COVER SHEET

Full Title

Comparison of metabolic syndrome prevalence using six different definitions in overweight pre-pubertal children enrolled in a weight management study.

Short running title

Defining Metabolic Syndrome in overweight pre-pubertal children

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Abstract

Objectives: To assess the implications of variation in Metabolic Syndrome (MS) definition (biochemical and anthropometric indicators) on MS prevalence estimates in a population of overweight and mildly obese children.

Design: Cross-sectional study

Subjects: Ninety-nine (64 girls) overweight or mildly obese, but otherwise healthy, pre-pubertal 6 to 9 year olds recruited for a randomised controlled trial of weight management

Measures: Height, weight and waist circumference were measured with BMI and waist z-scores calculated. Fasting cholesterol and fractions, glucose and insulin were measured, together with systolic and diastolic blood pressure (BP). Anthropometric and metabolic indicators were classified as normal or elevated using adult or child-specific cut points with clustering of MS indicators also assessed using 2 adult and 3 child-specific definitions.

Results: Zero to 4% of subjects were classified with MS when adult definitions were applied. This increased to between 39-60% using child-specific definitions, varying according to whether hyperinsulinaemia was central to the MS classification. Systolic BP, triglycerides, total cholesterol, high density lipoprotein cholesterol and waist z-score increased across insulin quartiles ($p<0.05$). The use of body mass index and waist circumference in the MS definition classified the same subjects.

Conclusions: The classification of MS in children depends strongly on the definition chosen, with MS prevalence estimates higher if insulin is part of the definition and child-specific cut points for metabolic indicators are used. Hyperinsulinaemia and MS are common consequences of childhood obesity but they are not commonly part of the assessment or management plan for weight management in children. There is a need for the establishment of normal insulin ranges and consistent definition of MS in childhood and adolescence.

Keywords: lipids; insulin; childhood; obesity; central adiposity; blood pressure; waist circumference; body mass index.

Introduction

Childhood overweight is increasingly common worldwide (1-3) as are the consequences that include increased risk of later cardiovascular disease and diabetes (4, 5). The Metabolic Syndrome (MS) describes the clustering of central obesity, dyslipidaemia (raised triglycerides and/or low high density lipoprotein), hyperinsulinaemia, impaired glucose tolerance and elevated blood pressure, and is a clear indicator of adult morbidity (6). The metabolic indicators of MS are present in early life, increase with severity of paediatric obesity and track over the lifecycle (7-9). While MS is a well recognised phenomenon, identification is problematic as definitions are numerous and there are no accepted definitions in adolescents and children.

In adults, the definition of MS varies in terms of the indicators featured and cut points used (10-12). Two (10, 12) of the three common definitions include measures of insulin resistance, reflecting the proposed causal or mediating role insulin action plays in the development of MS (13, 14). In the paediatric literature there is no single definition of MS (15-17). Barriers to a consistent, accepted definition for children and adolescents include: use of adult cut points or a single set of cut points for all ages of childhood; the fact that disturbances seen in the metabolic indicators in most children are quantitatively moderate; lack of a normal range for insulin concentration across childhood; the insulin resistance of puberty; and lack of central obesity (waist) cut points linked to obesity morbidity or MS for children. If hyperinsulinaemia alone is used as a marker of MS in children (18), it ignores the clustering of several metabolic indicators which is potentially of greater clinical significance.

The worsening childhood obesity epidemic and the long term health risks for both obese children and adults highlight the need for a workable, consistent definition of MS in children to enable investigation of prevalence and both short and long term health outcomes. Population studies of MS in children and adolescents have used inconsistent and arbitrary MS definitions, included all pubertal stages and a wide age range (15-17). No study to date has focused on pre-pubertal children and few on obese populations. The objective of this study is to assess the implications of variation in MS definition (both biochemical and anthropometric indicators) on MS prevalence estimates in a population of overweight and mildly obese pre-pubertal six to nine year olds. The secondary objective is to explore how the indicators of metabolic syndrome vary by insulin concentration and degree of obesity.

