

# An Apple from the Tree? A Look at Cardiometabolic Risk Factors in Parents and Offspring

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A THESIS

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Tanya L. Halvorsen, MD,PhD

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Antoinette Moran, MD

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<sup>1</sup> Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota 55454; <sup>2</sup>Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, 55455 USA

***DEDICATIONS***

This degree that I have earned  
And the sense of achievement that I have attained with it  
Are dedicated wholeheartedly to MY FAMILY,  
Without whom this work would not have been possible.  
You have my undying gratitude  
And my love  
Forever.

Should any future benefit arise from this work,  
I give it freely.

*~Tanya*

## ABSTRACT

**Objectives:** To relate parental cardiometabolic risk factors with corresponding values in their children and assess the influence of adiposity on these associations.

**Study Design:** Associations of adiposity, blood pressure, lipids, fasting insulin and glucose, and a risk factor cluster score were evaluated in a cross sectional study of 179 parents and their children (6-18 years, N=255). Insulin resistance was assessed by euglycemic clamp in parents and children aged 10 or older. Metabolic syndrome in parents was defined by ATPIII criteria. Cluster scores of the risk factors were created based on age-specific z-scores. Analyses included Pearson correlation and linear regression, adjusted for parent and child age, sex, race, and body mass index (BMI), accounting for within-family correlation.

**Results:** We found positive parent-child correlations for measures of adiposity (BMI, BMI percentile, waist, subcutaneous fat, and visceral fat;  $r=0.22-0.34$ , all  $p\leq 0.003$ ), systolic blood pressure (SBP) ( $r=0.20$ ,  $p=0.002$ ), total cholesterol ( $r=0.39$ ,  $p<0.001$ ), low-density lipoprotein cholesterol ( $r=0.34$ ,  $p<0.001$ ), high density lipoprotein cholesterol ( $r=0.26$ ,  $p<0.001$ ) triglycerides ( $r=0.19$ ,  $p=0.01$ ) and insulin sensitivity ( $r=0.22$ ,  $p=0.02$ ) as well as cluster scores ( $r=0.15$ ,  $p=0.02$ ). After adjustment for BMI all parent-child correlations, except systolic blood pressure, remained significant.

**Conclusions:** Although adiposity is strongly correlated between parents and children, many cardiometabolic risk factors correlate independent of parent and child BMI. Adverse parental cardiometabolic profiles may identify at-risk children independent of the child's adiposity status.

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## LIST OF ABBREVIATIONS

BMI, body mass index

cm, centimeters

kg, kilogram

m, meter

mm, millimeter

Hg, mercury

BP, blood pressure

SBP, systolic blood pressure

DBP, diastolic blood pressure

LDL-C, low density lipoprotein cholesterol

HDL-C, high density lipoprotein cholesterol

lbm, lean body mass

CS5, 5 component cluster score

CS6, 6 component cluster score

ICC, Interclass Correlation

## **Chapter 1: INTRODUCTION**

Cardiovascular (CV) risk factors such as hypertension and hyperlipidemia are well known to be shared traits between parents and children (1-5). Because adiposity is also commonly shared between generations (3-8) and because excess body fat is a known precursor of CV risk (9-12), it is possible that much of the generational transmission of CV risk factors could be mediated by adiposity. The literature is conflicting in this regard. It was recently suggested that associations between parental obesity and individual CV risk factor levels in their children are mediated primarily by obesity in the children (13), while a second study reported no evidence that parent-child correlations were affected by adiposity (3).

It is also known that the risk of CV disease is greatly increased when abnormal levels of multiple risk factors occur in combination, e.g., the metabolic syndrome (14, 15). While CV risk factor levels are significantly lower in children than adults, children with levels at the upper end of the normal range are thought to be at greater future risk (16). One way to look at this combined risk is to formulate a cluster score based on a simultaneous assessment of multiple risk factor measurements. We know of no studies that have examined how this combined risk associates between parents and children or the role of adiposity in this relation.

The present study was designed to analyze parent-child risk factor correlations, evaluate the influence of body mass index (BMI) on these associations and assess correlation between parent and child risk factor cluster scores.

## CHAPTER 2: METHODS

**Subjects:** The study was conducted in a cohort of parents (N=179, mean age 39 years) and their children (N=255, age 6-18 years). The parents, then aged 6-9 years, were originally enrolled in a longitudinal study of CV risk factors (17). Because parental participation in the current study was based on their prior childhood enrollment, only one parent per child was eligible. Individuals with chronic diseases including type 2 diabetes, end-stage kidney disease or cancer (n=14, all parents) were excluded. The University of Minnesota Institutional Review Board approved this study. All adult subjects signed informed consent documents for themselves and on behalf of their participating children, who gave signed informed assent.

**Anthropometric Measurements and Blood Pressure:** Parent and child anthropometric measurements were obtained using standardized protocols. Standing height was measured with a stadiometer to the nearest centimeter (cm). A balance scale was used to measure weight in kilograms (kg). Body mass index (BMI) was calculated as weight (kg) divided by height (meters) squared. BMI percentile was calculated for each participant based on age and sex (18). Waist circumference was measured at the umbilicus to the nearest 0.5 cm, taken in duplicate and the mean value reported. Percent body fat, fat mass and lean body mass (LBM) were determined by dual-energy x-ray absorptiometry (DXA) with a Lunar Prodigy scanner (pediatric software version 9.3; General Electric Medical Systems, Madison, WI, USA) in the total body scanning mode. Visceral adipose tissue (VAT) and total abdominal fat were measured by abdominal CT scan at the level of L4-L5 disk as

previously described (19). Blood pressure (BP) was measured in duplicate on the right arm after participants were sitting in a quiet room for at least five minutes using a digital BP cuff, and the average of the two values was reported.

**Laboratory Evaluations:** Fasting blood samples were collected for lipids (total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C)), glucose and insulin. Assays were conducted with standard procedures at the Fairview Diagnostic Laboratories, Fairview-University Medical Center (Minneapolis, MN), a Centers for Disease Control and Prevention-certified laboratory.

