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ARTICLE

Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the Princeton Lipid Research Cohort Study

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Abstract
Aims/hypothesis The aim of this study was to determine the long-term associations of a sex- and race/ethnicity-specific metabolic syndrome (MetS) severity *z* score from childhood and adulthood with a future diagnosis of type 2 diabetes mellitus.
Methods We performed a prospective cohort study with evaluations from the Cincinnati Clinic of the National Heart Lung and Blood Institute Lipids Research Clinic (LRC) 1973–1976 and Princeton Follow-up Study (PFS) 1998–2003, and further disease status from the Princeton Health Update (PHU) 2010–2014. We assessed MetS severity as a predictor of incident type 2 diabetes among 629 cohort participants assessed at both the LRC and PFS and 354 participants at the PHU.
Results Cohort participants had a mean age of 12.9 years at baseline (LRC), 38.4 years at the PFS and 49.6 years at the most recent follow-up. Childhood MetS *z* scores were associated with adult MetS *z* scores ($p<0.01$). Compared with individuals who were disease-free at all time-points, those who developed type 2 diabetes by 1998–2003 and 2010–2014 had higher MetS severity *z* scores in childhood ($p<0.05$). For every one-unit elevation in childhood MetS *z* score, the OR of developing future type 2 diabetes was 2.7 for incident disease by a mean age of 38.5 years ($p<0.01$) and 2.8 for incident disease by a mean age of 49.6 years ($p<0.05$). Regarding associations with the change in *z* score from childhood to adulthood, for every one-unit increase in MetS *z* score over time the OR of developing incident type 2 diabetes by a mean age of 49.6 years was 7.3 ($p<0.01$).
Conclusions/interpretation The severity of MetS in childhood was associated with the incidence of adult type 2 diabetes and the degree of increase in this severity predicted future disease. These findings provide evidence of potential clinical utility in assessing MetS severity to detect risk and follow clinical progress over time.

Keywords Insulin resistance · Metabolic syndrome · Risk · Type 2 diabetes mellitus

Abbreviations

AIC	Akaike's information criterion
ATP-III	Adult Treatment Panel-III
CVD	Cardiovascular disease
Hs-CRP	High-sensitivity C-reactive protein
LRC	Lipid Research Clinic
MetS	Metabolic syndrome
NDI	National Death Index
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute Lipid Research Clinic

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PFS	Princeton Follow-up Study
PHU	Princeton Health Update
ROC	Receiver operating characteristic
WC	Waist circumference

Introduction

The high morbidity and mortality from type 2 diabetes mellitus worldwide [1] highlights the need to identify and track risk in children and adults and to motivate patients toward lifestyle interventions [2, 3]. One factor associated with increased future disease risk is the metabolic syndrome (MetS), a cluster of cardiovascular disease (CVD) risk factors, including central obesity, high BP, elevated triacylglycerol, low HDL-cholesterol and elevated fasting glucose [4]. MetS is linked to insulin resistance [5] and obesity [6] and is associated with underlying abnormalities in cellular function [3, 7, 8]. MetS has traditionally been classified based on an individual exhibiting abnormal values for at least three of the five individual components [4]. Using such criteria, MetS has utility in predicting future disease among children [9, 10] and adults [11–15] that in some [12, 13] but not all cases [14, 15] equated to more than the sum of the individual CVD risk factors.

Use of a binary score for MetS has made it difficult to monitor changes in MetS over time [16, 17]. In addition, there appear to be differences in how MetS manifests on the basis of sex and race/ethnicity, with African-American men in particular being classified as having a low prevalence of MetS despite having high rates of type 2 diabetes and death from CVD [18–24]. We thus formulated a sex- and race/ethnicity-specific MetS severity score that takes into account differences in how MetS components segregate by sex and race/ethnicity, both for adolescents and adults [25, 26]. While other continuous MetS scores have been formulated [27, 28], none of these takes into account that the individual MetS components may require different weights in their contribution to MetS.

