A multidisciplinary lifestyle intervention for childhood obesity : effects on body composition, exercise tolerance, quality of life and gut hormones

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Chapter 6

The Predictive Value of the Individual Components of the Metabolic Syndrome for Insulin Resistance in Obese Children

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6

6 The Predictive Value of the Individual Components of the Metabolic Syndrome for Insulin Resistance in Obese Children

ABSTRACT:

Background/Aims

The usefulness of the concept of the Metabolic Syndrome (MS) in its current form was recently questioned and its association with insulin resistance is unknown. We assessed whether a multivariate model based on all components of MS expressed on a continuous scale would be a better predictor of a common marker of insulin resistance than the current dichotomous MS definitions (Cook, de Ferranti, IDF).

Methods

Data from 78 obese Dutch teenagers (13.0±2.1yr) were used for model development and the model was validated in 40 obese Hindustani children (12.6±2.0yr). The MS components and HOMA-IR were expressed as standard deviation scores (SDS), based on gender- and age-specific reference values.

Results

The prevalence of MS was 36% (Cook), 65% (De Ferranti) and 18% (IDF), with low mutual agreement. None of these dichotomous models were significant predictors for increased HOMA-IR SDS. The multivariate model incorporating the MS components expressed as SDS explained 58% of the variance of increased HOMA-IR SDS. In the validation group the predicted and observed HOMA-IR SDS (2.4±1.2 vs. 2.6±2.2) did not differ significantly.

Conclusion

A multivariate prediction model based on the MS components expressed as SDS has a good predictive value for increased HOMA-IR SDS.

Keywords: metabolic syndrome; children; prediction model; obesity; HOMA.

INTRODUCTION

Since the 1980s the prevalence of childhood obesity has increased dramatically worldwide (1-3). For example, in the Netherlands the prevalence of overweight and obesity in children (4-16 years) has more than tripled (from 3.9 to 14.5%) in boys in the period 1980-2003 and more than doubled (from 6.9 to 17.5%) in girls, and is still increasing (4). Several studies have demonstrated that 50% of children and 80% of adolescents with obesity become obese adults (5;6). In adults, obesity is associated with a higher risk for developing type 2 diabetes mellitus and cardiovascular disease (7-10), and in children and in adolescents obesity is associated with increased prevalence of hypertension, dyslipidemia and impaired glucose metabolism (11-14). The clustering of these risk factors was first reported in 1988 by Reaven as Syndrome X. Originally, the syndrome focused on the association with hyperinsulinemia and insulin resistance (15) , also in obese children (16). Furthermore, longitudinal studies have suggested that the Syndrome X in children and adolescents predicts the developing cardiovascular disease and type 2 diabetes mellitus in adulthood life (13;17-19). Therefore the syndrome was renamed as Metabolic Syndrome (MS).

For the pediatric age group several definitions have been proposed, with modifications of adult definitions most commonly used (16;20-24). Hyperinsulinenia is not included in most definitions. Consensus on the cut-off levels of the separate components of the MS for pediatric patients has still been difficult to obtain. One of the reasons is that in children and adolescents these cut-off levels are not only influenced by gender, but also by age and pubertal stage (20;22;25). Previous studies have shown that even in the same study group the prevalence of the MS varies considerably depending on the definition chosen (25-27). Furthermore, the dichotomous concept of the MS was recently questioned (28;29), and a recent WHO report has expressed doubt on the usefulness of the concept of MS in its current form (29). There is no accepted central underlying mechanism of the MS, although insulin resistance (10) and central obesity (30) have both been proposed to play this role.

In view of this current opinion on the limited usefulness of the MS, new strategies to overcome at least part of its limitations are needed. Insulin resistance is an independent predictor of cardiovascular disease and type 2 diabetes (31-34). In addition is was recently shown to be the best predictor of MS in first-degree relatives with type 2 diabetes (35). This study aimed to: 1) investigating the predictive value of the traditional parameters of MS as assessed by current dichotomous definitions of MS (Cook et al. (20), de Ferranti et al (22) and IDF (36;37)) for insulin resistance; and 2) develop a multivariate model incorporating all components of the MS expressed as standard deviation scores (SDS) to predict insulin resistance in obese Dutch children, and validate this in an independent group of obese Hindustani children.