**Euglycemic Insulin Clamp Studies:** Euglycemic clamp studies were performed in parents and older children (ages 10-18) as previously described (20). Younger children did not undergo the clamp procedure. Insulin sensitivity,  $M$ , was calculated based on the amount of glucose required to maintain euglycemia during the last 40 minutes of the clamp, corrected for lean body mass (LBM) and expressed as  $M_{LBM}$  (milligrams of glucose per kilogram of LBM per minute). A higher  $M_{LBM}$  represents greater insulin sensitivity (i.e. less insulin resistance).

**Risk factor Cluster Score, Metabolic Syndrome:** The components of the risk factor cluster scores were chosen to measure health risks similar to those represented in the adult metabolic syndrome (Figure 1). Five and six-component cluster scores (CS5 and CS6) were created by calculating age-group (6-18, 6-9 or 10-18 years old) specific z-scores for waist circumference, SBP, fasting glucose, fasting insulin, HDL-C and

triglycerides, summing the z-scores for waist, SBP, insulin and triglycerides +/- glucose, subtracting the z-score for HDL-C (which is protective), and dividing by 5 or 6 (depending on whether glucose was included) to create a mean risk score. The details of these calculations are presented in [Appendix I](#). We created the five-component cluster score (CS5) excluding the fasting glucose component because, although fasting glucose is one of the criteria in the diagnosis of adult metabolic syndrome, it virtually always falls within a narrow normal range in children and adolescents and is therefore less likely to provide useful information about children's future metabolic risk. The same method was used to calculate parent cluster scores, using z-scores derived from parent-specific risk factor means. A similar cluster score, which included fasting glucose but not fasting insulin levels, has been shown previously by our group to be a significant predictor of cardiometabolic risk in adolescents followed into adulthood (21).

Metabolic syndrome in parents was defined by ATP III criteria (22, 23), i.e., meeting at least 3 of the following 5 criteria: 1) fasting glucose  $\geq 110$  mg/dl, 2) HDL-C  $\leq 40$  mg/dL for men or  $\leq 50$  mg/dl for women, 3) BP  $\geq 130/85$  mmHg, 4) triglyceride level  $\geq 150$  mg/dl and 5) waist circumference  $\geq 102$  cm for men or  $\geq 88$  cm for women.

***Statistical Analyses:*** All analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA). BMI percentile was calculated for children by age and sex according to the CDC growth charts (18). Due to a skewed distribution, triglyceride levels were log-transformed before analysis, with means exponentiated and reported as geometric means. Multiple regression analyses (PROC MIXED) accounting for within

family correlation (interclass correlation, ICC) were used to estimate means (standard errors; SE) for demographic and clinical characteristics by sex for parents and children adjusted for age. Pearson partial correlation coefficients (computed using standardized deviates for both parental and child variables in PROC MIXED to account for within family correlation) were used to evaluate the relations of cardiometabolic risk factors between parents and their children, adjusted for parent and child age, sex, race, and BMI. P-values  $< 0.05$  was considered significant; however, because multiple comparisons were performed, we were cautious in the interpretation of p-values that were close to 0.05.

## CHAPTER 3: RESULTS

***Subject Characteristics:*** Demographic and clinical characteristics of parents and their children are reported by sex in [Table 1](#). Adult men had significantly greater CV risk than adult women as evidenced by larger waist circumferences, higher blood pressure, less favorable lipid levels, lower insulin sensitivity, higher fasting blood glucose and insulin levels, and higher prevalence of metabolic syndrome. Of the 255 children, 168 were between the ages of 10 and 18 years (mean age  $14\pm 2$ ) and 87 were 6-9 years old (mean age  $7\pm 1$ ). Among the children, both sexes were equally represented. A higher percentage of non-white children were in the older (10-18 year old) age group. There were no statistically significant differences between boys and girls in the 6-9 year old age group, except that girls' cluster scores tended to be lower. In the 10-18 year old age group, boys had greater insulin sensitivity (higher  $M_{lbm}$ ) and tended to have lower fasting insulin, lower BMI and slightly higher SBP.

***Parent-Child Correlations For Individual Risk Factors:*** There was a significant correlation between parents and children for most individual components of the cardiometabolic profile ([Table 2](#)). Every measure of adiposity (BMI, waist, subcutaneous fat, visceral fat and child BMI percentile/parent BMI) was correlated between parent and child (all  $p\leq 0.003$ ). SBP, total cholesterol, LDL-C, HDL-C, triglycerides and insulin sensitivity ( $M_{lbm}$ ) (10-18 year olds only) all correlated with p-values  $< 0.01$  except for triglycerides ( $p=0.01$ ) and insulin sensitivity ( $p=0.02$ ). The strength of these associations varied, with the greatest correlations noted between parent and child total cholesterol,



parent and child LDL-C, and parent BMI with child BMI percentile. There was no correlation between parent and child fasting glucose or parent and child insulin levels.

After adjustment for parent and child BMI, the parent-child correlation for SBP was attenuated, suggesting that this relation is at least partially mediated by adiposity (Table 2). In contrast, other parent and child risk factor associations were maintained (total cholesterol, LDL-C) or increased (HDL-C, triglyceride levels and insulin sensitivity).

Parent-child correlations were also analyzed separately by child age group (Table 2). With the exception of BMI percentile, which correlated with parent BMI in both age groups, measures of adiposity were significantly correlated between parents and 10-18 year old but not 6-9 year old children, with  $p$  for age interaction for waist and visceral fat = 0.05 and 0.02, respectively. The correlation between parent and child triglyceride levels was also higher in the 10-18 year old than younger children, but the age interaction  $p$ -value was high. An age interaction was not supported for parent-child correlations of any other risk factor. Parent-child trends for individual risk factors are also presented by comparing child means within parent tertiles for each age group (Table 3 and Figure 2 with additional illustrations in Appendix II). Among 10-18 year old children, the tertile means for most risk factors (excluding only DBP and total cholesterol) increased monotonically from one tertile to the next, supporting a linear model of parent-child risk factor associations. This was true even for fasting glucose and insulin levels, in which parent-child correlations were not significant, in that the shallow rise was consistent across tertiles in these cases. Patterns were much more variable in the 6-9 year old age

group, and tended to be flatter; clear linear associations were only present for BMI, BMI percentile (within parent BMI tertiles), HDL-C and fasting insulin.

