Defining the Metabolic Syndrome in Children and Adolescents: Will the Real Definition Please Stand Up?

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Objectives To review the use of definitions of the metabolic syndrome in studies of children and adolescents and to review results from studies that used factor analysis to examine structure among cardiometabolic variables.

Study design Literature review.

Results In 27 publications, authors used 40 unique definitions of the metabolic syndrome. Most of these definitions were adaptations of the adult definition developed by the National Cholesterol Education Program. In 11 studies that used exploratory factor analysis, the number of components ranged from 5 to 19, and the number of factors identified ranged from 1 to 5.

Conclusions The use of multiple definitions of the metabolic syndrome argues strongly for the development of a standard pediatric definition. *(J Pediatr 2008;152:160-4)*

The metabolic syndrome, which predisposes those affected to development of diabetes and cardiovascular disease, is a cluster of anthropometric, physiological, and biochemical abnormalities tied together by incompletely understood underlying mechanisms. In an early incarnation, the syndrome was described as consisting of hypertension, hyperglycemia, and hyperuricemia.[1] In 1988, Reaven[2] drew new attention to the field by focusing attention on the links between insulin resistance and many of the abnormalities associated with the metabolic syndrome. Although he referred to it as "syndrome X," another name that gained traction was the insulin resistance syndrome, in recognition of the role of insulin resistance. Until 1998, researchers had to cope with the lack of a standard definition, and, not surprisingly, the syndrome was defined in a myriad of ways, possibly impeding progress in delineating its pathophysiology and pathogenesis. In 1998, the World Health Organization (WHO)[3,4] was the first major organization to propose a standard definition for the syndrome. In response, the European Group for the Study of Insulin Resistance (EGIR) countered with a modification of the definition.[5] Next, the National Cholesterol Education Program[6,7] developed a definition that was simpler to implement in research and clinical practice. Subsequently, the American Association of Clinical Endocrinologists held a workshop to review the metabolic syndrome, and another definition emerged from these efforts.[8,9] A recent definition was offered by the International Diabetes Federation in 2005.[10]

After 2001, the pace of research into the metabolic syndrome in adults accelerated, possibly as a result of efforts to develop standard definitions, especially the one formulated by the National Cholesterol Education Program (NCEP). However, research relating to the metabolic syndrome in children and adolescents hummed along at a much slower pace. In contrast to the definitions of the metabolic syndrome in adults, no standard definition for use in pediatric populations exists. Nevertheless, interest in the metabolic syndrome among children and adolescents has blossomed, undoubtedly fueled by the secular trends in pediatric obesity and by the recognition of the high prevalence of the metabolic syndrome in adults. The development of a standard pediatric definition should benefit researchers and clinicians and bring some degree of standardization to the field. Having a standard definition would facilitate the conduct of surveillance for this syndrome in

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EGIR	European Group for the Study of Insulin Resistance	NCEP	National Cholesterol Education Program
HOMA	Homeostasis model assessment	WHO	World Health Organization

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populations of children, facilitate international comparisons of prevalence estimates, help in unraveling pathogenic mechanisms, serve in the conduct and interpretation of clinical trials, and assist clinicians in diagnosing and managing the syndrome.

The objectives of this study were to review definitions that have been used by researchers, primarily subsequent to the release of the WHO definition for adults, and to review information generated by studies applying factor analysis to sets of components related to the metabolic syndrome.

METHODS

We used PUBMED to look for studies, conducted among children and adolescents subsequent to the release of the WHO definition of the metabolic syndrome in 1998, in which the metabolic syndrome was defined or in which factor analysis was used to examine the underlying structure among a set of cardiometabolic factors. Additional studies were identified by reviewing cited reference in retrieved publications and by reviewing the authors' personal files.