METHODS

Subjects

Clinical data were collected of children with obesity (based on the cut-off level described by Cole et al. (1)) who were referred to two pediatric clinics (Juliana Children's Hospital/ HagaHospital (JKZ), the Hague, and Leiden University Medical Center (LUMC), Leiden. The age range was limited to 10.0-18.0 years, since MS is difficult to determine in children younger than 10 years (36;37). Children were excluded when their obesity was caused by an underlying medical condition or medication use. For developing the prediction model for insulin resistance, patients were divided into two groups: the first group included children of Dutch ancestry (n=78) and the other group children of Hindustani origin (n=40). The prediction model was based on the Dutch children and validated in the Hindustani children. Ethnicity was determined according to self-reports by the parents.

Definitions of the Metabolic Syndrome

The MS was defined according to the three most often used definitions for the pediatric age group by other research groups (Cook et al.(20), De Ferranti et al.(22), IDF(36;37) (Table 1)). The MS was considered present when three or more components were abnormal in the definitions of Cook and de Ferranti. According to the definition of the IDF, subjects were classified as MS when their waist circumference (WC) was increased and two or more of the other parameters were abnormal. In all definitions the Dutch gender- and age-specific WC diagrams were used for classification of central obesity (38). In the definitions of both De Ferranti and Cook the age-, height- and gender-specific percentiles of the National High Blood Pressure Education Program (NHBPEP)(39) were used for blood pressure. In the definition of the IDF the adult criteria for hypertension were used. The three definitions used different cut-off levels for impaired fasting HDL and fasting triglycerides (TG). Cut-off levels for impaired fasting glucose (FG) are the same in the definitions of De Ferranti and Cook. The IDF definition uses a different cut-off level for impaired FG (Table 1).

Table 1: *Definitions of the Metabolic Syndrome according to Cook, de Ferranti and IDF*

CRITERION	DEFINITIONS		
	Cook et al.[20]	**De Ferranti et al.[22]**	**IDF[37]**
	≥3 of the 5 criteria below:	≥3 of the 5 criteria below:	WC ≥ 90th percentile, age ≥10 yr and ≥2 of the other 4 criteria:
Waist Circumference (cm)	≥ 90th percentile (age-, sex specific)	≥ 75th percentile (age-, sex specific)	≥ 90th percentile (age-, sex specific)
Blood Pressure (mmHg)	≥ 90th percentile (age-, sex-, height specific)	≥ 90th percentile (age-, sex-, height specific)	SBP ≥ 130 and/or DBP ≥ 85
HDL (mmol/L)	HDL ≤ 1.04	HDL < 1.30	HDL < 1.03
Triglycerides (mmol/L)	TG ≥ 1.24	TG ≥ 1.1	TG ≥ 1.7
Glucose Intolerance (mmol/L)	FG ≥ 6.1	FG ≥ 6.1	FG ≥ 5.6

Measurements

Weight was measured to the nearest of 0.1 kg using an electronic scale (SECA 911, Vogel & Halke, Hamburg, Germany) and height to the nearest 0.1 cm with a stadiometer (Holtain, limited, Crymych, Dyfed, Britain) in underwear and barefoot. The Body Mass Index (BMI) was calculated as weight/height squared (kg/m^2). Subjects were classified as obese using BMI international gender- and age-specific cut-off levels developed by Cole et al. (1). The WC (in cm) was measured with an anthropometric tape midway between the lower rib margin and the iliac crest at the end of gentle expiration. Blood pressure was determined in a relaxed sitting position measurement with an electronic device (Criton Dinamap, No. 8100), in duplicate; the last measurement was used for further analysis.

Laboratory analysis

With the subject in the supine position, blood samples were taken by venipuncture after an overnight fast. Before blood sampling, the study participants and their parents were asked to confirm the fasting state. Fasting plasma HDL, TG and FG were collected with BD vacutainers (LH PST II Plus Blood Collection Tubes, BD Belliver Industrial Estate, Plymouth, UK). Plasma fasting insulin (FI) was sampled with Vacuette 2.5 mL Z Serum Sep Clot Activator (Greiner Bio-One GmbH, Kremsmüsterm Austria). Analysis for fasting plasma HDL, TG and FG was conducted by the hospital laboratory of the HagaHospital (The Hague, the Netherlands) and FI by the laboratory of the Leiden University Medical Center (Leiden, the Netherlands). HDL was analyzed by homogenic enzymatic colorimetry, TG by automatized colorimetry, all determined by bynchon Lx20 Pro/ unicel DXC 800 (Beckman Couter, Brea, US) and FG was analyzed by the glucose-oxidase method.
FI was analyzed by the Immulite 2500 immunoanalyser (Siemens healthcare Diagnostics, Deerfield, IL, US).
An index for insulin resistance was calculated according to the HOMA-IR formula: fasting insulin (μU/mL) x fasting glucose (mmol/L)) / 22.5 (40). Although a hyperinsulinemic-euglycemic clamp is considered to be the golden standard for determining insulin resistance, the non-invasive HOMA-IR model is considered a useful tool to assess insulin resistance in epidemiologic studies (40).