Such a metric of MetS severity raises potential benefits both for identifying individuals at particularly high risk based on the severity of their MetS score and for following the score over time to track disease progress and response to treatment. We recently reported the potential utility of this score as a predictor of CVD, revealing linear associations of the MetS severity score during childhood with risk for CVD 36.7 years later [29]. It remains unclear whether or not an increase in MetS severity over time also confers additional risk for future development of type 2 diabetes. We hypothesised that, as opposed to standard MetS classification criteria, variations in the severity of MetS—both assessed at baseline and as an increase in severity over time—would be important predictors of later type 2 diabetes development. We assessed this on long-term data from the Princeton Lipid Research Study, a group of white and African-American individuals evaluated for MetS components in childhood/adolescence, with long-term follow-up 25 and 36 years later as adults.

Methods

Participants were originally recruited as part of the Cincinnati Clinic of the National Heart Lung and Blood Institute (NHLBI) Lipid Research Clinic (LRC) Prevalence Program (1972–1978), a multistage survey of lipids and other CVD risk factors [30, 31]. In 1973–1976, the LRC enrolled students in grades 1–12 (ages 6–19 years) in the Princeton school district and a random sample of their parents. The Institutional Review Boards of NHLBI, the University of Cincinnati, West Virginia University and the University of Virginia approved the study and/or its analysis. The Princeton Follow-up Study (PFS, 1998–2003) was a 25–30 year follow-up of these student and parent-participants to prospectively assess changes in CVD risk factors from childhood into the fourth to fifth decades of life [9]. PFS eligibility required participation in LRC visits where lipoproteins were measured and participation of a first-degree relative at those same visits, with a 65% recruitment of eligible participant families. The Princeton Health Update (PHU, 2010–2014) was performed 8–14 years after the PFS to assess updated disease status of PFS participants. Participants in each of these studies provided informed consent.

Data were obtained by telephoning or mailing participants and first-degree relatives using a standardised questionnaire and by examining death certificates from the National Death Index (NDI) for cause of death. Inclusion criteria for the primary analysis of these participants were: LRC age <20 years and complete information on MetS and its components, and both the LRC and PFS visits. Participants with triacylglycerol values >2.26 mmol/l (200 mg/dl), LDL-cholesterol values >4.66 mmol/l (180 mg/dl), or glucose values >7.0 mmol/l (126 mg/dl) at the LRC visit were excluded from the analysis.

Clinical measures In both the LRC and PFS studies, data were collected via standard protocols [9, 30, 31], including measures of height and weight in the LRC [32] and height, weight and waist circumference (WC) in the PFS [9]. WC was measured in the PFS at the level of the umbilicus following normal expiration. In the LRC and PFS, BP was measured on a participant's right arm with a standard sphygmomanometer after sitting for 5 min. In the LRC and PFS, fasting blood was drawn and tested for lipid profiles in LRC–Centers for Disease Control and Prevention standardised laboratories. In the LRC, glucose was measured on the ABA-100 (Abbott Laboratories, North Chicago, IL, USA) by a hexokinase method [33]. In the PFS, glucose was measured on the Dade Dimension Xpand (Dade Behring, Deerfield, IL, USA), by the hexokinase-

glucose-6-phosphate-dehydrogenase method [34]. Diabetes was classified based on self-report or fasting glucose ≥7.0 mmol/l (126 mg/dl) at in all three studies.

Traditional MetS was defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel-III (ATP-III) criteria [4]. Specifically, participants had to meet three or more of the following five criteria: (1) concentration of triacylglycerol ≥1.69 mmol/l (150 mg/dl); (2) HDL-cholesterol level <1.04 mmol/l (40 mg/dl) for men and <1.3 mmol/l (50 mg/dl) for women; (3) WC ≥102 cm for men and 88 cm for women; (4) glucose concentration ≥5.55 mmol/l (100 mg/dl); (5) systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg. MetS in childhood was defined using a modification of these criteria [9, 35] in which participants had to meet three or more of the following criteria: (1) concentration of triacylglycerol ≥1.24 mmol/l (110 mg/dl); (2) HDL-cholesterol level ≥1.04 mmol/l (40 mg/dl); (3) BMI ≥90th percentile; (4) glucose level ≥5.55 mmol/l (100 mg/dl); (5) systolic or diastolic BP ≥90th percentile (age, height and sex-specific) [36].