***Parent Metabolic Syndrome and Child Risk:*** Children in the 10-18 year old age group whose parents had a diagnosis of metabolic syndrome had greater BMI percentile, waist circumference, fasting triglyceride levels and fasting insulin levels compared to those whose parents did not have the metabolic syndrome. No significant differences were observed between 6-9 year old children of parents with or without the metabolic syndrome (Table 4).

***Cluster Score Assessment:*** Cluster scores were computed for both parents and children to compare a more comprehensive measure of their cardiometabolic risk. Unlike the metabolic syndrome, which is classified categorically as present or not, cluster scores are continuous measures based on age group-specific Z-scores for each risk factor component. Parent and child cluster score correlations were lower than those for adiposity and blood lipids (Table 2). Adjustment for parent and child BMI did not change this relation appreciably. However, when we examined the two age groups separately, parent and child cluster scores were more highly correlated in the 10-18 year old age group, especially after adjustment for BMI (Table 2). The inclusion of fasting glucose levels in the cluster score calculation (CS6) reduced this association.

## CHAPTER 4: DISCUSSION

Several studies have compared individual cardiovascular risk factors between parents and children (1-5). Our study adds to the current body of literature by evaluating an extensive panel of individual parent-child risk factor associations in both young children and adolescents, and by taking the novel steps of including clustered risk factor associations and assessing the role of adiposity in each of these relations. Because obesity itself is associated with changes in blood pressure, lipid levels and insulin sensitivity within individuals (24-28), and because there is a strong association between parent and child BMI, we hypothesized that parent-child CV risk correlations might be mediated primarily by adiposity. We found significant correlations between parents and children for multiple measures of adiposity, SBP, lipid levels and insulin sensitivity, consistent with other studies that evaluated some of these same components (1-5). Contrary to our hypothesis, however, after adjusting these results for parent and child BMI, every significant correlation except for blood pressure retained statistical significance and, in some cases, even increased. The finding that children of parents with metabolic syndrome only had higher levels of risk factors that are included among the diagnostic criteria of the metabolic syndrome is also consistent with individual risk factors associating independently within parent-child dyads. Our study highlights the importance of shared genetic and/or environmental traits independent of obesity in the transmission of CV risk.

The heritability of blood pressure, independent of adiposity, remains controversial. In this study, parent-child correlations in SBP were at least partially mediated by BMI. This is

not surprising, considering that blood pressure has been shown to correlate with BMI in children (29, 30), and the prevalence of pre-hypertension and hypertension has been estimated to be 15 times higher in overweight and obese children and adolescents compared to normal-weight peers (29). Our results contrast with a previous report of a significant genetic effect on blood pressure in Polish twins after adjusting for BMI (31). Closer genetic similarities (about half of the twin dyads were monozygotic) and differences in statistical modeling methods may account for the different findings. Another consideration is that heritability of blood pressure may not be uniform across different populations. For example, in one study of hypertensive children, black children were much more likely to have a hypertensive parent than white children (32). Our study was not powered to explore this issue.

Cholesterol (total, LDL and HDL) levels correlated between parents and children more highly than any other risk factor, except for BMI. Our findings were consistent with other studies associating children's lipid profiles with those of their parents (1, 3-5). Furthermore, the fact that cholesterol levels remained highly correlated even after adjustment for BMI is a novel finding and supports the overall conclusions of the study for the associations of CV risk factors between parents and children independent of adiposity.

Insulin sensitivity in 10-18 year old children correlated with parental values.

Interestingly, the correlation between parent and child insulin sensitivity was strengthened after adjustment for child and parent BMI. Child Tanner stages were not

assessed, thereby complicating the interpretation of insulin sensitivity data in the older children, as pubertal subjects are known to have transient increases in insulin resistance (33). Results were adjusted for age and sex, which may help to account for pubertal changes, but imperfectly since children enter puberty at different ages. This relationship might have been interesting to explore in the younger children, but euglycemic clamps were not performed in this age group because of concerns about excessive participant burden.

The risk of developing cardiometabolic disease is higher when multiple risk factors are present. In particular, adults meeting criteria for metabolic syndrome have a demonstrable increase in the risk of future CV disease and type 2 diabetes (34). Attempts to define an analogous pediatric “metabolic syndrome” have been hampered by the fact that few children have cardiometabolic abnormalities in the overtly abnormal range and because the metabolic syndrome construct has been shown to lack stability through childhood (35). Nonetheless, there is a strong body of research demonstrating that higher levels of these risk factors, even within the normal range, tend to track into adulthood, are difficult to reverse, and are associated with increased morbidity over time (16, 36). Standard deviation “cluster scores” have been developed as a means of better defining risk in younger patients by considering each risk factor as a continuous variable that contributes to the total score (21, 37, 38). Thus, each subject can be assigned a relative risk rather than being grouped categorically as having or not having the metabolic syndrome. We have previously shown that a cluster score based on metabolic syndrome components predicts cardiovascular risk from adolescence (mean age 13 years) into

young adulthood (mean age 22 years) (21). The correlation of parent and child cluster scores and the association of parent metabolic syndrome with higher parent cluster scores (data not shown) in this study support this approach to identification of at-risk children. In this study we also found that the exclusion of the fasting glucose component from the cluster score increased the strength of the parent-child correlation, at least within the older (10-18 year old) subgroup. We were not surprised by this finding because fasting glucose levels did not correlate between parents and children, consistent with previous observations that fasting glucose is rarely abnormal in pediatric subjects and is not a useful predictor of glucose tolerance, even in obese youth (39, 40). The finding that children of parents with metabolic syndrome have statistically higher fasting insulin levels but not higher glucose levels is consistent with this observation as well.

