Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

The Progression of Cardiometabolic Disease: Validation of a New Cardiometabolic Disease Staging System Applicable to Obesity

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Objective: To validate a Cardiometabolic Disease Staging (CMDS) system for assigning risk level for diabetes, and all-cause and cardiovascular disease (CVD) mortality.

Design and Methods: Two large national cohorts, CARDIA and NHANES III, were used to validate CMDS. CMDS: Stage 0: metabolically healthy; Stage 1: one or two metabolic syndrome risk factors [other than impaired fasting glucose (IFG)]; Stage 2: IFG or impaired glucose tolerance (IGT) or metabolic syndrome (without IFG); Stage 3: two of three (IFG, IGT, and/or metabolic syndrome); and Stage 4: type 2 diabetes mellitus/CVD.

Results: In the CARDIA study, compared with Stage 0 metabolically healthy subjects, adjusted risk for diabetes exponentially increased from Stage 1 [hazard ratio (HR) 2.83, 95% confidence interval (CI): 1.76-4.55], to Stage 2 (HR 8.06, 95% CI 4.91-13.2), to Stage 3 (HR 23.5, 95% CI 13.7-40.1) (*P* for trend <0.001). In NHANES III, both cumulative incidence and multivariable adjusted HRs markedly increased for both all-cause and CVD mortality with advancement of the risk stage from Stages 0 to 4. Adjustment for body mass index (BMI) minimally affected the risks for diabetes and all-cause/CVD mortality using CMDS.

Conclusion: CMDS can discriminate a wide range of risk for diabetes, CVD mortality, and all-cause mortality independent of BMI, and should be studied as a risk assessment tool to guide interventions that prevent and treat cardiometabolic disease.

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Introduction

The spectrum of cardiometabolic disease begins with insulin resistance, a trait that is expressed early in life, and then progresses to the clinically identifiable high-risk states of metabolic syndrome and prediabetes, and then to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). The consequences of cardiometabolic disease are severe. T2DM, which is epidemic in the United States (1) and worldwide (2), is associated with elevated risk for morbidity and mortality (3) and high social costs (1), and CVD remains the leading cause of death in Western societies. To stem the increasing prevalence of T2DM and to reduce CVD risks, it will be necessary to identify high-risk individuals early in the progression of cardiometabolic disease and intervene with effective strategies for disease prevention.

Obesity can exacerbate insulin resistance and impel cardiometabolic disease progression. However, the relationship between generalized obesity, as measured by the body mass index (BMI, kg/m^2), and cardiometabolic disease is complex. For example, insulin resistance exists largely independent of BMI (4), and BMI is a poor predictor of CVD compared with measures of fat distribution such as waist/hip ratio (5). Also, up to 30% of obese individuals (i.e., BMI $\geq$ 30)

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are relatively insulin sensitive, giving rise to the term "healthy obese" (6). Thus, obesity is neither necessary nor sufficient to explain the pathophysiology underlying cardiometabolic disease. Even so, weight loss can be used as a therapeutic tool. Weight loss whether achieved by lifestyle intervention (7), medications (8), or bariatric surgery (9) can prevent progression to T2DM in high-risk individuals, ameliorate dyslipidemia, lower blood pressures, and improve glucose tolerance.

Before 2012, clinicians used lifestyle modification and a limited number of modestly effective medications in efforts to combat obesity, with bariatric surgery reserved for more severe or refractory cases (10). In the summer of 2012, the FDA approved two new medications, phentermine plus topiramate extended release (phentermine/topiramate ER) and locaserin, to be used as adjuncts to lifestyle modification in the treatment of overweight and obesity. The availability of these safe and effective weight loss drugs represents a landmark development in obesity pharmacotherapy, and enables an evidenced-based medical model that incorporates more effective and comprehensive application of lifestyle, drug, and surgical treatment options (11).

In developing a medical model for obesity management, it is important to consider that any intervention entails risk, and treatment must be targeted to those patients who will derive the greatest benefits from the intervention to optimally balance benefit and risk. Many treatment algorithms for obesity are based on BMI level, which determines thresholds for indications pertaining to pharmacotherapy and bariatric surgery (10,12). For the reasons discussed above, BMI is a poor indicator for use in this context; rather, patients who will benefit most from obesity treatment have obesity-related complications that can be ameliorated by weight loss (10,11,13). Given that medications and surgical procedures have inherent risks for patients and increase the cost of health care delivery, it is important to develop a staging system that identifies patients who can most benefit from weight loss interventions, based on complications rather than BMI *per se*.

In this article, we have validated a system for evaluating the stage and severity of cardiometabolic disease. Our studies used the NHANES III-linked mortality file (14) for cardiovascular and all-cause mortality, and longitudinal data from the national CARDIA study for incident T2DM (15). We have defined distinct categories using readily available clinical information that assess future risk for both T2DM and CVD mortality, and have called this system Cardiometabolic Disease Staging (CMDS). The studies have provided insight regarding risk progression in cardiometabolic disease, and have validated a tool that can be used by clinicians to identify treatment modality and intensity for obesity based on cardiometabolic disease severity. Such an approach may be useful to optimize the benefit/risk ratio for interventions, and achieve the best outcomes by aligning specific therapy with those patients who will derive the greatest benefit.

