Development of a Childhood Metabolic Syndrome Risk Score for Predicting Adult Disease

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Introduction

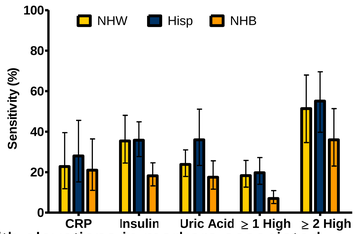
- The metabolic syndrome (MetS) is a cluster of clinical indices that increase risk for Type 2 diabetes (T2DM) and coronary artery disease (CAD).
- The diagnosis of MetS is based on cut-off points for these different components, including waist circumference, triglycerides, HDL cholesterol, blood pressure, and fasting glucose.
- However, the best way to diagnose MetS in children remains unclear, and current attempts result in racial/ethnic discrepancies.

Metabolic Syndrome: Ethnic Differences

- Initial research using NHANES demonstrates that the commonly-used pediatric adaptation of the ATP III definition of MetS (table below) is not sensitive to elevations in CRP (> 4.5), fasting insulin (> 16), and uric acid (> 5.5 for girls, > 7.0 for boys), and this sensitivity is worse for African Americans in particular.

Risk Factor*	Pediatric Adaptation of ATP III MetS
Obesity	Waist Circ. > 90%
Hypertension	SBP or DBP > 90% for age, sex, and height
Triglycerides	≥ 110 mg/dL
HDL	≤ 40 mg/dL
Fasting glucose	≥ 100 mg/dL

* "MetS" if ≥ 3 elevations



- Conclusion: Many individuals with elevations in markers associated with long-term T2DM/CAD risk are not identified as having MetS using the most popular definition of MetS

A Continuous Risk Score vs. Traditional MetS Criteria

- Individuals with borderline high values of MetS components may not be classified as having MetS.

Patient 1: 15 y.o. White female

Component values	Cut-off (ATP III criteria)
WC 100 cm*	89 cm
FBG 90 mg/dL	100 mg/dL
TG 112 mg/dL*	110 mg/dL
HDL 38 mg/dL*	40 mg/dL
SBP 119 mmHG	123 mm HG

Traditional MetS Criteria: (+) MetS Diagnosis (elevations in 3 components)

Theoretical MetS "Risk Score": Risk score 135 (moderate risk)

Patient 2: 17 y.o. African-American female

Component values	Cut-off (ATP III Criteria)
WC 100 cm*	94.6 cm
FBG 95 mg/dL	100 mg/dL
TG 100 mg/dL	110 mg/dL
HDL 41 mg/dL	40 mg/dL
SBP 125 mmHG*	125 mm HG

Traditional MetS Criteria: (-) MetS Diagnosis (elevations in only 2 components)

Theoretical MetS "Risk Score": Risk score 132 (moderate risk)

Methods

- Ideal: Use long-term data on children to develop predictive equations of real outcomes (T2DM, CAD). Unfortunately, a dataset of sufficient size does not exist to our knowledge.
- Using 1999-2008 data from children ages 12-19 years old in the National Health and Nutrition Examination Survey (NHANES), we performed a confirmatory factor analysis (CFA) to accomplish the following goals:
  1. Assess whether a single underlying factor can explain the (co)variability of the traditional MetS components that have clinical utility (BMI z-score, systolic blood pressure (SBP), triglycerides, HDL, fasting glucose).
  2. Test whether the correlation of these components with this single "MetS" factor varies by sex and/or race/ethnicity.
  3. If a CFA reveals that a one-factor model is useful, utilize the standardized scoring coefficients (either common across sex and race/ethnicity, or allowed to vary based on (2)) as the basis of a MetS risk score.
- In the absence of long-term data, we assessed the ability of the resulting MetS risk score to predict elevations of serum factors associated with long-term risk for T2DM and CAD: fasting insulin, C-reactive protein, and uric acid.