Methods

Subjects

The subjects (N=99) were baseline participants in a randomised controlled trial for the management of childhood overweight. They were recruited from metropolitan Adelaide, South Australia, via media publicity, health professional referral and school newsletter information. Study inclusion criteria were: age six to nine years (up to 10th birthday); overweight (based on body mass index [BMI], age and gender specific cut-points developed by Cole et al (19)) or mildly obese (BMI z-score <3.5, based on UK BMI reference curves (20)); pre-pubertal (Tanner Stage 1 (21)) and care-giver able to attend sessions and read and understand English. Exclusion criteria were: sibling enrolled in the study, known syndromal cause of obesity, medications influencing weight gain or loss, physical or developmental disability, chronic illness, and significant dietary restriction. Eligibility was initially assessed via telephone interview and confirmed at a screen by a medical practitioner. Study information sheets were provided and informed written consent obtained from both the parent and the child. This study was approved by the Flinders Clinical Research Ethics Committee and the Women's and Children's Hospital's Ethics Committee, Adelaide, Australia.

Measurements

All measurements were taken by a single trained observer at two sites (Flinders Medical Centre and Women's and Children's Hospital). Height, weight and waist circumference were measured with subjects lightly clothed and without shoes. Height to the nearest 1.0 mm was measured with a Trumeter^{TM} stadiometer (Manchester, UK) and weight to the nearest 0.1 kg with SECA^{TM} electronic scales (Hamburg, Germany). The waist circumference measurement was taken with subjects in a standing position, midway between the tenth rib and the iliac crest, using a non-elastic flexible tape, and recorded to the nearest mm.

Blood was collected via venepuncture following an overnight fast. Fasting glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were determined within 4 hours by standard automotive techniques using a Synchron CX5 Pro analyser (Beckman Coulter Inc, Fullerton, USA) in the clinical diagnostic laboratory, Division of Laboratory Medicine, Women's and Children's Hospital, Adelaide. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation as Cholesterol – (HDL + Triglycerides/2.2) (11). Immediately following sample collection, plasma was drawn off and stored at –70^{o}C until fasting serum insulin were measured in batched samples in the Diagnostic Laboratory Department of Endocrinology Royal Prince Alfred Hospital (RPAH), Sydney by radio-immunoassay using the Linco Human Insulin Specific Assay Kit (Linco Research Inc, Missouri USA). Blood pressure was measured on the right arm using a Dinamap^{TM} automated blood pressure monitor (GE Healthcare, UK). A variety of cuff-sizes were used (small-adult was the most common) to ensure that the length of the bladder completely encircled the arm and the width was at least two-thirds the length of the upper arm (22). A single measurement was taken after supine rest for 10 minutes following collection of the blood sample and anthropometric measures.

Definition of metabolic syndrome (MS)

Subjects were classified as displaying MS according to six definitions, two adult and four child-specific using age-adjusted cut points. The definitions used to classify MS in adults were included as they have already been applied and compared in adolescent populations and would potentially provide the easiest use in the clinical setting (23). The relevant indicators and associated cut points are shown in Table 1. Four of the definitions (1 adult, 3 child) include fasting insulin resistance and at least two other abnormal indicators and are defined as follows:

- Definition 1 is the European Group for the Study of Insulin Resistance (EGIR) (10) adult definition which includes waist circumference as a measure of central obesity. As no

cut point for fasting insulin is given in this definition, the upper 95% confidence limit (51pmol/L) of a normal volunteer adult sample from the Endocrinology Laboratory, Royal Prince Alfred Hospital, Sydney (N= 148) was used.

