflect important metabolic relationships in a large cohort with long-term follow-up, these analyses also have some limitations. We assessed risk for late CVD events through 20 years of follow-up, although the CVD risk scores were derived to predict 10-year risk; thus, interpretation of risk beyond 10 years should be done with caution. However, we were not focused on validation of risk prediction models, but strictly how these scores (and changes in scores) were associated with categories of future disease. In addition, although CVD outcomes data were adjudicated over 20 years of follow-up, we were more limited in our data on incident diabetes mellitus, which relied on a combination of patient report, medication use, and laboratory assessment; this was a conservative approach, potentially underrepresenting true T2DM incidence during the 3 follow-up visits, and furthermore lacking the long-term follow-up that was available for CVD. Also, participants in the ARIC Study (and FHS) were initially recruited in an era when statin use was unavailable, likely contributing to why the ASCVD and FRS scores overpredict future disease in more modern cohorts[36] and limiting some of the generalizability of these findings. Finally, we assessed for how baseline levels and 3-year changes in these scores were associated with development of CVD over a 20-year period, limiting our scope to be able to demonstrate a more tangible sequence, such as primordial stage (obesity/prediabetes/prehypertension) becoming cardiovascular risk factors (overt diabetes mellitus and hypertension) leading to cardiovascular events, which will be the subject of a future analysis.

In conclusion, we demonstrated the following: (1) common CVD risk prediction tools are associated with development of future T2DM, both in the presence and absence of future CVD; and (2) changes in these scores are associated with additional increased risk beyond baseline. Unsurprisingly, of the 3 scores evaluated, a MetS severity Z score exhibited the strongest associations with future T2DM, and future CVD subsequent to T2DM. Practitioners and patients should be cognizant that particularly elevated risk scores also confer risk for T2DM and T2DM-associated CVD. In all cases, elevations in score and greater increase in score over time should motivate all to redouble efforts toward preventative lifestyle improvements and risk reduction.

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Disclosures

None.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017: estimates of diabetes and its burden in the United States. 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed January 31, 2018.

2. Cheng YJ, Imperatore G, Geiss LS, Wang J, Saydah SH, Cowie CC, Gregg EW. Secular changes in the age-specific prevalence of diabetes among U.S. adults: 1988–2010. *Diabetes Care*. 2013;36:2690–2696.

3. Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM. Cardiovascular health behavior and health factor changes (1988–2008) and projections to 2020: results from the National Health and Nutrition Examination Surveys. *Circulation*. 2012;125:2595–2602.

4. Huffman MD, Lloyd-Jones DM, Ning H, Labarthe DR, Guzman Castillo M, O'Flaherty M, Ford ES, Capewell S. Quantifying options for reducing coronary heart disease mortality by 2020. *Circulation*. 2013;127:2477–2484.

5. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS,

Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492.

6. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–234.

7. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (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;106:3143–3421.

8. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73.

9. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.

10. Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, Folsom AR, Chambless LE; Atherosclerosis Risk in Communities Investigators. Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2005;28:2013–2018.

11. Bang H, Edwards AM, Bomback AS, Ballantyne CM, Brillon D, Callahan MA, Teutsch SM, Mushlin AI, Kern LM. Development and validation of a patient self-assessment score for diabetes risk. *Ann Intern Med*. 2009;151:775–783.

12. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2007;298:2654–2664.

13. Chen F, Knecht K, Birzin E, Fisher J, Wilkinson H, Mojena M, Moreno CT, Schmidt A, Harada S, Freedman LP, Reszka AA. Direct agonist/antagonist functions of dehydroepiandrosterone. *Endocrinology*. 2005;146:4568–4576.

14. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med*. 2014;371:2237–2238.

15. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112:2735–2752.

16. Gurka MJ, Lilly CL, Norman OM, DeBoer MD. An examination of sex and racial/ethnic differences in the metabolic syndrome among adults: a confirmatory factor analysis and a resulting continuous severity score. *Metabolism*. 2014;63:218–225.