The relation between parent and child cluster scores and parent-child correlations for measures of adiposity were stronger in older (10-18 year old) children compared to younger (6-9 year old) children. Increased risk factor levels in children of parents with metabolic syndrome only became apparent in the older age group as well. It is not surprising that these parent-child relations strengthen with age. Changes likely coincide with the transition to a more adult body habitus and physiology during puberty. We previously demonstrated a continuation of this trend into young adulthood, by describing the correlations of CV risk factors between parents and older children during the transition from adolescence (mean age 15 years) to young adulthood (mean age 22 years); parent-child correlations become stronger over this interval (41). Thus, there appears to be a natural progression where the correlations between shared CV risk factors

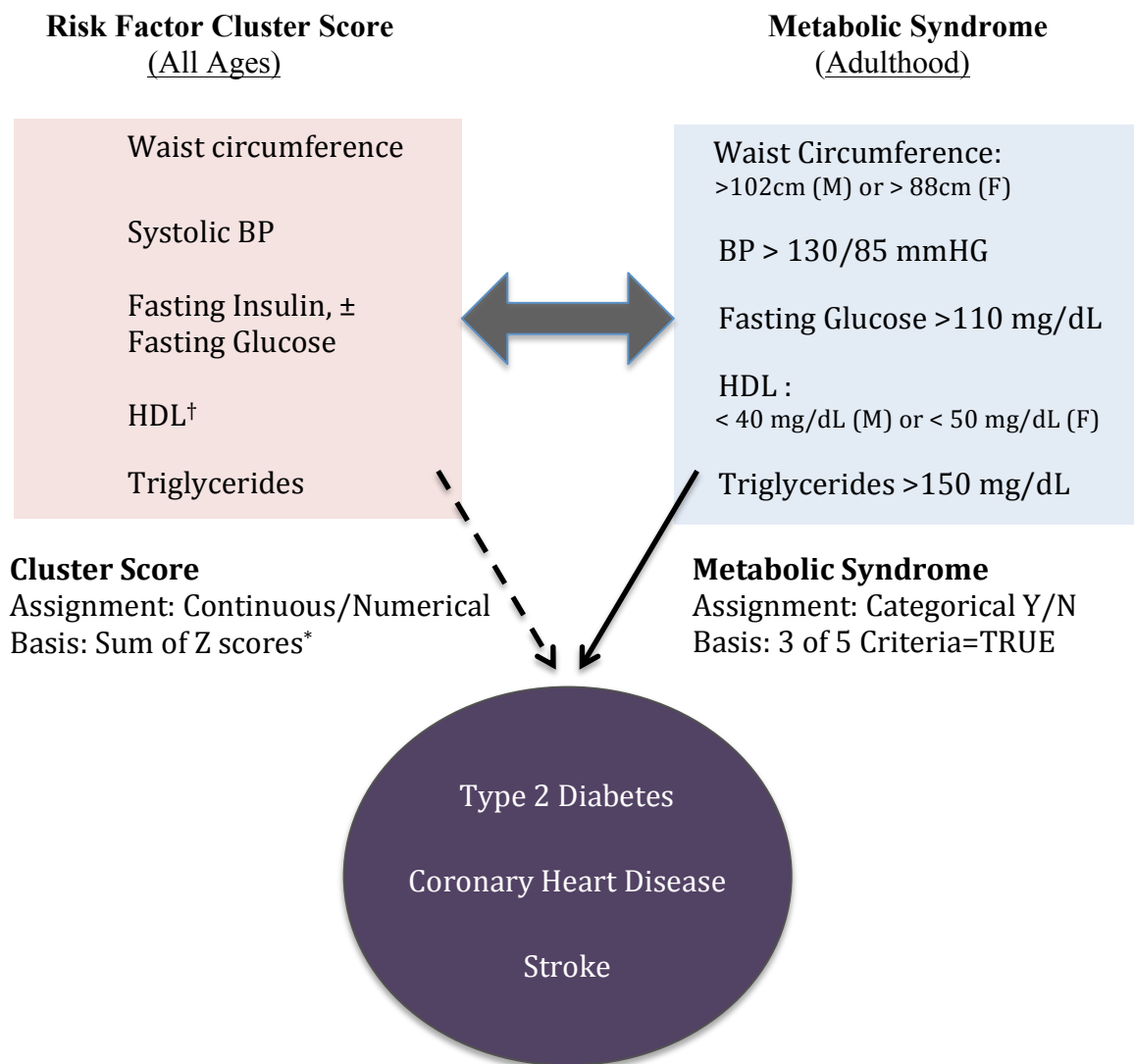
become more significant as young children transition through adolescence, and into adulthood.

An important limitation of this study is that parent factors were not fully represented since only one parent per child was included. This also limited sex-specific parental contribution analysis since we were not able to show differences in parent-child correlations between mothers and fathers (data not shown); our numbers were likely too small to allow accurate assessment. Strengths of the study include the large number of parent-child dyads representing a wide range of child ages, direct measurement of insulin sensitivity by euglycemic clamp, the multiple measurements used to assess adiposity, contemporaneous and state-of-the-art measurements for the entire study population, and the use of a cluster score applicable to both children and parents as a measure of CV risk burden.

In conclusion, individual risk factors correlate consistently between parents and children. With the exception of blood pressure, these risk relations were retained even after adjustment for parent and child BMI, demonstrating that they are not simply a product of the strong association between parent and child adiposity. While there are many public health reasons to tackle the problem of childhood overweight/obesity, these data support a role for early monitoring and more intensive intervention in children of parents with less favorable risk factors, even in normal weight children. Furthermore, similar to the concept of metabolic syndrome in adults, the development and use of risk factor cluster

scores may help to target children with relatively higher cardiometabolic risk prior to the development of overt disease.





**Figure 1. Comparison of Childhood Cluster Scores with Adult Metabolic Syndrome**

Children with a high cluster score are at risk for development of the metabolic syndrome as they mature into adulthood. Youth with high cluster scores and adults with metabolic syndrome are at increased risk of progressing to overt cardiometabolic disease.

\* Z scores based on age group-specific norms

<sup>†</sup>HDL z-scores were assigned a negative value because a higher HDL is associated with lower risk, in contrast to all other components in which the opposite is true.