- Definition 2 is the US National Cholesterol Education Program (NCEP) adult definition which includes abnormalities in any three of glucose, triglycerides, HDL-C, systolic BP (SBP) and waist circumference (insulin not included) (11).
- Definition 3 is that used by Lambert et al (2004) which includes fasting insulin (15). They used the 75th percentiles of a Canadian community based sample of 783 subjects aged nine years, as cut points for each indicator except BMI for which the 85th percentile was used. As the actual cut point values for SBP were not quoted, US percentiles for age (to the nearest year), gender and height were used in this study with the 95th percentile an indicator of high SBP (24). An adjustment was also required for BMI as cut point values were only quoted for 9 year-olds and our sample included six to nine-year-olds. The z-scores of the quoted BMI values were determined using UK reference curves (20) (boys 1.77, girls 1.51) and used as the BMI cut point value for all ages.
- Definition 4 is a modification of Definition 3 replacing the cut point for TG with the 75th percentile from the US Lipid Research Prevalence Study and the cut point for HDL-C cholesterol with recommendations from the American Academy of Paediatrics (25) using a lipid conversion factor of mg/dL x 0.0259.
- Definition 5 is a modification of Definition 1 replacing adult cut points with child-specific cut points as per Definition 4 and using the 91st percentile by age and gender for waist as a measure of central adiposity which in adults is the adiposity measure used to define MS. The 91st and 98th centiles are arbitrary but were chosen as they have previously been used in studies of young people and are similar to the cut points used to determine central overweight and obesity based on BMI (26, 27).
- Definition 6 is a modification of the NCEP definition (Definition 2) using the same cut points as per Definition 5.

Data analysis

Analyses were performed using SPSS for Windows version 11.0 (SPSS Inc, Chicago). The distribution of all indicators was normal except for triglycerides. Data are expressed as mean (SD) and proportions of the sample unless otherwise specified. BMI was calculated as weight divided by height squared (kg/m^2) and the subject's BMI z-score was calculated using UK reference data (20) provided as a computer program (Child Growth Foundation, London UK). This package allows calculation of BMI z-score using decimal age. Subjects were classified as overweight or obese using BMI age and gender specific cut points developed by Cole et al (19). Each subject's waist circumference was converted to a z-score using UK reference data and subjects were classified as being centrally overweight or obese if their waist measurement exceeded the 91^{st} or 98^{th} percentile (z-scores 1.34 or 2.05) respectively (27).

Using the cut points defined in Table 1, the absence or presence of each metabolic indicator was determined and the proportion of subjects identified with MS according to each of the definitions determined. In addition, the presence of elevated total and LDL-C cholesterol was determined based on recommendations from the American Academy of Paediatrics (25). The presence of elevated DBP was determined as for SBP as a value above the 95^{th} US percentiles for age (to the nearest year), gender and height (24).

ANOVA was used to compare all indicators by quartile of insulin, BMI z-score and waist z-score. Chi-squared analysis was used for comparisons of prevalence of MS by gender, weight status, and quartiles of BMI and waist z-scores. As the definitions for overweight and obesity in children used here have not been related to health outcomes, subjects were reclassified with MS using definitions 3 and 4, if two of the criteria, excluding BMI, were met and BMI and waist z-scores were compared by t-test between those with MS and those without. A significance level of 0.05 was used.

Results

Subject anthropometric measurements are shown in Table 2. Compared with females, males were older, taller, heavier and had greater waist circumference and waist z-score (all $p<0.05$) but there was no difference between the sexes for BMI or BMI z-score ($p=0.54$ and 0.35 respectively). Using the BMI cut-points published by Cole et al (19), all subjects were overweight and 78% (82% of males) were obese. If subjects were classified into weight status categories using waist circumference percentiles (centrally overweight $\geq 91^{st}$, centrally obese $\geq 98^{th}$ percentile) (26, 27) all but three females were classified as obese. Ninety percent of subjects identified as overweight by BMI were classified as centrally obese by waist percentile, and one female who was obese according to BMI was classified as centrally overweight based on waist percentile. Twenty-six percent of subjects (42% of males) had a waist z-score > 3.5.

Table 3 shows each of the MS indicators by insulin quartiles. Only HDL-C differed by gender with higher values in males compared with females, (1.40 (0.25) versus 1.26 (0.23) mmol/L; $p=0.008$). There were significant differences across the insulin quartiles for the four metabolic indicators (SBP, TG, TC, HDL-C, all $p<0.05$) as well as waist z-score ($P=0.03$), but not BMI z-score ($p=0.10$). A similar analysis comparing indicators according to BMI z-score quartile identified significant differences in waist z-score ($p<0.001$) and insulin ($p=0.008$) only, and comparison by waist z-score quartile showed significant differences in BMI z-score ($p<0.001$) and insulin ($p=0.003$) only (data not shown).