17. Gurka MJ, Ice CL, Sun SS, DeBoer MD. A confirmatory factor analysis of the metabolic syndrome in adolescents: an examination of sex and racial/ethnic differences. *Cardiovasc Diabetol*. 2012;11:128.

18. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the Princeton Lipid Research Cohort Study. *Diabetologia*. 2015;58:2745–2752.

19. Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Cardel M, Pearson TA, DeBoer MD. Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk in Communities Study and Jackson Heart Study. *Diabetologia*. 2017;60:1261–1270.

20. DeBoer MD, Gurka MJ, Morrison JA, Woo JG. Inter-relationships between the severity of metabolic syndrome, insulin and adiponectin and their relationship to future type 2 diabetes and cardiovascular disease. *Int J Obes (Lond)*. 2016;40:1353–1359.

21. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of metabolic syndrome as a predictor of cardiovascular disease between childhood and adulthood: the Princeton Lipid Research Cohort Study. *J Am Coll Cardiol*. 2015;66:755–757.

22. DeBoer MD, Gurka MJ, Hill Golden S, Musani SK, Sims M, Vishnu A, Guo Y, Pearson TA. Independent associations between metabolic syndrome severity & future coronary heart disease by sex and race. *J Am Coll Cardiol*. 2017;69:1204–1205.

23. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol*. 1989;129:687–702.

24. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W; Atherosclerosis Risk in Communities Study Group. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2001;104:1108–1113.

25. Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Eckfeldt JH. A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care*. 1997;20:935–942.

26. McNeill AM, Schmidt MI, Rosamond WD, East HE, Girman CJ, Ballantyne CM, Golden SH, Heiss G. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2005;28:385–390.

27. Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, Heiss G; the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. *Diabetes Care*. 1999;22:1077–1083.

28. Framingham Heart Study. Cardiovascular disease (10-year risk). 2018. https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/. Accessed July 13, 2018.

29. Sumner AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. *Atherosclerosis*. 2008;196:696–703.

30. DeBoer MD, Dong L, Gurka MJ. Racial/ethnic and sex differences in the ability of metabolic syndrome criteria to predict elevations in fasting insulin levels in adolescents. *J Pediatr*. 2011;159:975–981.

31. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34:1481–1486.

32. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010;362:800–811.

33. American Diabetes Association. 2: Classification and diagnosis of diabetes. *Diabetes Care*. 2018;41:S13–S27.

34. Guo Y, Musani SK, Sims M, Pearson TA, DeBoer MD, Gurka MJ. Assessing the added predictive ability of a metabolic syndrome severity score in predicting incident cardiovascular disease and type 2 diabetes: the Atherosclerosis Risk in Communities Study and Jackson Heart Study. *Diabetol Metab Syndr*. 2018;10:42.

35. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2005;28:2289–2304.

36. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015;162:266–275.

Supplemental Material

Table S1. Multinomial Logistic Regression by Score Results: Odds of Disease Category (Relative to No CVD or T2DM over Observed Time Period)*