Methods

Risk staging system

We propose a risk classification system using clinical parameters pertinent to diagnosis of the metabolic syndrome from Adult Treatment Panel III (ATP III) (3), and prediabetes/diabetes using fasting and 2-h OGTT glucose values according to the American Diabetes Association. The CMDS system is shown in Table 1, and was based on results from the epidemiological and physiological literature: (i) Stage 0 includes individuals who are relatively insulin sensitive, free of any cardiometabolic disease risk factors, and without increased risk of diabetes or CVD (6), referred to as "metabolically healthy obese" (16); (ii) Stage 1 includes patients who meet only one or two ATPIII criteria (waist circumference, elevated blood pressure, triglycerides, and HDL-C) but who are still at increased risk of future T2DM and CVD (17,18); (iii) Stage 2 is comprised of patients who meet criteria for either metabolic syndrome or impaired fasting glucose (IFG) alone or impaired glucose tolerance (IGT) alone; (iv) Stage 3 includes patients with any two of three of these conditions (metabolic syndrome, IFG, and IGT) who exhibit approximately double the risk for future diabetes compared with those who have either condition alone (18,19); finally, (v) Stage 4 subjects have diagnoses of T2DM and/or CVD as patients with previous myocardial infarction and T2DM patients without a previous myocardial infarction have equal risk of future coronary heart disease mortality (20). Thus, the CMDS system was rationally constructed based on multiple published observations. Then, we proceeded to empirically validate the predictive value of CMDS for differential risk of future T2DM and mortality using data from the Coronary Artery Risk Development in Young Adults (CARDIA) and the National Health and Nutrition Examination Survey (NHANES) cohorts.

CARDIA study

Data from the CARDIA study was used to validate CMDS against future risk for T2DM. The CARDIA study (15) is a large, ongoing cohort study, which began in 1985-1986. CARDIA recruited 5,115 young black and white adults (46% male) aged 18-30 years from four sites in the United States, including Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Oral glucose tolerance tests (OGTTs) with measurement of the 2-h glucose concentration were not initiated until CARDIA year 10, and, for this reason, year 10 served as baseline year for this study, with follow-up to year 20. These analyses included 3,315 participants with valid 2-h glucose measures at year 10 after excluding pregnant women, participants with diabetes or CVDs, and participants without enough information for assignment to risk category. Site institutional review committee approval and informed consent were obtained.

Measures. BMI (kg/m^2) was computed and standardized blood pressures were obtained by sphygmomanometer. Standing waist circumference was measured at a level laterally that is midway between the iliac crest and the lowest lateral portion of the rib cage and anteriorly midway between the xiphoid process of the sternum and the umbilicus. Serum glucose and plasma lipids were assayed using the fasting blood sample. Seventy-five-gram OGTTs were performed at the year 10 and year 20 examinations. Each participant was asked to fast for 12 h; however, participants were asked to report the time of their last meal, so the length of the fasting period could be calculated. Incident diabetes was defined as participants reporting a diagnosis of diabetes, or having a documented fasting plasma glucose $\geq$126 mg/dL, and/or 2-h glucose $\geq$200 mg/dL.

NHANES III

Data from NHANES III-linked mortality file was used to validate CMDS against mortality risk. NHANES III is a cross-sectional

TABLE 1 The Cardiometabolic Disease Staging (CMDS) system

The Cardiometabolic Disease Staging (CMDS) system

Stage	Descriptor	Criteria
Stage 0	Metabolically healthy	No risk factors
Stage 1	One or two risk factors	Have one or two of the following risk factors: (a) High waist circumference (≥112 cm in men and ≥88 cm in women) (b) Elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or on antihypertensive medication (c) Reduced serum HDL cholesterol (<1.0 mmol/L or 40 mg/dL in men; <1.3 mmol/L or 50 mg/dL in women) or on medication (d) Elevated fasting serum triglycerides (≥1.7 mmol/L or 150 mg/dL) or on medication
Stage 2	Metabolic syndrome or prediabetes	Have only one of the following three conditions in isolation (a) Metabolic syndrome based on three or more of four risk factors: high waist circumference, elevated blood pressure, reduced HDL-C, and elevated triglycerides (b) Impaired fasting glucose (IFG; fasting glucose ≥5.6 mmol/L or 100 mg/dL) (c) Impaired glucose tolerance (IGT; 2-h glucose ≥7.8 mmol/L or 140 mg/dL)
Stage 3	Metabolic syndrome + prediabetes	Have any two of the following three conditions: (a) Metabolic syndrome (b) IFG (c) IGT
Stage 4	T2DM and/or CVD	Have type 2 diabetes mellitus (T2DM) and/or cardiovascular disease (CVD): (a) T2DM (fasting glucose ≥126 mg/dL or 2-h glucose ≥200 mg/dL or on antidiabetic therapy) (b) active CVD (angina pectoris, or status post a CVD event such as acute coronary artery syndrome, stent placement, coronary artery bypass, thrombotic stroke, nontraumatic amputation due to peripheral vascular disease)

survey conducted by the National Center for Health Statistics (NCHS) during 1988-1994, using a complex, stratified, multistage probability sample to represent the civilian, noninstitutionalized, US population. The study was approved by the NCHS Institutional Review Board, and all adult participants provided written informed consent. Information on mortality from public-use mortality files was linked to the National Death Index, with follow-up through December 31, 2006. Males and nonpregnant females aged 40-74 years who had been randomized to the morning session of the mobile examination center and completed an oral glucose test were considered eligible. Participants without adequate information to assess risk staging classification were excluded.