Results: Single-Factor Confirmatory Factor Analysis

- Two single-factor confirmatory factor analyses including BMI z-score, SBP, triglycerides, HDL, and fasting glucose were performed on 3,815 children and adolescents from NHANES.
  1. Single factor common across sex and race/ethnicity combinations (non-Hispanic white (NHW), Hispanic, and non-Hispanic black (NHB))
  2. Single factor, allowing the loadings of the components to vary by sex and race/ethnicity
     - The equality of factor loadings was tested across groups in a stepwise fashion, constraining loadings across groups for components when the tests was not significant
- Final single factor model → Glucose was removed from all models (factor loadings < 0.30)
  → Only triglycerides were varied by group ($p < 0.01$)

	One Factor	One Factor: Sex and Race/Ethnicity Specific for Triglycerides					
Model Fit Indices							
Chi-square (df)	160.15 (2)	183.15 (27)					
AIC	156.15	129.15					
RMSEA	0.14	0.10					
SRMR	0.05	0.06					
CFI	0.89	0.90					
NNFI	0.68	0.87					
		Males			Females		
		NHW	NHB	Hisp	NHW	NHB	Hisp
Factor Loadings*							
BMI	0.52	0.61	0.61	0.61	0.61	0.61	0.61
SBP	0.28	0.32	0.32	0.32	0.32	0.32	0.32
HDL	0.63	0.55	0.55	0.55	0.55	0.55	0.55
Triglycerides	0.58	0.64	0.53	0.66	0.29	0.31	0.59

- A single factor provides an adequate fit when analyzing BMI z-score, SBP, HDL, and triglycerides in adolescents
- This factor does not correlate with fasting glucose
- This factor correlates differently with triglycerides depending on sex and race/ethnicity

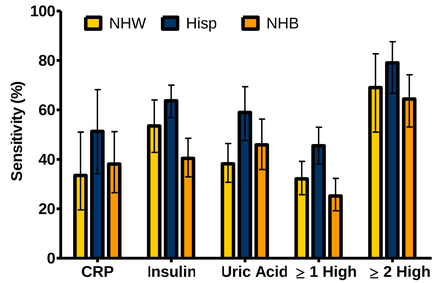
Results: Validity of a Metabolic Syndrome Score

- Use of the resulting factor score from the final CFA as a "MetS risk score" was validated using cross-sectional data from NHANES

1. Area under the curves (AUC) from receiver operating characteristic (ROC) analyses were estimated, measuring the predictive ability of the MetS score to identify "high" levels of CRP, fasting insulin, uric acid (as well as predict a traditional MetS diagnosis).

	MetS Diagnosis	High CRP	High Insulin	High Uric Acid	≥ 1 Elevations	≥ 2 Elevations
AUC	0.96	0.71	0.82	0.76	0.70	0.88

2. Using a simple cut-off of one SD above the mean as a new definition of "MetS", sensitivities for high levels of these markers were estimated to compare with the traditional "MetS". Prevalences of the "traditional" MetS and the "new" MetS (based on this risk score) were compared by ethnicity.



	Rate of: "Traditional" MetS	Rate of: "New" MetS
Overall	8.4	15.9
NHW	8.6	15.3
Hisp	10.8	21.9
NHB	4.4	11.7

Conclusions

- A careful series of single-factor confirmatory factor analyses confirms that while most of the traditional MetS components are associated with a single MetS factor, the level of association for triglycerides varies by sex and race/ethnicity.
  - Triglycerides is not strongly associated with this MetS factor for NHW and NHB females.
  - Glucose is not associated with this MetS factor for any group
- The focus was on components that are clinically accessible and valid, with the goal that the resulting score from the final CFA could be used as a MetS "risk score"
  - BMI z-score over waist circumference
  - Fasting glucose over insulin
- The resulting MetS "risk score" improves on the ability to predict elevations of serum factors associated with long-term risk for T2DM and CAD, for all racial/ethnic groups
- Next steps: Use these outcomes to further refine this score and presumably improve its ability to predict long-term disease

Acknowledgments

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