**Table 1. Subject Characteristics**

Variable	Parents			Children Ages 6-9			Children Ages 10-18			
	Men (n=69)	Women (n=110)	P	Boys (n=44)	Girls (n=43)	P	Boys (n=94)	Girls (n=74)	P	ICC
Age, y	39±1.3	39±1.4	0.02	7±1.2	7±1.2	0.96	14±2.5	14±2.3	0.04	
Race, %White	70	58	0.13	73	70	0.76	46	43	0.75	1.00
Adiposity										
BMI, kg/m <sup>2</sup>	30±6.0	29±6.9	0.21	18±3.7	17±2.5	0.09	23±5.7	25±6.2	0.02	0.37
BMI %tile	N/A	N/A		64±32.7	55±26.7	0.20	67±29.1	71±29.1	0.30	0.35
Waist, cm	105±16.3	96±17.8	0.001	64±11.1	59±6.9	0.04	78±14.1	80±14.1	0.24	0.43
Subcutaneous fat, cm <sup>2</sup>	155.4±81.2	183.6±83.8	0.03	40.3±4.2	35.3±26.2	0.52	74±72.9	130.3±85	<0.001	0.21
Visceral fat, cm <sup>2</sup>	73.4±34.1	51.6±26.8	<0.001	12.6±7.3	11.3±5.3	0.41	20.2±13.9	22.5±10.2	0.21	0.29
BP, mmHg										
Systolic BP	122±12.9	109±15.2	<0.001	101±10.3	98±7.6	0.19	108±10.5	104±8.6	0.02	0.33
Diastolic BP	78±11.5	71±11.6	<0.001	57±6.3	58±8.3	0.71	58±8.1	60±7.8	0.11	0.26
Lipids, mg/dL (mmol/L)										
Total cholesterol	195±36.6 (5.04±0.95)	175±29.0 (4.54±0.75)	<0.001	154±26.0 (3.99±0.67)	164±30.1 (4.23±0.78)	0.21	150±28.9 (3.88±0.75)	154±26.8 (3.98±0.69)	0.44	0.53
LDL-C	117±29.0 (3.04±0.75)	104±25.7 (2.70±0.66)	0.003	89±18.8 (2.30±0.49)	96±26.1 (2.47±0.68)	0.32	84±24.5 (2.17±0.63)	87±23.1 (2.24±0.60)	0.56	0.35
HDL-C	42±11.6 (1.09±0.30)	53±13.0 (1.36±0.34)	<0.001	52±10.3 (1.35±0.27)	56±11.1 (1.44±0.29)	0.13	51±12.9 (1.31±0.33)	50±12.0 (1.30±0.31)	0.88	0.47
Triglyceride	192±163.9 (2.17±1.85)	92±38.5 (1.04±0.44)	<0.001	65±36.9 (0.74±0.42)	60±19.8 (0.68±0.22)	0.48	77±37.4 (0.87±0.42)	85±49.3 (0.96±0.56)	0.30	0.42
Glucose Metabolism										
Fasting glucose, mg/dL (mmol/L)	97±36.7 (5.40±2.04)	88±21.0 (4.89±1.17)	0.03	65±8.5 (3.62±0.47)	61±7.7 (3.41±0.43)	0.09	86±9.5 (4.78±0.53)	83±9.7 (4.63±0.54)	0.04	0.39
Fasting insulin, μU/L (pmol/L)	10.5±8.62 (75.2±61.8)	7.2±6.12 (51.7±43.9)	0.004	3.2±2.88 (23.1±20.7)	2.4±1.54 (16.9±11.1)	0.24	9.1±6.53 (65.2±46.9)	11.2±6.96 (78.4±50.0)	0.09	0.54
Insulin Sensitivity, $\downarrow$ M <sub>Ins</sub>	9.8±4.15	13.9±4.61	<0.001	N/A	N/A	--	13±4.8	11±3.9	0.005	0.54
Composite										
CS6	0.38±0.63	-0.24±0.53	<0.001	0.18±0.62	-0.18±0.45	0.02	0.01±0.61	-0.01±0.59	0.79	0.57
CS5 (no glucose)	0.41±0.70	-0.26±0.55	<0.001	0.17±0.67	-0.17±0.48	0.03	-0.02±0.66	0.03±0.62	0.66	0.57
Metabolic syndrome, %	39	15	<0.001	N/A	N/A	--	N/A	N/A	--	--

All data presented as mean ± standard error except for metabolic syndrome and race. Measurements were obtained for all subjects with the following exceptions: 63 men had LDL-C levels, 108 women had fasting insulin levels, and insulin sensitivity (M<sub>Ins</sub>) was measured in 64 men, 90 women, 83 boys (age 10-18) and 66 girls (age 10-18).

**Table 2. Correlations Of Risk Factor Values Within Parent-Child Dyads.**

Variable	All Children			Children Age 6-9			Children Age 10-18			Age Int	P	
	No BMI Adjustment	Adjusted For BMI	No BMI Adjustment	Adjusted For BMI	No BMI Adjustment	Adjusted For BMI	No BMI Adjustment	Adjusted For BMI				
Adiposity												
BMI	0.28	<0.001	--	--	0.045	--	--	0.34	<0.001	--	--	0.10
BMI percentile	0.34	<0.001	--	--	0.30	0.03	--	0.34	<0.001	--	--	0.57
Waist	0.22	<0.001	--	--	0.14	0.19	--	0.31	<0.001	--	--	0.05
Subcutaneous Fat	0.30	<0.001	--	--	0.22	0.08	--	0.33	<0.001	--	--	0.11
Visceral Fat	0.20	0.003	--	--	0.06	0.62	--	0.27	0.002	--	--	0.02
BP												
Systolic BP	0.20	0.002	0.16	0.02	0.23	0.10	0.19	0.20	0.01	0.15	0.07	0.24
Diastolic BP	0.14	0.05	0.12	0.10	0.01	0.93	0.02	0.18	0.04	0.18	0.06	0.72
Lipids												
Total cholesterol	0.39	<0.001	0.39	<0.001	0.45	0.007	0.46	0.37	<0.001	0.37	<0.001	0.78
LDL-C	0.34	<0.001	0.34	<0.001	0.40	0.02	0.41	0.34	<0.001	0.33	<0.001	0.65
HDL-C	0.26	<0.001	0.36	<0.001	0.28	0.06	0.46	0.24	0.01	0.33	0.001	0.98
Triglycerides	0.19	0.01	0.22	0.003	0.11	0.42	0.12	0.20	0.03	0.24	0.009	0.27
Glucose Metabolism												
Glucose	-0.01	0.90	-0.02	0.68	-0.06	0.65	-0.17	0.02	0.77	0.04	0.66	0.36
Insulin	0.07	0.26	0.12	0.04	0.13	0.29	0.10	0.08	0.35	0.14	0.09	0.48
Insulin Sensitivity $M_{30s}$	--	--	--	--	--	--	--	0.22	0.02	0.32	0.003	--
Cluster Scores												
CS6	0.14	0.02	0.15	0.01	0.19	0.16	0.07	0.60	0.08	0.21	0.03	0.56
CS5 (no glucose)	0.15	0.02	0.18	0.007	0.13	0.33	0.05	0.69	0.03	0.27	0.005	0.37