Measures. Subjects were grouped into three BMI categories: ≥30 (obese), 25-29.9 (overweight), and <25 (normal). Race/ethnicity was self-reported as non-Hispanic White (NHW), non-Hispanic Black (NHB), Mexican American (MEX), other Hispanic, and other. Standardized blood pressures were obtained by sphygmomanometer. Standing waist circumference was measured just above the uppermost lateral border of the ilium. Plasma glucose and serum lipids were measured as delineated in the NHANES Laboratory Procedures Manual (21). The method of probabilistic matching (22) was used to link NHANES III participants with the National Death Index to ascertain vital status and mortality through December 31, 2006. It was found that 96.1% of the deceased participants and 99.4% of the living participants were correctly classified, using identical matching methodology applied to the NHANES I Epidemiological Follow-up Study for validation purposes (22).

Statistical analysis

Statistical analyses were carried out with SAS version 9.3 (SAS Institute). A two-sided $P < 0.05$ was determined to be statistically significant. Cox regression models were used to examine risk stage in relation to incident diabetes using CARDIA data. Follow-up time was calculated as the difference between the baseline set at year 10 of the CARDIA study and the year when diabetes was first identified, examination year 20, or the year a participant was censored, whichever came first. Multivariable adjusted Cox model 1 was adjusted for age, sex, race, income, education, current smoker, current alcohol drinker, and parent diabetes history. Model 2 was additionally adjusted for BMI.

All analyses for NHANES data took into account differential probabilities of selection and the complex sample design by using sample weights, following NHANES Analytic and Reporting Guidelines. Standard errors were calculated using Taylor series linearization. We analyzed all-cause and CVD mortality using Kaplan-Meier survival curve estimates and Cox regression models. Model 1 was adjusted for age, sex, race, income, education, current smoker, and current alcohol drinker. Model 2 was further adjusted for BMI. Sensitivity analysis was conducted after excluding participants with cancer, CVD, or hepatitis C in the full multivariable adjusted model.

TABLE 2 Sample size for the CARDIA study and NHANES-linked mortality file

	Number (weighted %)					
		Risk level				
	All	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
NHANES-linked mortality file						
All	3,964 (100.0)	390 (13.7)	892 (24.4)	992 (25.7)	673 (16.3)	1,017 (20.0)
Men	1,952 (49.0)	191 (6.2)	379 (10.3)	528 (13.0)	326 (8.4)	528 (11.1)
Women	2,012 (51.0)	199 (7.4)	513 (14.1)	464 (12.7)	347 (7.9)	489 (8.9)
NHW	1,792 (79.8)	204 (11.3)	401 (19.5)	462 (20.6)	316 (12.9)	409 (15.5)
NHB	1,015 (9.1)	99 (1.1)	272 (2.6)	251 (2.3)	130 (1.1)	263 (2.1)
MEX	989 (3.7)	65 (0.3)	181 (0.8)	238 (0.9)	198 (0.8)	307 (1.0)
Alive	2,952 (79.7)	337 (12.4)	734 (21.0)	781 (21.4)	499 (12.3)	601 (12.7)
Deceased	1,012 (20.3)	53 (1.3)	158 (3.5)	211 (4.3)	174 (3.9)	416 (7.3)
No CVD death	3,560 (92.6)	378 (13.5)	843 (23.5)	910 (24.0)	616 (15.2)	813 (16.4)
CVD death	404 (7.4)	12 (0.1)	49 (1.0)	82 (1.7)	57 (1.1)	204 (3.6)
The CARDIA study						
All	3,315	1,537	1,364	335	79	
Men	1,495	692	584	178	41	
Women	1,820	845	780	157	38	
Blacks	1,530	629	689	168	44	
Whites	1,785	908	675	167	35	
No events	3,112	1,509	1,283	274	46	
Incident diabetes	203	28	81	61	33	

For NHANES III-linked mortality file, participants aged 40-74 years with valid 2-h glucose measures and information for assigning risk category were included. Pregnant women were excluded. Weighted %: sample weights were used to calculate weighted percent.
For the CARDIA study, inclusion is participants with valid 2-h glucose measures at year 10 and information for assigning risk category. Pregnant women and participants with diabetes or cardiovascular diseases at year 10 were excluded.
CVD, cardiovascular disease; NHB, non-Hispanic Black; NHW, non-Hispanic White; MEX, Mexican American.

We examined the relationship between the risk system and incident diabetes, or mortality, in all study participants and in those subjects who were overweight and obese. The proportional hazards assumption for Cox models was assessed using Schoenfeld residuals, and no violation was found.

Results

Incident diabetes

The CARDIA study was used to assess incident diabetes, and baseline characteristics (i.e., CARDIA year 10 examination) are presented in Tables 2 and 3. Participants in CARDIA were relatively young with a median age of 35 years. A total of 29.3% of overweight or obese participants were metabolically healthy (i.e., no risk factors; Stage 0, Supporting Information Table).