Statistical analyses

The analysis was performed using the Statistical Package for Social Science (SPSS), version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and the level of significance was set at $p<0.05$. Data were checked for normality before analysis using descriptive statistics and histograms. Data are expressed mean ± standard deviation (continuous variables) and as count and percentage (categorical variables). Independent t-tests were used for comparison of the 'Dutch' and 'Hindu' subgroups with continuous data and the Chi-square test for comparison with categorical data. Standard deviation scores (SDS) were calculated for the individual parameters of the MS, based on gender- and age-specific reference values, for WC (38), HDL (41), TG (41), FG (42), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (43;44). Standard deviation scores for HOMA-IR (HOMA-IR SDS) were calculated, based on gender- and age-specific reference values (42). In order to test the agreement between the dichotomous definitions of MS the weighted kappa was used. The weighted kappa ranges between 1 (perfect agreement) and 0 (no agreement).
In general values less than 0.40 indicate poor, between 0.41-0.60 indicate moderate, between 0.61-0.80 indicate good and above 0.81 very good agreement.

To establish the predictive value of the three dichotomous definitions of the MS (Cook, de Ferranti, IDF) separate linear regression models were performed, with HOMA-IR SDS as dependent variable. The prediction model with the SDSs of the individual components of MS was developed by means of multiple linear regression in the group of Dutch children. Because fasting glucose is used to calculate the HOMA-IR, the model was also conducted without FG-SDS. The coefficients of the first model were used to calculate the predicted HOMA-IR SDS for all children. Differences between observed and predicted HOMA-IR SDS were expressed in terms of Studentized residuals. The residual is calculated as the observed HOMA-IR SDS minus the predicted HOMA-IR SDS for each observation, and the Studentized residual is the residual divided by its SE. For the validation of both models data was used from 40 Hindustani children, who fulfilled the inclusion criteria. Paired sample t-test was used to determine a significant difference between the observed and predicted HOMA-IR SDS in the Hindustani children. Pearson correlation was also used to assess the correlation between the observed and predicted HOMA-IR SDS in the model validation subgroup.

RESULTS

The characteristics of the 78 Dutch children (31 boys (40%)) studied and of the 40 Hindustani children (16 boys (40%)) are listed in Table 2. There is a trend towards a younger age in the group with Hindustani children. The FG-SDS is significantly higher and a trend towards a lower WC-SDS is found in the 'Hindu' compared to the 'Dutch' group.

Table 2: *Subject characteristics of the Dutch group of obese children group used for constructing the model and of the Hindustani validation group*

	DUTCH (N=78) Mean ± SD	HINDUSTANI (N=40) Mean ± SD	P-VALUE*
Age (years)	13.5 ± 2.1	12.6 ± 2.0	NS (0.06)
Weight (kg)	84.0 ± 17.5	80.8 ± 19.4	NS
Height (cm)	161.9 ± 9.8	157.7 ± 11.0	0.03
BMI (kg/m^2)	31.7 ± 3.9	32.0 ± 4.3 NS	NS
BMI-SDS	3.0 ± 0.7	3.1 ± 0.7	NS
WC (cm)	97.0 ± 10.6	91.6 ± 10.7	0.01
WC-SDS	4.4 ± 1.3	3.9 ± 1.2	NS (0.06)
SBP (mmHg)	125 ± 11	126 ± 12	NS
SBP-SDS	1.6 ± 1.0	1.8 ± 1.0	NS
DBP (mmHg)	66 ± 8.5	65 ± 9.6	NS
DBP-SDS	-0.0 ± 0.8	0.1 ± 0.9	NS
HDL (mmol/L)	1.2 ± 0.3	1.1 ± 0.2	NS
HDL-SDS	-0.8 ± 1.0	-0.9 ± 0.7	NS
TG (mmol/L)	1.2 ± 0.9	1.0 ± 0.4	NS
TG-SDS	0.3 ± 1.0	0.2 ± 0.5	NS
FG (mmol/L)	5.0 ± 0.4	5.2 ± 0.4	<0.01
FG-SDS	-0.2 ± 1.0	0.3 ± 1.0	0.02
FI (mU/L)	17.2 ± 11.2	20.7 ± 10.3	NS
HOMA-IR index	3.9 ± 2.7	4.8 ± 2.4	NS (0.06)
HOMA-IR SDS	1.9 ± 2.5	2.6 ± 2.2	NS