The MetS severity *z* score was calculated for adolescents at their LRC visit and then again as adults during their PFS visit using formulas published elsewhere [25, 26]. Briefly, these scores were formed using confirmatory factor analysis of the five traditional components of MetS (as mentioned above) to determine the weighted contribution of each of these components to a latent MetS 'factor' on a sex- and race/ethnicity-specific basis. Confirmatory factor analysis was performed on data from the National Health and Nutrition Examination Survey (NHANES) for adolescents aged 12–19 years [25] and adults aged 20–64 years [26]. The adolescents and adults were divided into six subgroups based on sex and the following self-identified race/ethnicities: non-Hispanic white, non-Hispanic black and Hispanic. For each of these six population subgroups, loading coefficients for the five MetS components were determined toward a single MetS factor. The loading coefficients were then used to generate equations to calculate a standardised MetS severity score for each subgroup (http://publichealth.hsc.wvu.edu/biostatistics/metabolic-syndrome-severity-calculator/, accessed 24 August 2015). These MetS severity scores are *z* scores (ranging from negative infinity to positive infinity) of relative MetS severity on a sex- and race/ethnicity-specific basis and are highly correlated to other surrogate markers of MetS risk, including high-sensitivity C-reactive protein (hs-CRP), uric acid and the homeostasis model of insulin resistance [25, 26]. In calculating these scores in the present study, individual measures of participants from the LRC and PHS were entered into these equations to calculate MetS severity as children and adults, respectively. For the LRC visit, BP data were missing for 185 of the 629 participants; for these individuals, systolic BP was estimated to be in the 50th percentile of normal based on published equations for sex, age and height percentile [36]. A sensitivity analysis of the data eliminating these individuals with imputed data did not alter the study's findings.

Statistical analysis All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Comparisons between groups for continuous and categorical variables were performed using *t* tests and χ^2 tests, respectively. Pearson's *r* correlation was calculated to estimate linear associations between MetS severity *z* scores at LRC and PFS visits. Mean (SD) severity *z* scores were calculated at both LRC and PFS visits, and compared between those participants who did not self-report with diabetes at either visit and those who self-reported diabetes at each of the two later visits. Given the lack of information on the precise date of the event (i.e. interval-censored data) and the primary interest in a time-varying predictor (MetS score), as well as an interest in clinical interpretation of the odds of future disease, the use logistic regression analysis was chosen over survival methods. Logistic models were fit estimating the odds of incident diabetes at the PFS and then again at the PHU (excluding those individuals who reported disease at the PFS). These models included traditionally defined MetS as well as the MetS severity *z* score, with comparisons made between the two using Akaike's information criterion (AIC). Smaller AIC values indicate a better model fit of the outcomes. Since the intent was to determine the predictive value of future disease/outcomes, models that included MetS severity scores included those scores at 'baseline' (LRC) and the change in score from the LRC to the PFS. Such models allow both for interpretation of the predictive value of a childhood score measured in a clinical setting and for monitoring of the score over time. Likewise, for models of type 2 diabetes by the PHU as an outcome, individuals who developed disease by the PFS visit were excluded. For models of incident disease that included the severity score as a predictor, receiver operating characteristic (ROC) curves were produced to display the ability of this new score to discriminate between those who developed future disease and those who did not, quantified by the AUC. An AUC value of 0.5 indicates no discriminative ability and a value of 1.0 indicates perfect predictive ability.

Results

Participant characteristics We evaluated data from 629 participants with adequate data from the LRC and PFS for analysis of MetS severity. Of the 629 participants, 354 were contactable or had NDI data available for disease status update in the PHU (Table 1; electronic supplementary material [ESM] Table 1 provides a further breakdown by sex and race/ethnicity). The remainder of participants in the analytic cohort was lost to follow-up. Compared with those not evaluated in the PHU, those with updated data were more likely to