Odds Ratios (95% CI)† (relative to No Diabetes, no CVD; n=6268))	Model 1: Glucose Z		Model 2: MetS Z		Model 3: ASCVD Z‡		Model 4: Framingham Z‡	
	Visit 1	Change (V2-V1)	Visit 1	Change (V2-V1)	Visit 1	Change (V2-V1)	Visit 1	Change (V2-V1)
No Diabetes (by V4), Incident Late CVD (n=1093)	**1.22 (1.13, 1.31)**	**1.10 (1.02, 1.18)**	**1.64 (1.49, 1.80)**	1.04 (0.89, 1.22)	**2.19 (2.02, 2.38)**	**1.50 (1.23, 1.81)**	**2.11 (1.96, 2.27)**	**1.42 (1.21, 1.65)**
No Diabetes (by V4), Incident Early CVD (n=272)	**1.40 (1.22, 1.60)**	**1.26 (1.10, 1.45)**	**2.43 (2.03, 2.91)**	**1.66 (1.24, 2.23)**	**4.03 (3.36, 4.84)**	**2.41 (1.64, 3.55)**	**3.68 (3.16, 4.30)**	**2.15 (1.59, 2.90)**
Incident "Early" Diabetes , no CVD (n=456)	**4.25 (3.77, 4.79)**	**2.70 (2.41, 3.03)**	**5.12 (4.39, 5.98)**	**3.56 (2.80, 4.53)**	**1.65 (1.48, 1.85)**	**1.43 (1.08, 1.88)**	**1.68 (1.51, 1.86)**	**1.35 (1.08, 1.69)**
Incident "Early" Diabetes, Incident Late CVD (n=151)	**4.56 (3.75, 5.55)**	**2.99 (2.47, 3.61)**	**6.85 (5.28, 8.89)**	**3.47 (2.33, 5.16)**	**3.41 (2.71, 4.30)**	1.47 (0.90, 2.40)	**3.17 (2.60, 3.86)**	**1.48 (1.01, 2.19)**
Incident "Early" Diabetes, Incident Early CVD (n=33)	**4.11 (2.76, 6.12)**	**2.82 (1.91, 4.16)**	**7.88 (4.57, 13.57)**	**5.23 (2.28, 12.01)**	**8.50 (4.63, 15.62)**	2.65 (0.87, 8.07)	**5.59 (3.51, 8.89)**	**2.79 (1.19, 6.53)**

*   Early = Incident Disease between Visit 2 and Visit 4 (between ~3 and ~9 years after Visit 1)
Late CVD = Incident adjudicated CVD event after Visit 4 (> ~9 years after Visit 1)

†   Odds ratios in bold indicate statistical significance (p < 0.05). No collinearity was present when using both MetS Z and either of the CVD risk score in the same model.

‡   Z-scores were calculated for Fasting Glucose, ASCVD, and Framingham Risk Scores to allow for comparisons of odds ratios across the three scores. These z-scores were based on the Visit 1 mean and SD. Odds ratios calculated for a 1-unit increase in z-score (i.e., a 1 SD increase)

Table S2. Odds of Disease Progression, Examining Fasting Blood Glucose*

	Odds of CVD (no T2DM), n=1365		Odds of T2DM → No CVD, n=456		Odds of T2DM → CVD‡, n=184	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Individual Models						
Model 1: Glucose Z Only						
Visit 1	1.25 (1.17, 1.34)	< 0.0001	4.24 (3.77, 4.78)	< 0.0001	4.47 (3.74, 5.35)	< 0.0001
Change (Visit 2 – Visit 1)	1.13 (1.06, 1.21)	0.0003	2.70 (2.41, 3.03)	< 0.0001	2.95 (2.49, 3.51)	< 0.0001
Model 2: MetS Z Only						
Visit 1	1.77 (1.63, 1.93)	< 0.0001	5.10 (4.37, 5.95)	< 0.0001	6.99 (5.51, 8.88)	< 0.0001
Change (Visit 2 – Visit 1)	1.14 (0.99, 1.32)	0.0663	3.55 (2.79, 4.51)	< 0.0001	3.71 (2.58, 5.33)	< 0.0001
Joint Model						
Model 3: MetS and Glucose Z						
Visit 1						
MetS Z	1.73 (1.58, 1.91)	< 0.0001	2.74 (2.30, 3.26)	< 0.0001	3.88 (2.98, 5.04)	< 0.0001
Glucose Z†	1.03 (0.95, 1.11)	0.4789	3.15 (2.77, 3.58)	< 0.0001	3.04 (2.50, 3.69)	< 0.0001
Change (Visit 2 - Visit 1)						
MetS Z	1.10 (0.94, 1.29)	0.2222	2.12 (1.61, 2.79)	< 0.0001	2.03 (1.35, 3.07)	0.0007
Glucose Z†	1.04 (0.97, 1.12)	0.2501	2.17 (1.91, 2.46)	< 0.0001	2.33 (1.93, 2.82)	< 0.0001

* Relative to no T2DM or CVD throughout study

† Z-scores were calculated for fasting glucose to allow for comparisons of odds ratios with MetS Z. These z-scores were based on the Visit 1 mean and SD. Odds ratios calculated for a 1-unit increase in z-score (i.e., a 1 SD increase).