** p-value < 0.05 is considered statistically significant, NS= not significant.*

In the Dutch group the highest prevalence rate of the MS was found using the definition of De Ferranti (65%), followed by Cook (36%), and the lowest prevalence rate was found according to the IDF criteria (18%) (Table 3). The weighted Kappa, used to test the agreement between these definitions was 0.56 (Cook vs. IDF), 0.46 (De Ferranti vs. Cook) and 0.21 (De Ferranti vs. IDF), thus the agreement between these definitions was poor to moderate. Mean BMI-SDS in subjects with vs. without the MS according to the definition of De Ferranti was not significantly different (3.1 ± 0.8 SDS vs. 3.0 ± 0.7 SDS, respectively). A significantly higher BMI-SDS was found for children with vs. without the MS by Cook (3.3 ± 0.7 SDS vs. 2.8 ± 0.8 SDS, p=0.03) and by the IDF criteria (3.5 ± 0.8 SDS vs. 2.9 ± 0.6 SDS, p=0.01).

Table 3: *Prevalence of the metabolic syndrome and the frequencies of its criteria according to the three proposed definitions*

COOK ET AL.[20]	FREQUENCY N (%)	DE FERRANTI ET AL.[22]	FREQUENCY N (%)	IDF[37]	FREQUENCY N (%)
≥3 of the 5 criteria below:	28 (36)	≥3 of the 5 criteria below:	51 (65)	WC ≥ 90th percentile, age ≥10 yr and ≥2 of the other 4 criteria:	14 (18)
WC ≥ 90th percentile	78 (100)	WC ≥ 75th percentile	78 (100)	WC ≥ 90th percentile	78 (100)
BP ≥ 90th percentile	50(64)	BP ≥ 90th percentile	50 (64)	SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg	23 (30)
TG ≥ 1.24 mmol/L	23(30)	TG ≥ 1.1 mmol/L	31 (40)	TG ≥ 1.7 mmol/L	13 (17)
HDL ≤ 1.04 mmol/L	22(28)	HDL < 1.30 mmol/L	51 (65)	HDL < 1.03 mmol/L	21 (27)
FG ≥ 6.1 mmol/L	1(1)	FG ≥ 6.1 mmol/L	1 (1)	FG ≥ 5.6 mmol/L	4 (5)

Increased HOMA-IR SDS was not significantly predicted by the dichotomous definitions of MS. This is also reflected in the low explained variance in increased HOMA-IR SDS by the three definitions; 17.8% (2.3SE) according to De Ferranti, 16.3% (2.3SE) according to Cook and 16.1% (2.3SE) according to IDF. Because the risk is expressed as 'present' or 'not present', with no distinction in severity of increased metabolic risk, this finding indicates that by dichotomizing increased metabolic risk much predictive information is lost.

The multiple linear regression model incorporating the SDSs of the individual components of the MS as predictive variables and HOMA-IR SDS as outcome variable is shown in Table 4. The most important predictor of HOMA-IR SDS (apart from FG-SDS) is WC-SDS. The explained variance of the model with FG-SDS is 58%, with a standard error of 1.8 and is described by the following multiple linear regression equation: HOMA-IR SDS = 2.2 + 0.9 x Gender (male=0, female=1) –0.3 x Age (year) +1.0 x FG-SDS + 0.7 x WC-SDS - 0.8 x DBP-SDS + 0.6 x SBP-SDS + 0.7 x TG-SDS – 0.2 × HDL-SDS.

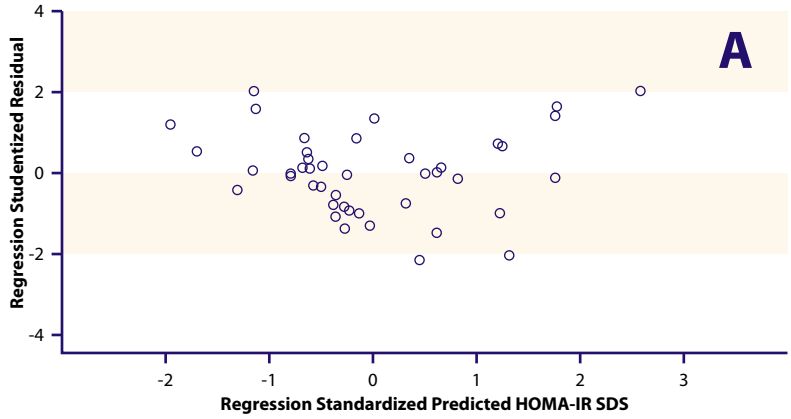
Table 4: *Prediction model for increased HOMA-IR SDS according to the enter procedure. Rank order is based on a backward procedure*