Table 4 shows the number of subjects identified with abnormal values for metabolic indicators used in the six definitions of MS. No subjects had abnormal fasting glucose values. Additionally, forty-seven percent of subjects had total cholesterol ≥ 4.40 mmol/l and 43% had an LDL-C cholesterol ≥ 2.85mmol/l. The prevalence of elevated diastolic blood pressure defined as > 95^{th} percentile for height, age and gender was low (1%). The

prevalence of these cardiovascular risk factors was neither different by gender nor according to presence or absence of MS by any definition.

Prevalence of MS was low when applying cut points used in adults, 4% and none of the sample respectively for definitions 1 and 2. Focusing on the child-specific definitions, using Definition 3, 60% (54% of males) of subjects were classified with MS. Fewer subjects (39%; 34% of males) were classified with MS using Definition 4 in which the cut points for TG and HDL-C are more conservative. The same 39% of subjects were classified with MS if waist circumference was used instead of BMI (Definition 5). There were no differences in prevalence of MS according to gender but the prevalence of MS did increase across insulin quartile regardless of which definition was used (Figure 1, $p<0.05$). There was no difference in presence of MS according to BMI z-score or waist z-score quartile using the three child-specific definitions. MS was present in 48% of overweight subjects and 63% of obese subjects when Definition 3 was used. The corresponding figures for Definition 4 were 29% and 42%.

There were no significant differences in BMI or waist z-scores between those with and without MS defined by Definitions 3 and 4 (MS v non MS: BMI z-score = 2.82 v 2.67, waist z-score = 3.31 v 3.14; $p = 0.2$). A similar analysis based on Definition 3 alone showed a significant difference between the groups in both measures of adiposity (BMI z-score 2.82 v 2.60 $p = 0.03$; waist z-score 3.31 v 3.03 $p = 0.02$).

Discussion

In this cross-sectional study of overweight children at entry into a weight management trial, we have clearly shown the central role of elevated insulin in metabolic disturbance in children. With increasing insulin quartiles, there is an increase in systolic blood pressure, fasting triglyceride, total cholesterol, HDL-C and waist z-score, but not BMI z-score. Disturbingly, up to 60% of children in this study may be classified with MS, with children in the highest insulin quartile more likely to be classified with MS. The prevalence of MS in young children depends strongly on the definition chosen, with higher prevalence rates estimated if child specific cut points for metabolic indicators were used (39-59%), compared to an estimated MS prevalence of 0-4% using adult MS definitions. In young children, use of a MS definition where measures of insulin resistance are not used, whether age modified or not, produces a low prevalence of MS.

This is the first study in which the variation in MS prevalence according to definition has been described in pre-pubertal children. The findings are consistent with those observed in adolescents where agreement between prevalence of MS using 2 adult MS definitions was poor (k statistic=0.41) (23). The lower prevalence of MS estimated in children using adult definitions compared to variation in adolescents is not unexpected. Limitations of the classifications of MS are less likely to occur in adolescents than in younger children as the cut points for adolescents will be closer to those of adults.

The MS in adults is associated with increased morbidity and mortality (6). The indicators of MS are increasingly recognised in adolescence (16, 17, 23, 28); however, there are no associated long term morbidity and mortality data available for this age group. A recent US report on MS in adolescents, based on an age-adjusted NCEP definition, suggests that the prevalence of MS has risen from 4.2% in 1988-1992 to 6.4% in 1999-2000 (28). Studies in children and adolescents aged two to 20 years report varying prevalence rates

of MS (15, 16, 29). Our results show a higher prevalence of MS in an overweight and mildly obese sample (39-59%), when compared to estimates of 11-15% using study-derived cut-points applied to the EGIR definition in a representative community sample of Canadian 9-13 year olds (15).

The prevalence rates found in our study are similar to those reported by Weiss et al (16) in the US and by Viner et al (29) from the UK. Viner et al applied a WHO-modified definition in 103 obese (BMI > 95th percentile) 2-18 year olds and estimated MS prevalence at 33% (29). Weiss et al defined MS using the EGIR definition (modified using child-specific US cut points for MS indicators) in a mixed race US overweight (n=31) and obese (n=439) population of 4-20 year olds (16). Prevalence rates varied between 38-49% depending on severity of obesity (16). A notable difference of our study, using the Lambert criteria, to that of Weiss and colleagues is that none of the overweight subjects in the Weiss study had MS, compared to just over one quarter of overweight subjects in our study, a finding which shows how 'definition-sensitive' MS prevalence is in childhood (16).