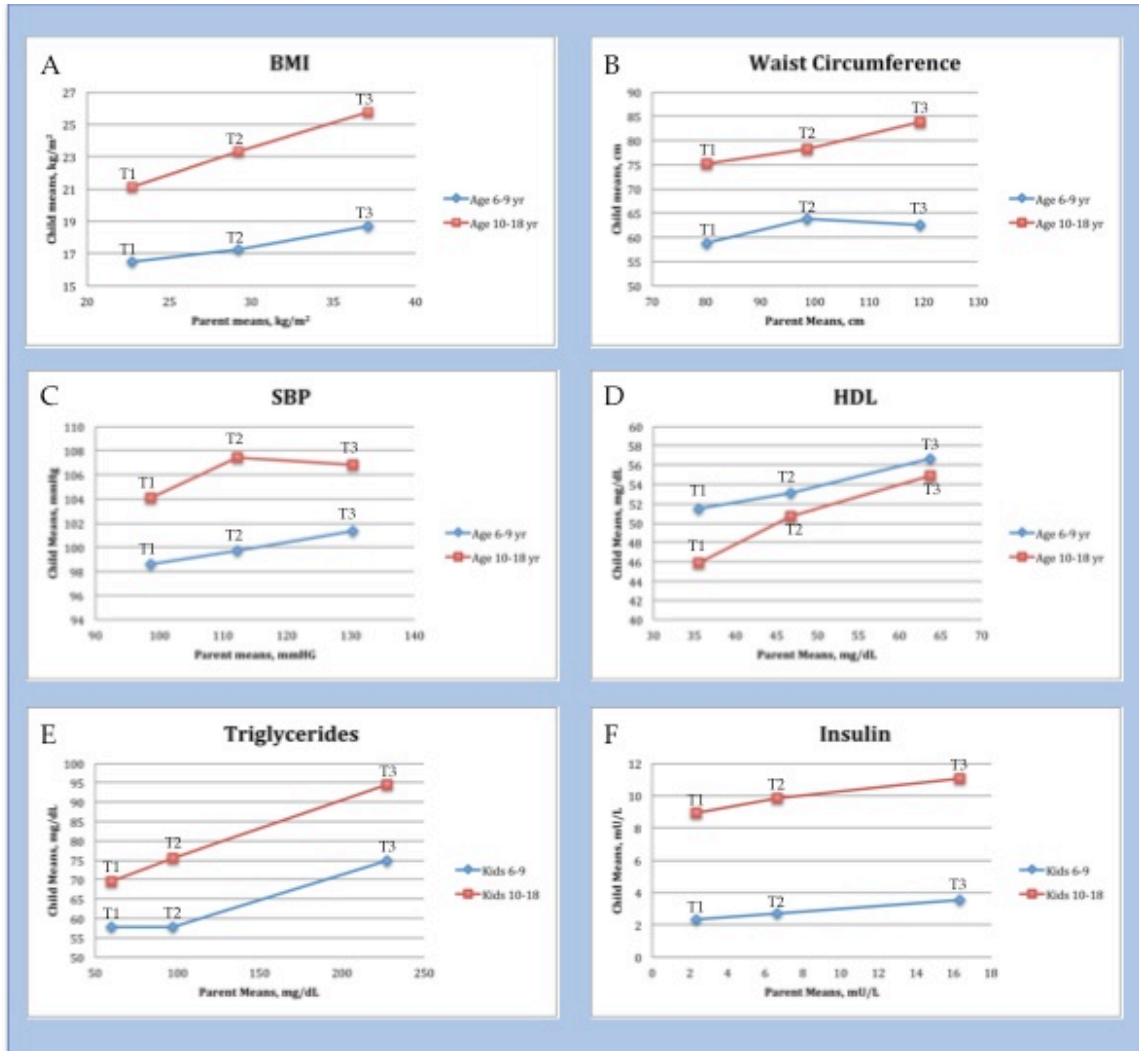
N=245 for LDL-C, n=149 for Insulin Sensitivity, n=255 for all others. All comparisons are adjusted for parent and child age, race and sex. BMI-adjusted correlations were adjusted for both parent and child BMI. Int = Interaction, r = Pearson Partial correlation coefficient.