MODEL	PREDICTOR	COEFFICIENT [95%CI]	RANK
Linear Regression with all SDSs in the model	(constant)	2.2 [-4.2;8.6]	
	Gender	0.9 [-0.3;2.1]	
	Age	-0.3 [-0.6;0.0]	
	FG-SDS	1.0 [0.3;1.6]	1
	WC-SDS	0.7 [0.2;1.2]	2
	DBP-SDS	-0.8 [-1.7;0.1]	3
	SBP-SDS	0.6 [-0.2;1.4]	4
	TG-SDS	0.7 [-1.1;2.6]	5
	HDL-SDS	-0.2 [-0.9;0.5]	6

The multiple linear regression equation for HOMA-IR SDS without FG-SDS in the model has an explained variance of 46%, with a standard error of 2.0 and can be described as follows: HOMA-IR SDS = - 0.8 + 0.8 x Gender (male=0, female=1) –0.2 x Age (year) +1.1 x WC-SDS - 0.8 x DBP-SDS + 0.7 x SBP-SDS + 0.8 x TG-SDS – 0.3 × HDL-SDS.

For the mathematical validation of both prediction models a Studentized residual plot is used to identify outliers, nonlinearity, and non-constant error variants in the prediction model. The observed randomly clustered observations imply that there is no heterogeneity in the Dutch group with respect to relevant importance of the different predictors (Figures 1A and 2A). The paired student t-test to determine the difference between observed HOMA-IR SDS (2.6 ± 2.2) and predicted HOMA-IR SDS (2.4 ± 1.2) in the Hindustani children was not statistically significant (p=0.550). This indicated that HOMA-IR SDS of these children can be predicted by the model for predicting HOMA-IR SDS, based on the data in the Dutch children. Also the correlation between the observed and the predicted HOMA-IR SDS in the Hindustani children is statistically significant ($r=0.540$, $p<0.01$). In addition, the plot of the Studentized residual vs. the predicted HOMA-IR SDS in the validation group (Figures 1B and 2B) showed a similar pattern of randomly clustered observations as in the plot of the Dutch group.

Figure 1: *Studentized rediduals vs. predicted HOMA-IR SDS in the Dutch children with obesity (A) and the validation group (B) according to the derived prediction model including all SDSs of the individual parameters of MS*



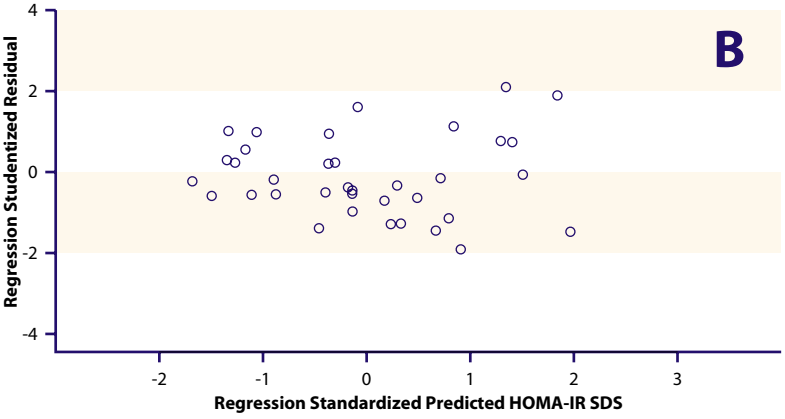
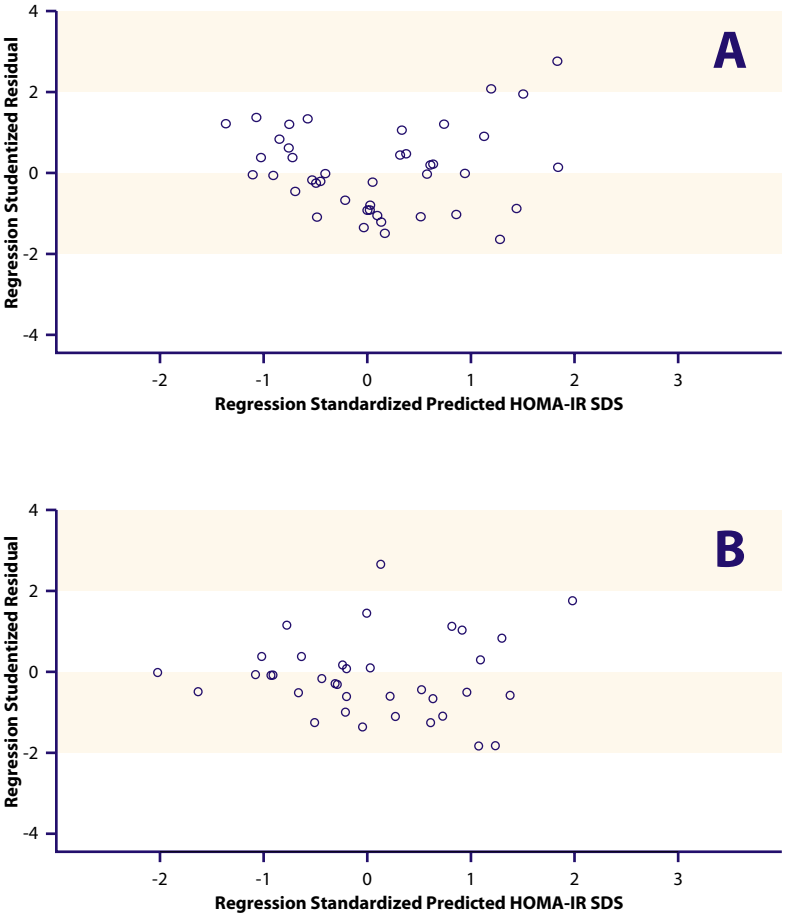