Table 1 Descriptive statistics

Variable	LRC 1973–1976	PFS 1998–2003	PHU 2010–2014
n	629	629	354
Mean (SD)			
Age, years	12.9 (3.3)	38.4 (3.5)	49.6 (3.5)
BMI, kg/m^2	19.9 (4.3)	28.7 (6.8)	–
Waist, cm	–	97.2 (16.7)	–
Glucose, mmol/l	4.72 (0.44)	5.0 (1.51)	–
Glucose, mg/dl	85.1 (8.0)	90.1 (27.2)	
HDL-cholesterol, mmol/l	1.41 (0.30)	1.18 (0.37)	–
HDL-cholesterol, mg/dl	54.5 (11.7)	45.6 (14.3)	
Triacylglycerol, mmol/l	0.81 (0.33)	1.49 (1.25)	–
Triacylglycerol, mg/dl	71.5 (29.0)	132.3 (110.3)	
Systolic BP, mmHg	102.7 (12.7)	120.4 (14.9)	–
Diastolic BP, mmHg	63.3 (11.0)	79.6 (10.9)	–
MetS *z* score	−0.5 (0.7)	0.1 (1.1)	–
Frequency (%):			
Male	275 (43.7)	275 (44.5)	142 (40.1)
White	437 (69.5)	451 (69.5)	269 (76.0)
Overweight[a]	76 (12.1)	204 (32.4)	–
Obese[a]	58 (9.2)	217 (34.6)	–
MetS	17 (2.7)	201 (32.0)	–
Type 2 diabetes[b]	–	30 (5.0)	48 (13.6)
Myocardial infarction[b]	–	3 (0.5)	9 (2.6)
Stroke[b]	–	1 (0.2)	8 (2.4)
Angioplasty, stent, bypass or other heart surgery[b]	–	1 (0.2)	10 (2.9)
CVD[b]		5 (0.9)	20 (5.8)
Deceased [b]	–	0	5 (1.5)

Participants with valid MetS severity *z* scores at LRC and PFS visits, ability to safely classify MetS status at LRC and PFS visits, and <20 years old at LRC

[a] Overweight=BMI ≥85th percentile for LRC, ≥25th percentile for PFS; Obese=BMI ≥95th percentile for LRC, ≥30th percentile for PFS

[b] Cumulative frequencies by the designated visit

be female (60% vs 52%; p=0.039) and white (76% vs 61%; p<0.001) but had similar baseline MetS scores (mean scores −0.47 vs −0.49; p=0.776). Participants had a mean age of 12.9 years in the LRC, 38.4 years in the PFS and 49.6 years at the PHU visit. There was a low prevalence of overweight (12.1%) and obesity (9.2%) during the LRC compared with the PFS (32.4% and 34.6%, respectively). As expected, each of the components of MetS was more abnormal during the PFS than during the LRC visit. During the LRC, participants had a childhood/adolescent MetS severity *z* score of −0.5 compared with an adult MetS *z* score of 0.1 during the PFS. During childhood, participants had a low prevalence of MetS by traditional criteria (2.7%) that increased greatly by the PFS (32.0%). At the PFS and PHU, respectively, 5% and 13.6% of individuals had diabetes and 0.9% and 5.8% had CVD. By the PHU visit, 1.5% of cohort members accounted for had died.

MetS severity predicting type 2 diabetes There was a high degree of correlation in MetS severity score between childhood at the LRC and mid-adulthood at the PFS visit (r=0.41; p<0.01 [Fig. 1]). Figure 2 provides MetS severity scores at the LRC and PFS visits by diabetes disease status for three groups of individuals: (1) those who did not have diabetes at any of the three visits; (2) those who developed type 2 diabetes between the LRC and PFS visits; (3) those who developed type 2 diabetes between the PFS and PHU. In each case, MetS severity scores in childhood and adulthood were lowest among those who never had disease, highest among those who developed diabetes by the PFS (mean age 38.4 years) and intermediate among those who developed diabetes later (between the PFS and PHU, by a mean age 49.6 years; Fig. 2).

Figure 3 displays ROC curves evaluating risk of incident diabetes, using MetS severity either from the LRC or the PFS.