**Table 3: Risk Factor Means of Children within Parent Tertiles**

Parent Tertile	Children Ages 6-9 yr			Children Ages 10-18		
	1	2	3	1	2	3
<b>Variable</b>						
<b>Adiposity</b>						
BMI, kg/m <sup>2</sup>	16.5 <sup>c</sup>	17.3	18.7	21. <sup>a,cc</sup>	23.3 <sup>b</sup>	25.8
BMI percentile	49.3 <sup>c</sup>	61.6	73.8	55.6 <sup>aa,cc</sup>	70.7	79.3
Waist, cm	58.9	63.8	62.4	75.2 <sup>cc</sup>	78.2 <sup>b</sup>	83.7
Subcutaneous Fat, cm <sup>2</sup>	35 <sup>c</sup>	29.2 <sup>b</sup>	57.9	63.9 <sup>a,cc</sup>	98.2	125.3
Visceral Fat, cm <sup>2</sup>	11.8	11.6	12.5	16.9 <sup>cc</sup>	20.5 <sup>b</sup>	26
<b>BP, mmHg</b>						
SBP	98.6	99.8	101.4	103.4	107.4	106.9
DBP	56.8	56.6	58.2	56.9	60.1	60.2
<b>Lipids, mg/dL (mmol/L)</b>						
Total cholesterol	147.1 <sup>cc</sup>	151.1 <sup>b</sup>	176.4	140.1 <sup>cc</sup>	148.5 <sup>bb</sup>	167.8
	(3.80)	(3.91)	(4.56)	(3.62)	(3.84)	(4.34)
LDL-c	84.4 <sup>c</sup>	84.9 <sup>b</sup>	105.7	76.8 <sup>cc</sup>	85.1 <sup>b</sup>	95.9
	(2.18)	(2.20)	(2.73)	(1.99)	(2.20)	(2.48)
HDL-c	51.5	53.1	56.6	45.9 <sup>cc</sup>	50.7	54.9
	(1.33)	(1.37)	(1.46)	(1.19)	(1.31)	(1.42)
Triglycerides	57.9	57.7	74.9	69.6 <sup>c</sup>	75.6 <sup>b</sup>	94.4
	(0.65)	(0.65)	(0.85)	(0.79)	(0.85)	(1.07)
<b>Glucose Metabolism</b>						
Fasting glucose, mg/dL	64.3	63.9	62.1	83.1 <sup>c</sup>	84.2	87.6
(mmol/L)	(3.57)	(3.55)	(3.45)	(4.61)	(4.68)	(4.86)
Fasting insulin, mU/L	2.3	2.7	3.5	8.9	9.8	11.1
(pmol/L)	(16.8)	(19.5)	(25.2)	(64.0)	(70.7)	(79.4)
Insulin sensitivity, M <sub>lbm</sub>	--	--	--	11.0 <sup>c</sup>	12.8	13.6
<b>Cluster Score</b>						
6 components	-0.076	0.068	0.039	-0.047	0.008	0.1
5 components (no glucose)	-0.125	0.094	0.076	-0.107	0.03	0.132

Parent tertiles were defined separately for each risk factor. Superscripts: a: P-diff between 1<sup>st</sup> and 2<sup>nd</sup> tertile <0.05; aa: P-diff between 1<sup>st</sup> and 2<sup>nd</sup> tertile <0.01; b: P-diff between 2<sup>nd</sup> and 3<sup>rd</sup> tertile <0.05; bb: P-diff between 2<sup>nd</sup> and 3<sup>rd</sup> tertile <0.01; c: P-diff between 1<sup>st</sup> and 3<sup>rd</sup> tertile <0.05; cc: P-diff between 1<sup>st</sup> and 3<sup>rd</sup> tertile <0.01

**Figure 2. Trends of Means within Parent Tertiles**



Parents were grouped into tertiles for each risk factor. Children were assigned to the same tertile as their parents, regardless of their own risk factor values. The mean of the children within each parent tertile was plotted against the corresponding parent tertile mean. Pictured here are the child means within parent tertiles for BMI (A), waist circumference (B), SBP (C), HDL-C (D), Triglycerides (E) and Insulin (F). T1=1<sup>st</sup> tertile, T2=2<sup>nd</sup> tertile and T3=3<sup>rd</sup> tertile

**Table 4. Risk Factor Levels in Children of Parents with and without Metabolic Syndrome.**

Variable	All Children		Children Age 6-9		Children Age 10-18		P
	- (n=198)	+ (n=57)	- (n=69)	+ (n=18)	- (n=129)	+ (n=39)	
Age (y)	12±0	12±9	7±0	7±0	14±0	14±0	0.5
Race, %White	53	56	70	75	44	47	0.73
Adiposity							
BMI, kg/m <sup>2</sup>	21±0	22±1	17±0	18±1	23±1	25±1	0.13
BMI %tile	64±2	74±4	58±4	66±7	67±3	78±5	0.05
Waist (cm)	72±1	76±2	61±1	62±2	78±1	83±2	0.04
BP, mmHG							
Systolic BP	104±1	104±1	100±1	102±2	105±1	106±1	0.60
Diastolic BP	59±1	57±1	57±1	58±2	59±1	57±1	0.10
Lipids, mg/dL (mmol/L)							
Total cholesterol	154±2 (4.0±0.1)	157±4 (4.1±0.1)	158±3 (4.1±0.1)	165±7 (4.3±0.2)	152±2 (3.9±0.1)	154±4 (4.0±0.1)	0.69
LDL-C	88±2 (2.3±0.0)	89±3 (2.3±0.1)	90±3 (2.3±0.1)	101±5 (2.6±0.1)	86±2 (2.2±0.1)	84±4 (2.2±0.1)	0.63
HDL-C	52±1 (1.3±0.0)	51±2 (1.3±0.0)	55±1 (1.4±0.0)	52±3 (1.3±0.1)	51±1 (1.3±0.0)	50±2 (1.3±0.1)	0.83
Triglyceride	71±3 (0.8±0.0)	87±5 (1.0±0.1)	62±4 (0.7±0.0)	64±7 (0.7±0.1)	75±4 (0.9±0.0)	98±7 (1.1±0.1)	0.004
Glucose Metabolism							
Fasting glucose, mg/dL (mmol/L)	77±1 (4.3±0.0)	77±1 (4.3±0.1)	64±1 (3.5±0.1)	62±2 (3.4±0.1)	85±1 (4.7±0.0)	84±2 (4.7±0.1)	0.62
Fasting insulin, mU/L (pmol/L)	7.0±0.4 (50±3)	9.4±0.8 (67±10)	2.7±0.3 (19±2)	3.3±0.5 (24±4)	9.3±0.6 (67±4)	12.2±1.1 (88±8)	0.02
Insulin Sensitivity, M <sub>30m</sub>	12±0	13±1	N/A	N/A	12±0	13±1	0.34

All data presented as mean ± standard error except for race: %. Measures other than age and race were adjusted for age, race and sex of the child.