Figure 2: *Studentized rediduals vs predicted HOMA-IR SDS in the Dutch children with obesity (A) and the validation group (B) according to the derived prediction model including all SDSs of the individual parameters of MS except FG-SDS*



DISCUSSION

The results of our study demonstrate a different impact for the individual components of the metabolic syndrome (MS) on increased insulin resistance. The regression model with all the standard deviation scores of the individual components of MS in the model, showed an explained variance of 58%. From the individual variables of the MS, not included in the HOMA-IR index, the standard deviation score of WC provided to be the best predictor for increased insulin resistance, confirming the previously reported superior role of the WC in predicting health risk (45;46).

The predictive value of the dichotomous definition of the MS on increased HOMA-IR SDS was poor (16.1-17.8%) and not statistically significant. Furthermore, no significant difference was found for BMI-SDS between children with and without MS by the definition of De Ferranti, suggesting that this definition provides the least information on which child is most at risk.

It is now widely recognized that the definition of the MS in its current form has limitations. A major disadvantage of the MS definition is its dichotomous character. As pointed out by the WHO (29), dichotomization of a health risk makes it impossible to determine the absolute risk of a subject and to assess whether this health risk increases or decreases. In addition, in children the cut-off levels of the individual components of the proposed definitions of the MS are age-, and gender-dependent. Since no consensus exists on the optimal cut-off values for the parameters of the MS and reference values are often lacking for age and gender, prevalence rates are study design dependent. As a result, widely varying prevalence rates have been found, as shown by us (20-55%) and others (13-50%) (16;22;24-27;47;48) in the same study population, when different definitions are used. As a consequence it is difficult to compare the results of prevalence rates of the MS between different study populations.

A previously suggested alternative for the dichotomization of the metabolic risk is to calculate a continuous metabolic risk score, including fat mass (DXA), waist circumference, BMI, HOMA-IR and systolic blood pressure (28). However, the metabolic risk score in this study was calculated by subtracting the sample's mean from the individual mean, which was then divided by the standard deviation of the sample mean. By definition the mean score for metabolic risk of the study sample was zero. The sum of the sample-based Z-scores was divided by the number of variables, included in the risk score. So again a relative risk is obtained which is only applicable for the studied sample at the time of data collection. Another problem not solved by this alternative approach, is that by using the average of the Z-scores a similar weight is given to the Z-scores of the individual components. In contrast, the frequency and impact of the specific components are probable not equivalent.

To overcome these obstacles we propose to express the individual metabolic risk variables as standard deviation scores, based on gender- and age specific reference values. In this way changes can be detected easier, which provides the clinician with a long-term perspective on change in health risk. This will help the clinician in deciding about the frequency of consultations and the level of care to be provided to the child. Furthermore, by using a regression model to predict increased health risk, differences in the impact of the individual components of MS on health risk are taken into consideration. A similar approach was used by Ranke et al to predict growth velocity during growth hormone treatment based on a series of clinical parameters (49).

We determined the predictive value of the SDSs of the individual MS components on increased insulin resistance. As expected, we found a different impact for the individual MS parameters on increased HOMA-IR SDS. However, although this model showed a quite reasonable predictive value (58% with and 46% without FG-SDS), the predictive power of the presence and severity of the MS for type 2 diabetes mellitus in later years is unknown. Moreover, during childhood, it is known that the degree of insulin resistance varies, with many unknown influencing factors. For that reason, it is not unexpected that a substantial part of the variance in the prediction model remains unexplained.