Over the 10-year follow-up period, there were 203 cases of newly diagnosed diabetes resulting in an overall crude cumulative diabetes incidence of 6.1%. The cumulative diabetes incidence across risk levels of Stages 0, 1, 2, and 3 was 1.8, 5.9, 18.2, and 41.8%, respectively, as shown in Figure 1A. Among overweight or obese participants, cumulative diabetes incidence was 8.9% overall, and across risk levels of Stages 0, 1, 2, and 3 was 2.2, 7.3, 19.0, and 41.0%, respectively (Supporting Information Figure 2). Clearly, patients categorized in Stage 0 (metabolically healthy) exhibited little tendency to progress to diabetes, while cumulative diabetes incidence rose at progressively higher rates as the risk stage was advanced from Stage 1 to Stage 3. The impact of risk stage on diabetes incidence was similar in both genders and in Whites and Blacks (Supporting Information Figure 1).

In the same manner, multivariable adjusted hazard ratios (HRs) for diabetes increased as a function of advancing CMDS as shown in Figure 1B. Compared with Stage 0 metabolically healthy subjects, adjusted risk for diabetes exponentially increased from Stage 1 (HR 2.83, 95% confidence interval (CI) 1.76-4.55), to Stage 2 (HR 8.06, 95% CI 4.91-13.2), to Stage 3 (HR 23.5, 95% CI 13.7-40.1) (P for trend <0.001). Even after adjusting for BMI in Figure 1C, HRs increased as a function of risk stage with statistically significant higher risk in Stage 1 (HR 1.75, 95% CI 1.05-2.92), Stage 2 (HR 4.60, 95% CI 2.67-7.94), and Stage 3 (HR 11.0, 95% CI 5.96-20.2), although the magnitude of the risk increments was reduced. Adjusted HRs for incident diabetes also increased with higher stage when only overweight or obese participants were included in the analysis (Supporting Information Figure 3).

All-cause and CVD mortality

NHANES III was used to assess effects on all-cause and CVD mortality, and baseline characteristics are presented in Tables 2 and 3. The NHANES III sample was comprised of 3,964 subjects who reported that they had fasted for at least 8 h before OGTT with

TABLE 3 Characteristics of participants from the CARDIA study and NHANES-linked mortality file

	Mean or % (95% CI)	
	CARDIA	NHANES
Age (years)	35.0 (34.9-35.1)	54.2 (53.8-54.7)
BMI (kg/m^2)	27.1 (26.9-27.3)	27.4 (27.2-27.7)
Waist circumference (cm)	85.1 (84.6-85.5)	96.0 (95.3-96.6)
SBP (mmHg)	109.6 (109.2-110.0)	123.4 (122.6-124.2)
DBP (mmHg)	72.3 (72.0-72.6)	73.9 (73.5-74.4)
HDL cholesterol (mg/dL)	50.5 (50.0-51.0)	50.2 (49.5-50.9)
Total cholesterol (mg/dL)	177.7 (176.5-178.9)	216.1 (214.2-218.0)
Triglyceride (mg/dL)	89.7 (87.4-92.1)	155.5 (148.3-162.7)
Higher education (%)	72.3 (70.8-73.8)	40.3 (37.9-42.6)
Non-smoker (%)	59.3 (57.6-61.0)	39.1 (36.8-41.4)
Current smoker (%)	23.7 (22.3-25.2)	24.9 (22.9-26.9)
Obesity (%)	24.2 (22.7-25.6)	27.5 (25.5-29.6)
Elevated blood pressure (%)	13.0 (11.9-14.2)	48.4 (46.0-50.7)
Reduced HDL-cholesterol (%)	36.0 (34.4-37.7)	41.0 (38.7-43.4)
Elevated triglycerides (%)	11.6 (10.5-12.7)	39.7 (37.4-42.0)
High waist circumference (%)	21.3 (19.9-22.7)	48.6 (46.3-51.0)
Elevated total cholesterol (%)	22.6 (21.2-24.0)	65.9 (63.7-68.2)

BMI, body mass index; DBP, diastolic blood pressure; elevated blood pressure, (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or on antihypertensive medication; elevated fasting serum triglycerides, ≥1.7 mmol/L or 150 mg/dL; or on medication; elevated total cholesterol, ≥180 mg/dL or on medication; HDL, high-density lipoprotein; higher education, have completed some college or higher education; high waist circumference, ≥112 cm in men and ≥88 cm in women; reduced HDL cholesterol, <1.0 mmol/L or 40 mg/dL in men; <1.3 mmol/L or 50 mg/dL in women; or on medication; SBP, systolic blood pressure.

sufficient information for risk staging. For the most part, participants were evenly distributed into risk category stages.

Over a median follow-up of 173 months, there were 1,012 all-cause mortality cases ascertained, and the cumulative mortality rate was 14.7 per 1,000 person-years. The cumulative mortality rates increased progressively with advancing CMDS risk stage ($P < 0.001$ for trend), and were 6.5, 10.1, 11.9, 17.7, and 29.2 per 1,000 person-years across risk Stages 0 to 4, respectively. In total, 404 cases of CVD-related deaths were reported. The CVD cumulative mortality rate was 5.4 per 1,000 person-years overall, and also increased with risk stage ($P < 0.001$ for trend), with 0.7, 2.8, 4.6, 4.9, and 14.3 per 1,000 person-years across risk Stages 0 to 4, respectively.