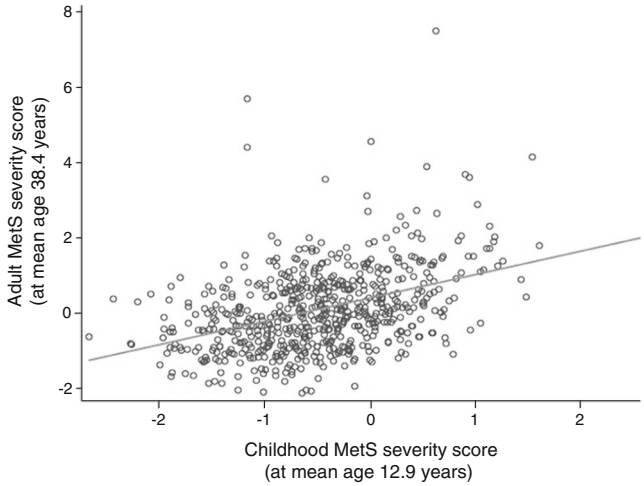

Fig. 1 Correlation of MetS severity scores within individuals over time. MetS severity *z* scores on the *x*-axis during childhood (LRC, 1973–1976) and on the *y*-axis during adulthood (PFS, 1998–2003). Pearson's $r=0.41$ ($p<0.01$)

As a linear measure, childhood MetS severity was significantly associated with risk of diabetes 24–41 years later (AUC 0.69 and 0.68 by PFS and PHU visits, respectively [Fig. 3]). MetS severity in adulthood at the PFS was also linked to diabetes incidence over the ensuing 6–14 years (AUC 0.89).

Using logistic regression, each 1.0 *z* score increase in childhood MetS severity score carried elevated OR of 2.7 for incident diabetes by the PFS (both $p<0.001$) and 2.8 for incident diabetes between the PFS and PHU (both $p<0.05$ [Table 2]). When change in MetS severity score from the LRC to the PFS was added to the baseline LRC MetS severity score in the model, the OR for incident diabetes by the PHU was further elevated to 7.3 ($p<0.01$). AIC values indicate that compared with the use of traditional MetS criteria as a predictor of diabetes, using MetS severity scores provide a better fit of outcomes at both time points, particularly when using LRC scores and the change from LRC to PFS.

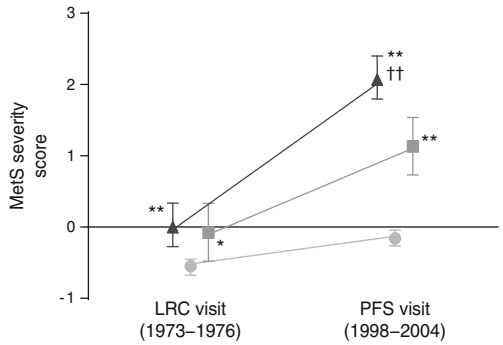

Fig. 2 Mean MetS severity scores within individuals by later diabetes status. MetS severity *z* score (mean, 95% CI) by disease status for diabetes. Scores shown are those obtained during childhood (LRC) and adulthood (PFS) among individuals who remained disease-free at LRC, PFS and PHU visits (grey circle, $n=310$), those who were disease-free at the PFS but later developed disease by the PHU visit (grey square, $n=17$), and those with incident disease between LRC and PFS visits (black triangle, $n=30$). Comparison with disease-free group: $^{*}p<0.05$, $^{**}p<0.01$. Comparison with incident disease between PFS and PHU: $^{\dagger\dagger}p<0.01$

Discussion

We found that the degree of severity of MetS as a linear measure in childhood and adulthood served as a predictor of future diabetes over 36 year and 11 year periods, respectively. This association was overall modest during childhood (AUC on the ROC curve 0.68) and stronger during adulthood (AUC 0.89). Moreover, the change in MetS severity *z* score from adolescence to adulthood conveyed further disease risk. Thus, the MetS severity score functioned similarly to that for the prediction of CVD [29]. Given that the current obesity epidemic begins early in life, tools are needed both to identify those at highest risk for future disease and to motivate individuals toward lifestyle changes [3]. The MetS severity *z* score—which could possibly be calculated automatically using electronic medical records—holds potential for clinical use, such as a screening tool to identify individuals in childhood and mid-adulthood who are at high risk for future diabetes, who would particularly benefit for preventative interventions [37]. Moreover, as a linear measure, the score could be used to monitor within-individual changes in MetS severity, including assessment of the effectiveness of treatments to decrease MetS severity.