These studies on the prevalence of MS in young people raise a number of important issues. First, is it possible to define the MS in children and adolescents? A single definition would be invaluable for comparative studies. It is likely that the prevalence of MS as defined in adults is uncommon in children, except perhaps in those with more extreme obesity. This is borne out by our findings of a low prevalence of MS using adult definitions. Prevalence rates based on adult cut points could therefore be presumed to be an underestimation, as cut points used to define adult MS are too high for a paediatric population. The use of age-adjusted indicator criteria to define MS in children may allow better comparisons with adult prevalence rates which would be important in assessing the long term evolution of MS and is consistent with the concept of tracking of cardiovascular risk factors, many of which are indicators of MS (7-8, 15, 29). Secondly, there may exist in

children a pre-MS condition which can evolve to adult MS and for which intervention should be considered. Finally, any MS definition needs to be practical in a clinical setting and the necessary age-adjustments, may hinder this requirement.

The comparison of MS definitions as performed in this study has not been previously described in pre pubertal children. Raised fasting insulin is central to and was the most common metabolic disturbance observed in 85% of this overweight and mildly obese sample. Children with hyperinsulinaemia were found to have significantly higher levels of other common cardiovascular risk factors. This finding confirms that, although group average values of these cardiovascular risk factors may still lie within the normal or recommended range for age, cardiovascular risk factor values which trend towards abnormal are associated with higher insulin levels. In this study, the prevalence of individual cardiovascular risk factors was different from that seen in work from the US and UK (7, 29). There was a lower prevalence of abnormal TG and a higher prevalence of elevated SBP, LDL-C or TC compared to both the US and UK. There was a lower prevalence of abnormal HDL-C versus the US but a higher prevalence versus the UK. It could be postulated that absolute fasting insulin levels in children could be used for early detection of a pre-MS. There is at present no generally accepted clinical definition for insulin resistance in children, primarily because of limited normative data for either fasting or stimulated insulin responses in normal or overweight children and variation in insulin level results with different assays.

In this study, weight status, as defined using BMI or waist circumference cut points (19, 26-27), were poor identifiers of MS, even when using age appropriate cut-points (Definitions 3, 4 and 5). This is a clinically relevant finding that is in line with other studies (30), as it implies the necessity for metabolic risk factor assessment to define a risk category in children. An additional finding in our study is the observation that, while 20% of

children were identified as overweight using BMI, only 3% of children were classified as centrally overweight rather than centrally obese using a waist z-score equivalent to < 98th percentile and > 91st percentile. Further study in children is required on a morbidity-related definition of overweight using waist circumference, which in adults and probably children, is a better predictor than BMI of metabolic risk (6, 30). Higgins et al have suggested a single circumference cut point (71cm), not adjusted for age in children (31); we were unable to confirm the Higgins' data, as the mean waist circumference of the sample was too high.

Hyperinsulinaemia was the most common metabolic abnormality in overweight pre-pubertal children, yet this is potentially the least likely test to be performed as part of the medical assessment of such patients. To our knowledge only one set of national clinical obesity management guidelines has addressed the measurement of fasting insulin levels in children (32). In these guidelines assessment of endocrine risk factors in obese children is linked to the presence of family risk of overweight and diabetes or clinical signs such as acanthosis nigricans. The findings from this study suggest that there is a need to measure fasting insulin concentration in overweight and obese children, regardless of family history of diabetes or ethnic background. This is in agreement with Viner et al who found that family history was not related to MS risk (29). This has implications for screening costs for children identified as overweight or obese. Early detection of hyperinsulinaemia may indicate changes in metabolic profile before other more commonly measured cardiovascular risk factors are outside recommended ranges. The common or shared aetiologies of obesity and MS may also impact on who is targeted for obesity treatment and the management approach chosen (33).

The strengths of this study are recent data collection allowing assessment of MS prevalence within a background of high obesity prevalence and the narrow age range

which limits the effect of age-related differences, including the possible confounding of puberty on insulin resistance. The limitations of the study are the lack of a (non-overweight) control group to enable comparison and that the cut points used for MS definitions were not derived from local data. The cross-sectional design does not allow comment on how MS indicators evolve over time or what effect the physiological insulin resistance of puberty might have on the evolution of MS.