Kaplan-Meier plots for survival probability as a function of CMDS are shown in Figure 2A for all-cause mortality and in Figure 3A for CVD mortality. Both all-cause and CVD mortality increased with advancing risk stage in the entire cohort. This applied to both genders and all ethnic/racial subgroups (Supporting Information Figures 4 and 7), and when the analyses were confined to only those subjects who were overweight or obese at baseline (Supporting Information Figures 5 and 8). Similarly, multivariable adjusted HRs for all-cause mortality are also clearly increased as a function of higher CMDS risk stage. In Figure 2B, with Stage 0 metabolically healthy subjects as the referent group, risk Stage 2 (HR 1.53, 95% CI 1.01-2.32), Stage 3 (HR 2.19, 95% CI 1.38-3.47), and Stage 4 (HR 3.12, 95% CI 1.90-5.10) were associated with progressively higher adjusted mortality HRs. These results were similar after adjusting for baseline BMI (Figure 2C) or after excluding participants with CVD, cancer, or hepatitis C at baseline (data not shown). Adjusted HRs for all-cause mortality also increased with higher stage in overweight or obese participants (Supporting Information Figure 6). Higher CMDS risk stages also predicted progressively greater risk for CVD mortality. In Figure 3B, Stage 1 (HR 3.63, 95% CI 1.36-9.65), Stage 2 (HR 5.65, 95% CI 2.17-14.7), Stage 3 (HR 5.67, 95% CI 2.30-14.08), and Stage 4 (HR 14.6, 95% CI 6.06-35.4) risk categories were associated with progressively higher adjusted hazard for CVD mortality with the lowest risk category Stage 0 serving as the referent group. We further observed that these results were similar after adjusting for BMI (Figure 3C) or after excluding participants with CVD, cancer, or hepatitis C at baseline (data not shown). Adjusted HRs for CVD mortality also increased with higher stage in overweight or obese participants (Supporting Information Figure 9).

Over a 10-year follow-up period in CARDIA, CMDS risk categories (Stages 0 to 3) discriminated ~20-fold differences in both the cumulative incidence (1.8-41.8%) and adjusted HRs (1.0-23.5) for diabetes. In NHANES, CMDS Stages 0 to 4 differentiated cumulative all-cause mortality rates ranging from 6.5 to 29.2 per 1,000 person-years and adjusted HRs from 1.0 to 3.12, and CVD mortality rates from 0.7 to 14.3 per 1,000 person-years and adjusted HRs from 1.0 to 14.6. Thus, CMDS is a strong predictor of incident diabetes, all-cause mortality, and CVD mortality.

Discussion

Cardiometabolic disease staging

We used two large national cohorts, the CARDIA study for incident diabetes and the NHANES III-linked mortality file for all-cause or CVD mortality, to validate a single risk staging system for both metabolic and vascular outcomes in cardiometabolic disease. We established five categories (Stages 0 to 4) for predicting increasing risk for future T2DM and CVD mortality using parameters from the physical examination and laboratory measurements that would be immediately available to clinicians. These parameters are relevant to the diagnosis of metabolic syndrome using ATPIII guidelines (23) and prediabetes as defined by the American Diabetes Association, and include waist circumference, systolic and diastolic blood pressures, fasting and 2-h OGTT blood glucose levels, triglycerides, and HDL-C. Our intention was to establish a clinically useful paradigm that will allow clinicians to identify modalities and intensities of therapy for prevention and treatment of cardiometabolic diseases in a manner that optimally balances benefit and risk. Our analyses clearly established that the five stages: (i) define populations at progressively increasing risk of future T2DM and all-cause and CVD mortality; (ii) partition populations with substantial numbers into all the various risk categories; (iii) serve to differentiate individuals over a wide range of disease risk; and (iv) maintain predictive value in both genders and across ethnic/racial subpopulations.

CMDS and the progression of cardiometabolic disease

The staging system that was validated in this study confirms isolated observations but, moreover, provides an integrated understanding of the progressive nature and spectrum of cardiometabolic disease. For example, our data confirm that a significant proportion of