To validate our prediction model for increased HOMA-IR SDS, we used the data of a separate group of children meeting the same inclusion criteria, but of different ethnic origin. In this group the predicted and observed HOMA-IR SDSs were comparable and their correlation was statistically significant. Also the Studentized residual plot showed randomly clustered observations, implying no heterogeneity in the validation group with respect to relevant importance of the different predictors. These findings indicate that our prediction model may be useful for predicting increased HOMA-IR SDS in other groups of obese children.

We are aware that our study has some limitations. The sample sizes of both groups were relatively small for constructing and validating a prediction model. However we feel that despite this limitation our study can offer a valuable contribution to the discussion on ways to improve the concept of the MS for predicting which obese child is most at risk for developing morbidity. Furthermore, data from a clinical sample of obese subjects may be influenced by selection and referral bias and may therefore not be representative for all obese children in the general population. However, obese children, referred to a pediatrician, are probable most at risk for developing obesity related co-morbidity. Future research with a larger sample size is recommended to validate and refine our model.

In conclusion, the variation in prevalence rates for the MS between three dichotomous definitions in the same pediatric study population is high, and mutual agreement is poor. Since the individual parameters of the MS are age-dependent and gender-dependent they can better be expressed as SD scores than be compared with fixed cut-off levels. We developed a model for predicting increased insulin resistance, taken into considerations the different impact of the standardized components of the MS. We speculate that using such a model to predict obesity-related co-morbidities may prove superior to the current definitions, because it provides an indicator for the severity of MS and a tool for assessing amelioration or deterioration of metabolic risk factors in obese children and adolescents.

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CONFLICT OF INTEREST STATEMENT

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REFERENCE LIST

1 Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; **320/7244**: 1240-1243.

2 Fredriks AM, Van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. *Arch Dis Child* 2000; **82/2**: 107-112.

3 Reilly JJ. Descriptive epidemiology and health consequences of childhood obesity. *Best Pract Res Clin Endocrinol Metab* 2005; **19/3**: 327-341.

4 van den Hurk K, van DP, van BS, Verkerk PH, Hirasing RA. Prevalence of overweight and obesity in the Netherlands in 2003 compared to 1980 and 1997. *Arch Dis Child* 2007; **92/11**: 992-995.

5 Guo SS, Roche AF, Chumlea WC, Gardner JD, Siervogel RM. The predictive value of childhood body mass index values for overweight at age 35 y. *Am J Clin Nutr* 1994; **59/4**: 810-819.

6 Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med* 1992; **327/19**: 1350-1355.

7 Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; **365/9468**: 1415-1428.

8 Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; **109/3**: 433-438.

9 Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; **24/4**: 683-689.

10 Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; **37/12**: 1595-1607.

11 Berenson GS, Srinivasan SR, Bao W, Newman WP, III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J* Med 1998; **338/23**: 1650-1656.

12 Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics* 1999; **103/6 Pt 1**: 1175-1182.

13 Li X, Li S, Ulusoy E, Chen W, Srinivasan SR, Berenson GS. Childhood adiposity as a predictor of cardiac mass in adulthood: the Bogalusa Heart Study. *Circulation* 2004; **110/22**: 3488-3492.

14 Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002; **346/11**: 802-810.

15 Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006; **444/7121**: 881-887.

16 Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004; **350/23**: 2362-2374.

17 Huang TT, Nansel TR, Belsheim AR, Morrison JA. Sensitivity, specificity, and predictive values of pediatric metabolic syndrome components in relation to adult metabolic syndrome: the Princeton LRC follow-up study. *J Pediatr* 2008; **152/2**: 185-190.