It is difficult to clarify the meaningfulness of the different definitions or make recommendations for suitable cut point values. In the clinical setting, use of a definition that includes a measure of fasting insulin and uses age-appropriate cut points is important. However the need to minimise the number of cut points that must be remembered or calculated to make any definition workable highlights that none of those posed here are ideal. There may be other markers suitable as a simple clinical tool for screening of MS risk in overweight children. For example recent work in adults and adolescents show that CRP, as a marker of systemic inflammation, is a risk factor for type 2 diabetes and CVD, and strongly correlates with BMI and insulin levels which can be detected early in life (34-35). This is an area that should be considered and further explored in finding a consensus for definition of MS in young children.

In conclusion, this study emphasises the central role for hyperinsulinaemia in the definition of MS in overweight children. While problematic from a clinical and laboratory perspective, there remains a clear need for normal insulin reference ranges to be established in children and adolescents over a range of clearly defined weights and pubertal status. It is likely that these ranges will need to be assay and population-specific (36, 37). We agree with Lambert et al that the insulin resistance syndrome (IRS) of childhood, or pre-MS, may be a better name than MS in this age group.

Acknowledgements

This research was funded by the Australian Health Management Group Assistance to Health and Medical Research Fund. Rebecca Golley is supported by an Australian National Health and Medical Research Council Postgraduate Research Scholarship (# 229978). We thank the children and families for participating in the study including blood sample collection. Many thanks for assistance from following: Ms Sarah Garnett, Institute of Endocrinology, The Children's Hospital at Westmead and Ms Margie Gruca, Lab Manager James Fairfax Institute Paediatric Nutrition, The Children's Hospital at Westmead for calculation of waist circumference z-scores: Division of Laboratory Medicine, Women's and Children's Hospital, Adelaide: Diagnostic Laboratory, Department of Endocrinology Royal Prince Alfred Hospital (RPAH), Sydney.

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Table 1 Metabolic indicators and cut points included in six definitions used to classify Metabolic Syndrome (MS)

		Indicator criteria[1]						
	Definition of Metabolic Syndrome	**Glucose (mmol/L)**	**Triglycerides (mmol/L)**	**HDL-C (mmol/L)**	**Systolic blood pressure (mmHg)**	**BMI**	**Waist Circumference (cm)**	**Insulin (pmol/L)**
1	Adult European Group for the Study of Insulin Resistance (EGIR) (10)[2]	6.1	2.0[3]	1.0 [3]	140	-	M[4]: 94 F[4]: 80	51[5]
2	Adult US National Cholesterol Education Program (NCEP) (11)[6]	6.1	1.7	1.0	130	-	m: 102 f: 88	-
3	Lambert child (15)[2]	6.1 – 5.9	m: 0.9 f: 1.00	m: 1.2 f:1.2	P-95% height [7]	P-85%[8]	-	m: 35.0 f: 40.6
4	Lambert child modified (15)[2]	6.1-7.9	1.8	0.8	P-95% height [7]	P-85%[8]	-	m: 35.0 f: 40.6
5	Adult EGIR modified[2]	6.1-7.9	1.8[3]	0.8[3]	P-95% height [7]	-	P-91%[9]	m: 35.0 f: 40.6
6	Adult NCEP modified [6]	6.1-7.9	1.8	0.8	P-95% height [7]	-	P-91%[9]	-

[1] greater than or equal to value except HDL-C for which less than or equal to value
[2] MS present if insulin and any other 2 indicators meet criterion
[3] high triglyceride and/or low HDL-C
[4] m = males, f = females
[5] upper 95% confidence limit of a normal volunteer adult sample from the Endocrinology Laboratory, Royal Prince Alfred Hospital, Sydney (N= 148)
[6] MS present if any 3 indicators meet criteria
[7] used P-95% for height as P-75% cut points not available (22)
[8] only 9 y values available; percentile equivalent of these values in UK data determined (20) (m: 1.8, f: 1.5) and extrapolated for all ages
[9] age and gender specific UK waist circumference reference curves (25)