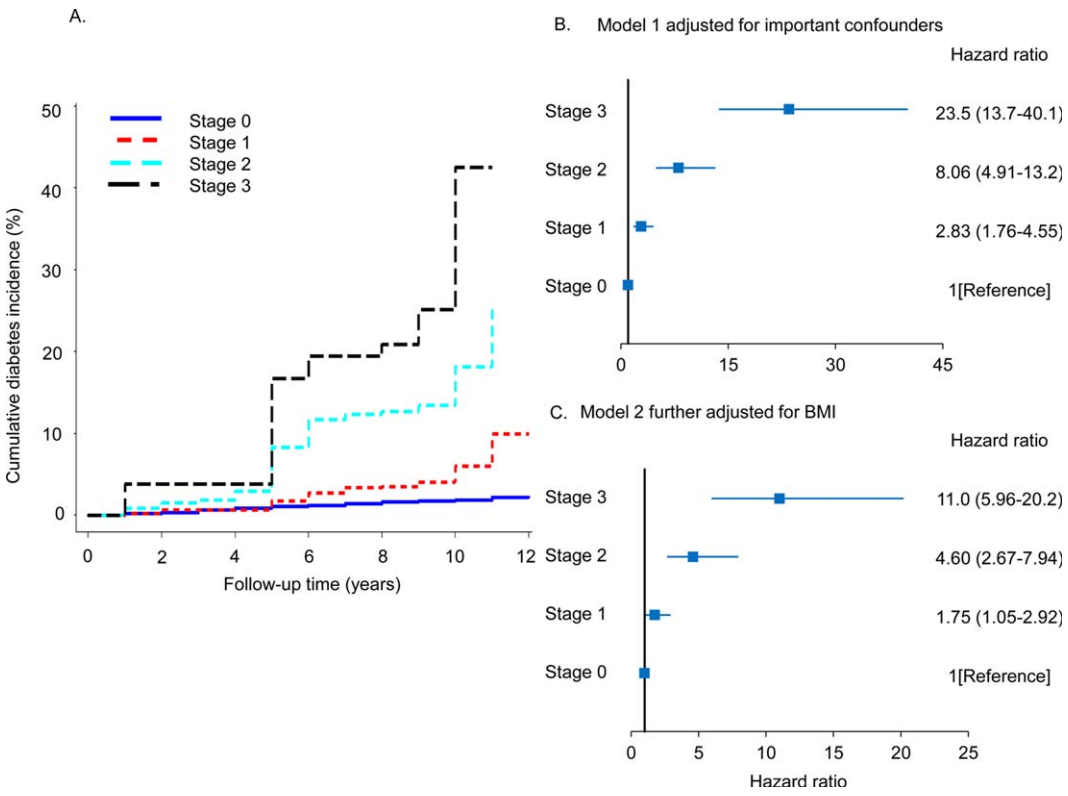

FIGURE 1 (A) Cumulative diabetes incidence according to risk staging system. (B, C) Adjusted hazard ratios for incident diabetes. Model 1 adjusted for age, sex, race, income, education, current smoker, current alcohol drinker, and parent diabetes history. Model 2 additionally adjusted for BMI. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

overweight and obese individuals do not have cardiometabolic risk factors (6,24), equivalent to 19% of the CARDIA cohort, and now prospectively demonstrate that these individuals (i.e., Stage 0) also exhibit low rates of future diabetes and all-cause and CVD mortality. Our study also indicates that patients with one or two risk factors (Stage 1), who do not meet criteria for either metabolic syndrome or prediabetes, exhibit increased risk of future diabetes. This is consistent with the idea advanced by us (25) and others (17,18) that these diagnostic categories have high specificity but low sensitivity for identifying insulin resistance and cardiometabolic disease. Nevertheless, as cardiometabolic disease progresses to fulfillment of criteria for metabolic syndrome or IFG or IGT (Stage 2), patients are at increased risk for T2DM and CVD, and the risks approximately double when any two of these three are present (Stage 3). This is consistent with previous data showing patients who meet criteria for both metabolic syndrome and prediabetes are at substantially higher risk for T2DM than patients who satisfy criteria for only one of these diagnoses (18-20). Stage 3 is identical to a high-risk state for future diabetes identified in a position statement from the American Association of Clinical Endocrinologists, who recommend consideration of treatment with antidiabetic drugs in these patients (26). Stage 4 is defined by the presence of overt T2DM and/or CVD, and reflects the high risk conferred by T2DM *per se*, even in the absence of known CVD, for future CVD events (20). Thus, in single cohorts of patients, our study demonstrates the full continuum of the cardiometabolic disease process, and elucidates the progressive severity of the disease using quantifiable clinical markers and manifestations relevant to both metabolic and vascular components.

BMI was not included in the determination of cardiometabolic disease risk because previous studies have indicated that insulin resistance exists largely independent of generalized adiposity (4,25,27) and that BMI is a poor independent predictor of CVD (28). This data substantiate that BMI is weak independent predictor of future diabetes as well as all-cause and CVD mortality because adjustment for BMI did not substantially alter risks predicted by CMDS. Also, the predictive value of CMDS was unchanged when lean subjects were omitted and CMDS was applied only to overweight and obese individuals. In contrast, waist circumference is a strong independent predictor of insulin resistance and CVD (28,29), and is incorporated into CMDS. It is also apparent that HbA1c was not used as a measure of diabetes or prediabetes, and this is because we (30) and others (31) have shown that HbA1c has low sensitivity for these diagnoses, and is responsible for a high false-negative rate among patients diagnosed using the gold standard measures of fasting glucose combined with 2-h glucose values. It is also important to consider that a high proportion of patients with prediabetes on the basis of IGT (i.e., elevated 2-h OGTT only) will be missed when only fasting glucose and HbA1c are available, and that this proportion of missed diagnoses increases as a function of age (32). Elevated 2-h glucose is also a strong independent risk factor for CVD (33). These