18 Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics* 2007; **120/2**: 340-345.
19 Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr* 2008; **152/2**: 201-206.
20 Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 2003; **157/8**: 821-827.
21 Cruz ML, Weigensberg MJ, Huang TT, Ball G, Shaibi GQ, Goran MI. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab* 2004; **89/1**: 108-113.
22 de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation* 2004; **110/16**: 2494-2497.
23 Ford ES, Ajani UA, Mokdad AH. The metabolic syndrome and concentrations of C-reactive protein among U.S. youth. *Diabetes Care* 2005; **28/4**: 878-881.
24 Viner RM, Segal TY, Lichtarowicz-Krynska E, Hindmarsh P. Prevalence of the insulin resistance syndrome in obesity. *Arch Dis Child* 2005; **90/1**: 10-14.
25 Reinehr T, de Sousa G, Toschke AM, Andler W. Comparison of metabolic syndrome prevalence using eight different definitions: a critical approach. *Arch Dis Child* 2007; **92/12**: 1067-1072.
26 Golley RK, Magarey AM, Steinbeck KS, Baur LA, Daniels LA. Comparison of metabolic syndrome prevalence using six different definitions in overweight pre-pubertal children enrolled in a weight management study. *Int J Obes (Lond)* 2006; **30/5**: 853-860.
27 Lee S, Bacha F, Gungor N, Arslanian S. Comparison of different definitions of pediatric metabolic syndrome: relation to abdominal adiposity, insulin resistance, adiponectin, and inflammatory biomarkers. *J Pediatr* 2008; **152/2**: 177-184.
28 Thivel D, Malina RM, Isacco L, Aucouturier J, Meyer M, Duche P. Metabolic syndrome in obese children and adolescents: dichotomous or continuous? *Metab Syndr Relat Disord* 2009; **7/6**: 549-555.
29 Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia* 2010; **53/4**: 600-605.
30 Carr MC, Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. *J Clin Endocrinol Metab* 2004; **89/6**: 2601-2607.
31 Graner M, Syvanne M, Kahri J, Nieminen MS, Taskinen MR. Insulin resistance as predictor of the angiographic severity and extent of coronary artery disease. *Ann Med* 2007; **39/2**: 137-144.
32 Lorenzo C, Wagenknecht LE, D'Agostino RB, Jr., Rewers MJ, Karter AJ, Haffner SM. Insulin resistance, beta-cell dysfunction, and conversion to type 2 diabetes in a multiethnic population: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2010; **33/1**: 67-72.
33 Nguyen QM, Srinivasan SR, Xu JH, Chen W, Kieltyka L, Berenson GS. Utility of childhood glucose homeostasis variables in predicting adult diabetes and related cardiometabolic risk factors: the Bogalusa Heart Study. *Diabetes Care* 2010; **33/3**: 670-675.

34 Webb DR, Khunti K, Silverman R, Gray LJ, Srinivasan B, Lacy PS et al. Impact of metabolic indices on central artery stiffness: independent association of insulin resistance and glucose with aortic pulse wave velocity. *Diabetologia* 2010; **53/6**: 1190-1198.

35 Utzschneider KM, Van de Lagemaat A, Faulenbach MV, Goedecke JH, Carr DB, Boyko EJ et al. Insulin resistance is the best predictor of the metabolic syndrome in subjects with a first-degree relative with type 2 diabetes. *Obesity (Silver Spring)* 2010; **18/9**: 1781-1787.

36 Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S et al. The metabolic syndrome in children and adolescents. *Lancet* 2007; **369/9579**: 2059-2061.

37 Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S et al. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatr Diabetes* 2007; **8/5**: 299-306.

38 Fredriks AM, Van Buuren S, Fekkes M, Verloove-Vanhorick SP, Wit JM. Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? *Eur J Pediatr* 2005; **164/4**: 216-222.

39 Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. *Pediatrics* 1996; **98/4 Pt 1**: 649-658.

40 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28/7**: 412-419.

41 Cook S, Auinger P, Huang TT. Growth curves for cardio-metabolic risk factors in children and adolescents. *J Pediatr* 2009; **155/3**: S6-26.

42 Allard P, Delvin EE, Paradis G, Hanley JA, O'Loughlin J, Lavallee C et al. Distribution of fasting plasma insulin, free fatty acids, and glucose concentrations and of homeostasis model assessment of insulin resistance in a representative sample of Quebec children and adolescents. *Clin Chem* 2003; **49/4**: 644-649.

43 The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; **114/2 Suppl 4th Report**: 555-576.

44 Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res* 2000; **47/3**: 316-323.

45 Lee S, Bacha F, Arslanian SA. Waist circumference, blood pressure, and lipid components of the metabolic syndrome. *J Pediatr* 2006; **149/6**: 809-816.

46 Maffeis C, Banzato C, Talamini G. Waist-to-height ratio, a useful index to identify high metabolic risk in overweight children. *J Pediatr* 2008; **152/2**: 207-213.

47 Bokor S, Frelut ML, Vania A, Hadjiathanasiou CG, Anastasakou M, Malecka-Tendera E et al. Prevalence of metabolic syndrome in European obese children. *Int J Pediatr Obes* 2008; **3 Suppl 2**: 3-8.

48 Kolsgaard ML, Andersen LF, Tonstad S, Brunborg C, Wangensteen T, Joner G. Ethnic differences in metabolic syndrome among overweight and obese children and adolescents: the Oslo Adiposity Intervention Study. *Acta Paediatr* 2008; **97/11**: 1557-1563.

49 Ranke MB, Lindberg A. Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. *J Clin Endocrinol Metab* 2010; **95/3**: 1229-1237.