The majority of previous work on MetS used dichotomous criteria whereby MetS was classified when an individual exceeded population-based cut-off values for three or more of the individual MetS components [4, 11, 38]. There has been some controversy regarding which of these criteria to use, both in adults [39] and among children [40]. We elected to use either the commonly employed ATP-III criteria (for adults [4]) or a version of these adapted for use in adolescents [35]—though clearly our results may have differed had we chosen a different set of criteria.

These traditional MetS criteria were effective in the present cohort in identifying increased risk of future diabetes, with ORs of 4.4 for MetS in childhood (based on relatively small numbers) and 9.7 in mid-adulthood compared with individuals without MetS. However, the criteria have several limitations: (1) an inability to assess for changes in MetS over time (with the exception of its presence or absence); (2) an inability to assess risk among individuals who have measures of multiple MetS components that lie just outside of the cut-offs; (3) attribution of equal importance to each individual MetS component, despite evidence that certain components such as elevated WC or high triacylglycerol levels are more highly associated with MetS risk over time [41, 42] and may be more tightly linked to the abnormal cellular processes underlying MetS [7]. The MetS severity *z* score accounts for the

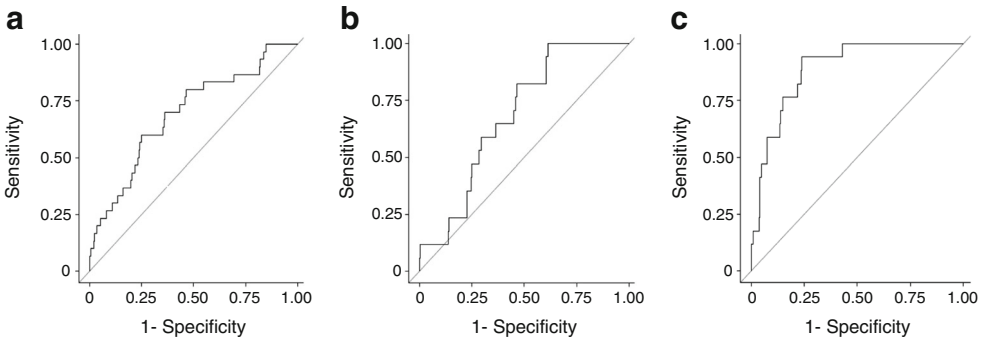

Fig. 3 ROC curves displaying predictive value of MetS severity scores for future diabetes. Childhood MetS severity *z* score (LRC, 1973–1976) predicting incident diabetes by the (**a**) PFS (2000–2004; AUC 0.69) and (**b**) PHU (2010–2014; AUC 0.68). (**c**) Adult MetS severity *z* score (PFS) predicting incident diabetes by the PHU (AUC 0.89)

limitations of traditional criteria and produces a score that is linearly associated with risk for diabetes.

An additional problem with current binary criteria for MetS has been racial/ethnic variation in this score, particularly among African-American men, who have a high prevalence of diabetes and death from CVD but paradoxically a low prevalence of MetS as determined by traditional criteria [18–22, 24]. It is primarily for this reason that we took race/ethnicity into account in formulating the MetS severity *z* scores. Nevertheless, while the current cohort had both white and African-American participants, there were too few study participants overall to assess for any added benefit of this score regarding racial/ethnic differences in MetS. Thus, further analyses in larger multi-ethnic cohorts are needed to confirm any potential benefit of this score on a race/ethnicity-specific basis.

While the durability of MetS within an individual has been disputed when using traditional criteria [16, 17], we found a moderate degree of association (R^2=0.18) of MetS severity scores between childhood and 26 years later. It is important to note that the equations to calculate these childhood and adult severity scores were derived separately from NHANES data, producing *z* scores of MetS severity relative to a group of adolescents aged 12–19 years and a group of adults aged 20–64 years. Using these measures, the present cohort at baseline (mean age 12.9 years) had a below-average MetS severity *z* score of −0.5. This lower score may have been related to the younger age of this cohort at baseline or to the lower degree of obesity seen when the cohort was evaluated in the early 1970s (9.7%) compared with the derivation population in 1999–2010 (19.2%). As adults with mean age 38.4 years, there remained a relatively low severity *z* score of 0.1 (i.e. near the mean for all adults) that may again reflect that participants had ages in the middle of the adult range, and potentially that they had completed their childhood growth in the mid-1980s prior to the current US obesity epidemic. MetS appears to be produced by genetic factors and multiple pathophysiological processes, including cellular dysfunction, oxidative stress and low-grade inflammation—processes that are also associated with insulin resistance [3, 7, 8]. These MetS severity *z* scores had previously been associated with surrogates for these processes, including uric acid, hs-CRP and fasting insulin levels [25, 26]. The high correlation between these scores over 26 year suggests a degree of durability of MetS in a given