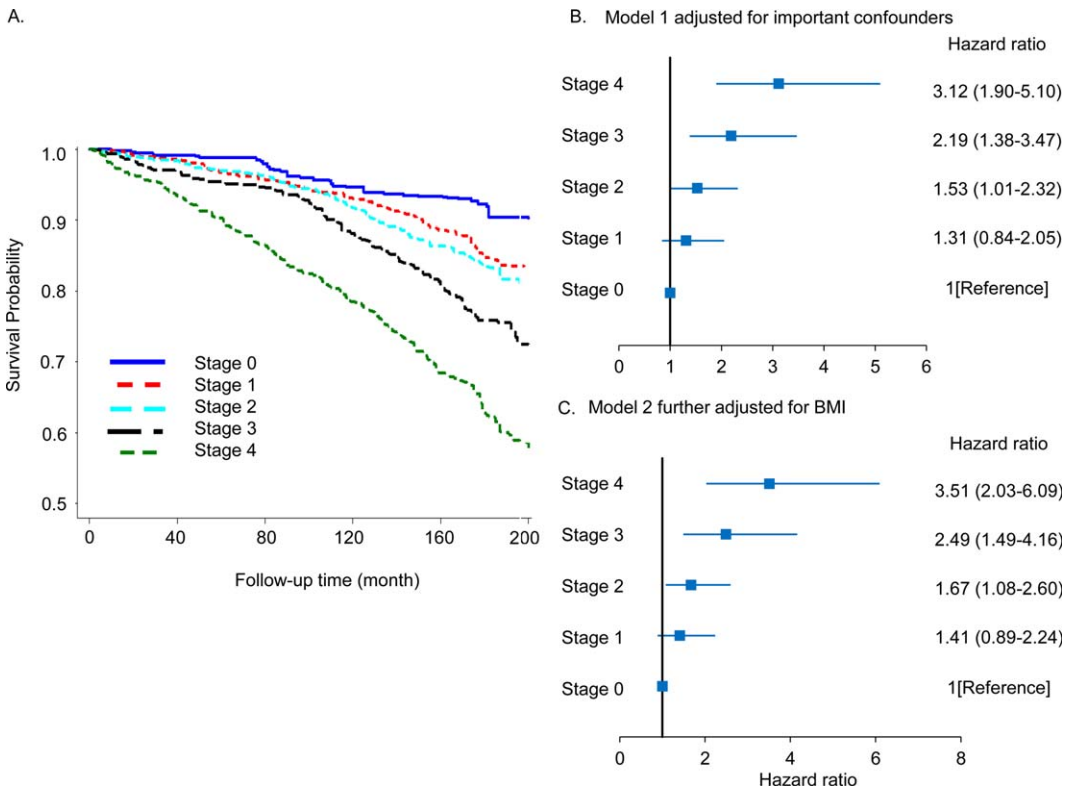

FIGURE 2 (A) Kaplan-Meier plots for all-cause mortality according to risk staging system. (B, C) Adjusted hazard ratios for all-cause mortality for risk staging system. Model 1 adjusted for age, sex, race, income, education, current smoker, and current alcohol drinker, and model 2 additionally adjusted for BMI. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

data provide rationale for increased utilization of OGTT in evaluating cardiometabolic disease risk and for the incorporation of 2-h glucose in CMDS.

Application of CMDS

Thus, we have validated a single staging system for cardiometabolic disease that can be used to estimate risk for both T2DM and all-cause and CVD mortality. CMDS should be studied as a tool to optimize the benefit/risk ratio when selecting interventions with variable safety and efficacy for the prevention or treatment of cardiometabolic diseases risk. Although CMDS can be used as a guideline for any intervention, it is the recent advances in treatment of obesity that have impelled this study. The availability of two new effective medications, phentermine/topiramate ER (8) and lorcaserin (34), has enabled a comprehensive evidence-based medical model for effective and balanced utilization of lifestyle modification, drugs, and bariatric surgery (11). It is important to identify which patients will derive the greatest benefit from these interventions because, with ~70% of US adults being overweight or obese (35), it is not desirable or feasible to treat all patients with medical or surgical therapy. Furthermore, available therapies are often unable to achieve optimal cosmetic results but can dramatically improve both the cardiometabolic and mechanical complications of obesity (8,11,12,34). The patients who will benefit most from therapy have obesity-related complications that can be ameliorated by weight loss.

Currently, BMI is featured predominantly in treatment algorithms that determine therapeutic indications for overweight and obesity, such as that proposed by the NHLBI (12). However, the cardiometabolic and many mechanical complications of obesity exist independent of BMI (4,16,25,28), and may not identify patients who will most benefit from treatment. From this perspective, baseline BMI is less important in targeting patients who will benefit most from weight loss than the existence and severity of complications at baseline (11,13,36). CMDS can be used to identify patients at various degrees of risk for T2DM and CVD mortality, and serve as a guideline for selection of therapeutic modality and intensity. This concept underscores a complications-centric model, as opposed to a BMI-centric model, for obesity management (11,12,23).

Other approaches to risk staging

There are other approaches to risk evaluation for cardiometabolic disease. The clinician should certainly evaluate patients for metabolic syndrome and prediabetes, even though metabolic syndrome has high specificity but low sensitivity for identifying patients with insulin resistance and cardiometabolic disease (25). Various risk scores have also been constructed using information from the history and physical examination (37) or using clinical laboratory assays (38), and these can be used to stage risk in insulin-resistant patients whether or not they meet diagnostic criteria for metabolic syndrome or prediabetes. The Edmonton Obesity Staging System has been