‡ Includes the 33 individuals who had incident T2DM and CVD between Visits 2 and Visit 4, with some of them having a CVD event before classification as T2DM

Table S3. Multinomial Logistic Regression: Odds of Disease Progression, Baseline Scores Only*

	Odds of CVD (no T2DM), n=1472§		Odds of T2DM → No CVD, n=953§		Odds of T2DM → CVD§, n=392	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Model 1: Visit 1 MetS Z Only	1.79 (1.65, 1.93)	< 0.0001	4.35 (3.91, 4.83)	< 0.0001	6.40 (5.46, 7.51)	< 0.0001
Model 2: Visit 1 ASCVD Z Only[†]	2.34 (2.18, 2.51)	< 0.0001	1.64 (1.52, 1.77)	< 0.0001	3.72 (3.22, 4.30)	< 0.0001
Model 3: Visit 1 Framingham Z Only[†]	2.29 (2.14, 2.44)	< 0.0001	1.65 (1.54, 1.77)	< 0.0001	3.36 (2.96, 3.80)	< 0.0001
Model 4: Visit 1 Glucose Z Only[†]	1.21 (1.14, 1.28)	< 0.0001	3.30 (3.09, 3.59)	< 0.0001	3.41 (3.08, 3.78)	< 0.0001
Model 5: Visit 1 MetS and ASCVD‡						
MetS Z	1.15 (1.05, 1.26)	0.0032	**4.20 (3.75, 4.72)**	< 0.0001	**4.44 (3.73, 5.27)**	< 0.0001
ASCVD Z[†]	**2.23 (2.07, 2.41)**	< 0.0001	1.01 (0.92, 1.10)	0.8584	2.28 (1.96, 2.66)	< 0.0001
Model 6: Visit 1 MetS and Framingham‡						
MetS Z	1.04 (0.95, 1.15)	0.4099	**4.36 (3.87, 4.91)**	< 0.0001	**4.31 (3.61, 5.14)**	< 0.0001
Framingham Z[†]	**2.24 (2.07, 2.41)**	< 0.0001	0.95 (0.87, 1.04)	0.2259	2.01 (1.75, 2.31)	< 0.0001
Model 7: Visit 1 MetS and Glucose‡						
MetS Z	**1.76 (1.62, 1.92)**	< 0.0001	2.48 (2.20, 2.79)	< 0.0001	**3.87 (3.25, 4.60)**	< 0.0001
Glucose Z[†]	1.01 (0.95, 1.08)	0.6964	2.60 (2.40, 2.82)	< 0.0001	2.40 (2.15, 2.69)	< 0.0001

*   Relative to no T2DM or CVD throughout study

†   Z-scores were calculated for ASCVD, Framingham Risk Scores, as well as glucose, to allow for comparisons of odds ratios across the four measures. These z-scores
        were based on the Visit 1 mean and SD. Odds ratios calculated for a 1-unit increase in z-score (i.e., a 1 SD increase)

‡   For Models 4 and 5 (that include MetS and one of each of the CVD risk scores), OR's are highlighted in bold for the score that significantly out-
        performs the other (evidenced by non-overlapping 95% CI's). No collinearity was present when using both MetS Z and either of the CVD risk score in
        the same model.

§   Unlike primary analysis, includes individuals who developed disease (T2DM and/or CVD) after Visit 1 (but before Visit 2)