Table 2 Odds of future type 2 diabetes using traditional MetS criteria and MetS severity *z* scores

	Incident diabetes by PFS visit		Incident diabetes by PHU visit[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
MetS at LRC	4.4 (1.2, 16.4)	0.0249	7.8 (1.4, 43.8)	0.0189
Model AIC	238.95		132.39	
MetS at both time points				
LRC			3.5 (0.6, 20.8)	0.1745
PFS			5.2 (1.8, 15.0)	0.0023
Model AIC			124.87	
MetS severity *z* score at LRC	2.7 (1.6, 4.4)	0.0001	2.8 (1.3, 6.0)	0.0093
Model AIC	227.68		129.01	
MetS severity *z* score at				
LRC			7.6 (3.0, 19.4)	<0.0001
Change in score (PFS – LRC)			7.3 (3.0, 17.3)	<0.0001
Model AIC			101.98	

[a] Excluding prevalent cases of diabetes at PFS

individual over time or a genetic susceptibility that is manifest already in childhood.

As a predictor of future disease, the MetS severity *z* score functioned overall similarly in predicting diabetes and CVD [29]. The ORs for each 1.0 increase in the childhood MetS severity *z* scores in predicting diabetes and CVD by a mean age of 38.4 years were 2.7 and 9.8, respectively, and 2.8 and 2.4 for predicting type 2 diabetes and CVD, respectively, by a mean age of 49.6 years. The improved performance in predicting CVD is somewhat surprising given that MetS has been viewed as being more strongly associated with incidence of type 2 diabetes than CVD [11]. Nevertheless, the links between childhood MetS and future disease for both diagnoses underscores the potential utility for this score in assessing future risk and motivating toward early lifestyle change.

While a key benefit of linear MetS severity scores is in following for change over time, the clinical use of cut-off values can provide added utility to determine elevated risk. We were unfortunately unable to determine cut-off values due to limitations in sample size. Further evaluations of MetS severity scores in other longitudinal cohorts are needed to generate cut-off levels corresponding to high risk for future disease. These cut-offs could then be used to guide the initiation of targeted adjunct therapies, while less severe elevations in MetS severity could serve on a larger-scale basis as a trigger for insulin-sensitising lifestyle therapy for optimal prevention overall.

This study had several additional limitations. We lacked BP data on 185 children in the LRC and imputed BP data for these participants; however, eliminating these participants from the analysis did not alter the study's findings. Our analysis was based on an outcome (incidence of diabetes) that had occurred in only 30 individuals by the PFS visit and in 48 individuals by the PHU visit. For the PHU study, we were unable to obtain complete follow-up and relied on self-report of outcomes without adjudicated outcomes or in-person assessments of MetS severity status. While the cohort had both white and African-American participants, Hispanic participants were lacking, reflecting the population base from which they were drawn in the early 1970s. However, the study also had several strengths, including 37 year follow-up in a biracial cohort originally studied as children in the 1970s.

In summary, we found that a sex- and race/ethnicity-specific MetS severity *z* score had modest within-person durability over a 26 year period and predicted future diabetes based both on baseline values in childhood and adulthood and on the change in score between these time points. These data provide evidence for a role for MetS severity as a marker of disease risk and suggest potential clinical utility in following MetS severity over time. Future research in determining risk thresholds in the score is still needed.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Author contributions MDD, MJG, JGW and JAM designed the study. JGW and JAM oversaw participant recruitment and data collection. MDD and MJG planned the analysis. MJG performed the analysis. MDD, MJG, JGW and JAM wrote the manuscript. All authors have read and given final approval of the manuscript. MDD is responsible for the integrity of the work as a whole.

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