Table 2 Mean (SD) anthropometric characteristics of a sample of 6 to 9 year old overweight and mildly obese pre-pubertal children

	All	Boys	Girls	P value[1]
N	99	35	64	
Age (years)	8.3 (1.1)	8.7 (1.0)	8.0 (1.1)	<0.01
Height (cm)	136.4 (8.3)	140.1 (7.8)	134.4 (8.0)	<0.01
Weight (kg)	45.4 (8.9)	48.4 (10.5)	43.8 (7.5)	0.01
BMI (kg/m^2)	24.2 (2.5)	24.4 (3.0)	24.1 (2.3)	0.54
BMI z-score	2.7 (0.5)	2.8 (0.4)	2.7 (0.5)	0.35
Waist circumference (cm)	77.2 (7.0)	79.3 (7.6)	76.1 (6.5)	0.03
Waist z-score	3.2 (0.6)	3.5 (0.7)	3.0 (0.5)	<0.01

485 [1] Significance of independent t-test for comparison by gender

Table 3 Mean (SD) metabolic and anthropometric characteristics of a sample of 6 to 9 year old overweight and mildly obese pre-pubertal children

		Insulin quartile				P value[1]
	All	1	2	3	4	
N	99	25	26	25	23	
Insulin (pmol/l)	79.9 (37.3)	36.6 (9.4)	65.6 (8.9)	92.0 (9.1)	130.0 (27.2)	<0.01
Systolic BP (mmHg)	116 (11)	111 (9)	116 (12)	116 (11)	120 (9)	0.04
Diastolic BP (mmHg)	57 (7)	57 (8)	56 (6)	57 (6)	60 (8)	0.19
Triglyceride (mmol/l)	0.7 (0.6)	0.4 (0.2)	0.6 (0.4)	0.9 (0.7)	1.1 (0.7)	<0.01
Total cholesterol (mmol/l)	4.5 (0.9)	4.1 (0.6)	4.6 (0.7)	4.4 (0.7)	4.9 (1.3)	0.04
LDL cholesterol (mmol/l)	2.8 (0.8)	2.5 (0.6)	2.9 (0.6)	2.7 (0.6)	3.2 (1.3)	0.07
HDL cholesterol (mmol/l)	1.3 (0.2)	1.4 (0.2)	1.4 (0.2)	1.2 (0.2)	1.2 (0.2)	<0.01
Glucose (mmol/l)	4.4 (0.8)	4.1 (1.1)	4.5 (0.7)	4.5 (0.5)	4.6 (0.7)	0.16
BMI z-score[2]	2.7 (0.5)	2.6 (0.5)	2.7 (0.5)	2.7 (0.4)	2.9 (0.5)	0.10
Waist z-score[3]	3.2 (0.6)	3.0 (0.6)	3.1 (0.5)	3.2 (0.6)	3.5 (0.6)	0.03

[1] significance of ANOVA for comparison across quartiles

[2] reference 19

[3] reference 25

Table 4 Frequency of abnormal values for metabolic indicators and the number of overweight and mildly obese pre-pubertal children (N=99) classified with metabolic syndrome using the six definitions

Definition	Triglyceride	HDL	Systolic BP	BMI	Waist circumference	Insulin	MS
1 European Group for the Study of Insulin Resistance (EGIR) [1]	3	12	0	na	17	74	4
2 US National Cholesterol Education Program (NCEP) [2]	5	12	6	na	3	na	0
3 Lambert[1]	26	31	41	99	na	85	59
4 Lambert modified[1]	3	2	41	99	na	85	39
5 EGIR modified[1]	3	2	41	na	99	85	39
6 NCEP modified[2]	3	2	41	na	99	na	3

[1] MS present if insulin and any other 2 indicators meet criterion
[2] MS present if any 3 indicators meet criterion

Figure 1 Prevalence of Metabolic Syndrome using five different definitions[1, 2] according to insulin quartile[3] in overweight and mildly obese pre-pubertal children (N=99)

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[1] see table 1 for details of definitions

510 [2] Definition 2 not included as no subjects were classified with MS by this definition

[3] $p<0.05$ for increasing prevalence of MS across insulin quartile for definition 1, 3-5