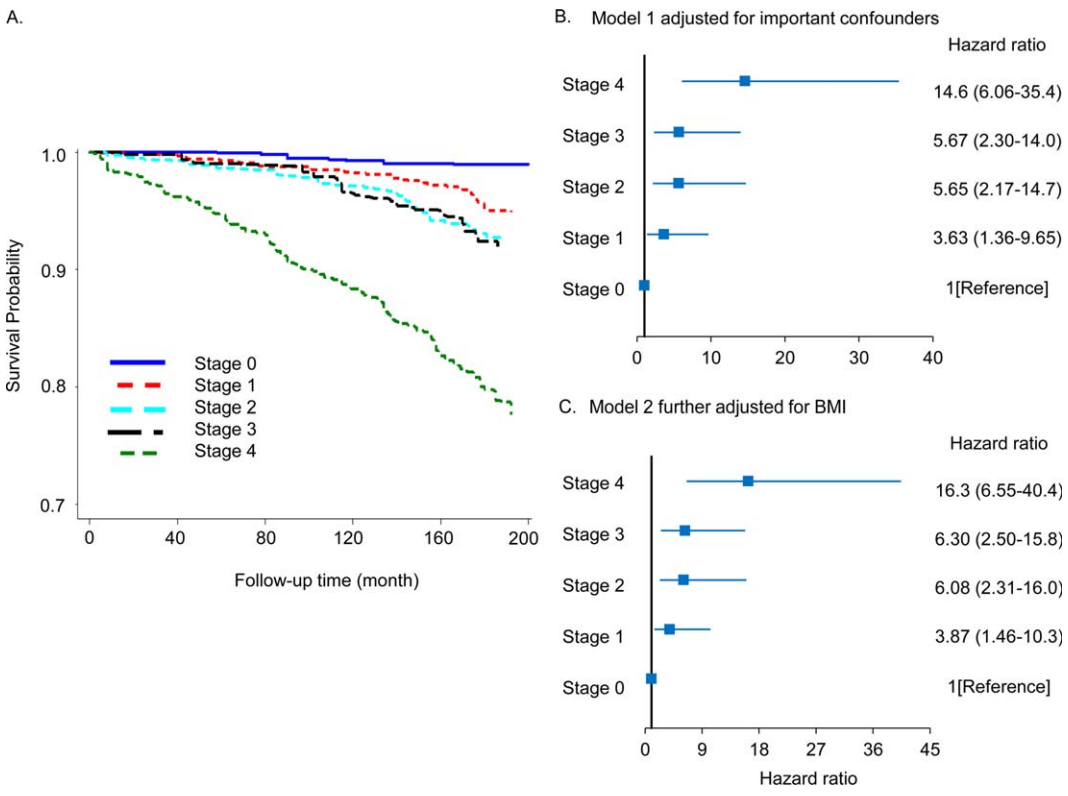

FIGURE 3 (A) Kaplan-Meier plots for CVD mortality according to risk staging system. (B, C) Adjusted hazard ratios for CVD mortality for risk staging system. Model 1 adjusted for age, sex, race, income, education, current smoker, and current alcohol drinker, and model 2 additionally adjusted for BMI. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

developed as a valuable guideline for obesity management and incorporates an assessment of both cardiometabolic disease and mechanical complications (13). The Edmonton system features five stages (stages 0 to 4), and has been validated to predict only all-cause mortality. Even so, CMDS Stages 1, 2, and 3 would all be included in Edmonton Stage 1. As we have clearly demonstrated that there was a significant range of differential risk among patients in CMDS Stages 1 to 3, from this perspective, CMDS provides a more granular dissection of cardiometabolic disease risk.

Study strengths and limitations

Strengths include the use of longitudinal data from two large national cohorts, the CARDIA study and the NHANES III-linked mortality file. The studies involved both genders and several racial/ethnic groups, and this has enabled our findings to be readily applied to the general population. Second, we validated CMDS for predicting risk of incident diabetes, CVD mortality, and all-cause mortality over a wide range of BMI. These aspects substantiate the broad application of CMDS for interventions designed to prevent or treat cardiometabolic disease.

This study also has limitations. NHANES, as in any survey, may have sampling and nonsampling errors. Additionally, only a subset of participants received a glucose tolerance test, and some of those participants did not fast over 8 h, hence they were also excluded from the analysis. The sample size is not large enough to permit extensive subgroup analyses, especially for CVD mortality. Further, mortality follow-up was available only till late 2006, and updated follow-up information has not yet been released. In the CARDIA study, ascertainment of diabetes in year 15 was made by fasting glucose only, whereas diabetes in year 20 was ascertained by both fasting and 2-h OGTT glucose. Finally, clinical trials will be needed to determine whether the application of CMDS will enhance outcomes, benefit/risk ratio, safety, and cost-effectiveness of interventions, such as weight loss therapy, to prevent and treat cardiometabolic disease (e.g., T2DM).

Conclusions

CMDS can discriminate a wide range of risk for diabetes, CVD mortality, and all-cause mortality independent of BMI, and can be used as a risk assessment tool to guide interventions that prevent and treat cardiometabolic disease. In particular, such a tool can be useful in a complications-centric approach to the treatment of obesity (11,39,40), wherein the goal of weight loss is to ameliorate the complications of obesity, particularly those related to cardiometabolic disease risk. Prospective interventional trials are needed to validate whether that application of CMDS, as a guide to the selection of obesity treatment, will enhance patient outcomes and cost-effectiveness of care. The goal is to target treatment intensity, whether involving lifestyle modification, weight loss medication, or bariatric surgery options, to those patients who will derive the greatest benefits from the intervention according to considerations that optimally balance benefit and risk. O

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