For publications of definitions of the metabolic syndrome, we abstracted the following data from each publication: authors' names, year of publication, number of participants, age range or mean age, criteria used in the definition, the adult definition that the authors either adapted or appeared to adapt, and prevalence of the syndrome. For publications that used factor analysis, we abstracted the following data from each publication: authors' names, year of publication, number of participants, age range or mean age type of factor analysis (exploratory or confirmatory), variables used in factor analysis, and number of factors identified.

RESULTS

Definitions in Current Use

We found at least 27 articles with 46 definitions of the metabolic syndrome, most of them unique (Table I; available at www.jpeds.com).[11-37] A few studies applied adult definitions to the young participants.[18,20,35] Twenty-eight emulated the NCEP model, 9 the WHO model, 3 the EGIR model, 1 the American Association of Clinical Endocrinologists model, and the remainder had unique definitions. Unless the model was specifically specified, we assigned studies that defined the metabolic syndrome on the basis of the presence of a certain number of components as having emulated the NCEP approach and studies that considered the presence of impaired fasting glucose, impaired glucose tolerance, diabetes mellitus, or insulin resistance (or its surrogate measure) as a mandatory requirement along with 2 or more additional criteria as having emulated the WHO approach. Use of 3 or more abnormalities to define the syndrome was common. All the studies used multiple components, all but 2 studies[11,22] used either body mass index or waist circumference as the anthropometric measure of choice, all included concentrations high-density lipoprotein cholesterol and triglycerides, all included systolic blood pressure or diastolic blood pressure, and all but 2 included a determination of concentration of blood glucose.[11,14] The criteria used to determine high blood pressure and hyperglycemia were most consistent across studies. Percentiles used to define elevated blood pressure ranged from the 75th to the 95th percentile. The 1996 guidelines developed by the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents were commonly used.[38] However, guidelines from other countries were used as well. Hyperglycemia was generally defined as either ≥100 mg/dL or ≥110 mg/dL according to guidelines from the WHO and the American Diabetes Association. The 90th percentile was a commonly used threshold for waist circumference, but there was some variation in the way that these values were standardized for age, sex, or ethnicity. Thresholds for concentrations of triglycerides were quite variable. Percentile thresholds ranged from the 75th percentile to the 95th percentile and thresholds expressed in units ranged from about 80 mg/dL to about 177 mg/dL.[35] Thresholds for percentiles of concentrations of high-density lipoprotein cholesterol ranged from the 5th to the 25th percentile, and thresholds for units of concentrations of high-density lipoprotein cholesterol ranged from 35 mg/dL to 45 mg/dL for males and 39 mg/dL to 50 mg/dL for females. However, many studies used a single threshold for high-density lipoprotein cholesterol for both males and females. Twelve studies included hyperinsulinemia or homeostasis model assessment (HOMA) as one of the components.[11,12,14,17,18,20,22,23,25,28,30,36]

Factor Analysis

We identified at least 11 studies that had used exploratory factor analysis to examine the structure among a starting set of variables that included ones commonly believed to be related to the metabolic syndrome (Table II; available at www.jpeds.com).[16,17,39-47] The number of components included in these analyses ranged from 5 to 19, and the number of factors identified ranged from 1 to 5. Studies with a higher starting number of components tended to produce a larger number of factors. All studies used a measure of blood pressure (usually systolic blood pressure and diastolic blood pressure). All studies but one[42] used one or more anthropometric measures and concentrations of triglycerides and high-density lipoprotein cholesterol.[44] In addition, 9 studies included measurements of concentrations of insulin, 8 studies included concentrations of glucose, and 3 studies included measurements of concentrations of leptin. Six of the 9 studies produced a factor that included anthropometric measures and lipids. Seven of the 9 studies produced a separate factor that included blood pressure variables.

Recently, the first confirmatory factor analysis in children and adolescents was published.[48] Using data from 1262 participants aged 12 to 17 years from the National Health and Nutrition Examination Survey 1999–2002, the authors attempted to confirm in children and adolescents the results of a confirmatory factor analysis in adults.[49] After replacing mean arterial pressure with systolic blood pressure, the au-