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## APPENDIX A

### Computation of Cluster Scores

#### 1. Means And Standard Deviations Used To Derive Age-Specific Z-Scores

Risk Factor	Age 6-9		Age 10-18	
	Mean	SD	Mean	SD
Waist	61.4425287	9.5277060	78.9672619	14.1302898
SBP	99.9195402	9.1654285	105.9166667	9.9184801
HDL	54.0114943	10.7654640	50.4345238	12.4931789
Trig	62.7126437	29.6274967	80.3214286	43.0827530
Glucose	63.3082621	8.2929458	84.8633714	9.6417120
Insulin	2.7931034	2.3458917	9.8958333	6.7668296

Risk Factor	All Children*		Adult	
	Mean	SD	Mean	SD
Waist	72.9882353	15.2090537	99.6005587	17.6839156
SBP	103.8705882	10.0617639	114.1787709	15.5957138
HDL	51.6549020	12.0310673	48.5810056	13.4380759
Trig	74.3137255	39.8439328	130.7765363	116.3611450
Glucose	77.5092753	13.7569327	91.5768276	28.3951131
Insulin	7.4725490	6.5843431	8.4774011	7.3528788

#### 2. Age Specific Z-Score and Cluster Score (Cs5 And Cs6) Calculations

##### Ages 6-9

$$\text{Waist } Z_{6-9} = (\text{Waist} - 61.4425287) / 9.527706$$

$$\text{SBP } Z_{6-9} = (\text{SBP} - 99.9195402) / 9.1654285$$

$$\text{HDL } Z_{6-9}^{\dagger} = -(\text{HDL} - 54.0114943) / 10.765464$$

$$\text{Trig } Z_{6-9} = (\text{Trig} - 62.7126437) / 29.6274967$$

$$\text{Gluc } Z_{6-9} = (\text{Gluc} - 63.3082621) / 8.2929458$$

$$\text{Ins } Z_{6-9} = (\text{Ins} - 2.7931034) / 2.3458917$$

---

\* This score was used to calculate parent-child cluster score correlation coefficients for "all children." †Because HDL is a protective factor, the HDL Z scores used to calculate the cluster scores are the actual Z scores multiplied by negative 1. Trig = triglycerides

$$CS6_{6-9} = \text{sum}(\text{Waist } Z_{6-9}, \text{SBP } Z_{6-9}, \text{HDL } Z_{6-9}, \text{Trig } Z_{6-9}, \text{Gluc, Ins } Z_{6-9})/6$$

$$CS5_{6-9} = \text{sum}(\text{Waist } Z_{6-9}, \text{SBP } Z_{6-9}, \text{HDL } Z_{6-9}, \text{Trig } Z_{6-9}, \text{Ins } Z_{6-9})/5$$

### Ages 10-18

$$\text{Waist } Z_{10-18} = (\text{Waist} - 78.9672619) / 14.1302898$$

$$\text{SBP } Z_{10-18} = (\text{SBP} - 105.9166667) / 9.9184801$$

$$\text{HDL } Z_{10-18}^{\dagger} = -(\text{HDL} - 50.4345238) / 12.4931789$$

$$\text{Trig } Z_{10-18} = (\text{Trig} - 80.3214286) / 43.0827530$$

$$\text{Gluc } Z_{10-18} = (\text{Glucose} - 84.8633714) / 9.6417120$$

$$\text{Ins } Z_{10-18} = (\text{Insulin} - 9.8958333) / 6.7668296$$

$$CS6_{10-18} = \text{sum}(\text{Waist } Z_{10-18}, \text{SBP } Z_{10-18}, \text{HDL } Z_{10-18}, \text{Trig } Z_{10-18}, \text{Gluc } Z_{10-18}, \text{Ins } Z_{10-18})/6$$

$$CS5_{10-18} = \text{sum}(\text{Waist } Z_{10-18}, \text{SBP } Z_{10-18}, \text{HDL } Z_{10-18}, \text{Trig } Z_{10-18}, \text{Ins } Z_{10-18})/5$$

### All Children\*

$$\text{Waist } Z_{\text{child}} = (\text{Waist} - 72.9882353) / 15.2090537$$

$$\text{SBP } Z_{\text{child}} = (\text{SBP} - 103.8705882) / 10.0617639$$

$$\text{HDL } Z_{\text{child}}^{\dagger} = -(\text{HDL} - 51.6549020) / 12.0310673$$

$$\text{Trig } Z_{\text{child}} = (\text{Trig} - 74.3137255) / 39.8439328$$

$$\text{Gluc } Z_{\text{child}} = (\text{Glucose} - 77.5092753) / 13.7569327$$

$$\text{Ins } Z_{\text{child}} = (\text{Insulin} - 7.4725490) / 6.5843431$$

$$CS6_{\text{child}} = \text{sum}(\text{waist } Z_{\text{child}}, \text{sbp } Z_{\text{child}}, \text{hdl } Z_{\text{child}}, \text{trig } Z_{\text{child}}, \text{gluc } Z_{\text{child}}, \text{ins } Z_{\text{child}})/6$$

$$CS5_{\text{child}} = \text{sum}(\text{waist } Z_{\text{child}}, \text{sbp } Z_{\text{child}}, \text{hdl } Z_{\text{child}}, \text{trig } Z_{\text{child}}, \text{ins } Z_{\text{child}})/5$$

### Parents

$$\text{Waist } Z_{\text{par}} = (\text{Waist} - 99.6005587) / 17.6839156$$

$$\text{SBP } Z_{\text{par}} = (\text{SBP} - 114.1787709) / 15.5957138$$

$$\text{HDL } Z_{\text{par}}^{\dagger} = -(\text{HDL} - 48.5810056) / 13.4380759$$

$$\text{Trig } Z_{\text{par}} = (\text{Trig} - 130.7765363) / 116.361145$$

$$\text{Gluc } Z_{\text{par}} = (\text{Glucose} - 91.5768276) / 28.3951131$$

$$\text{Ins } Z_{\text{par}} = (\text{Insulin} - 8.4774011) / 7.3528788$$

$$CS6_{\text{parent}} = \text{sum}(\text{Waist } Z_{\text{par}}, \text{SBP } Z_{\text{par}}, \text{HDL } Z_{\text{par}}, \text{Trig } Z_{\text{par}}, \text{Gluc } Z_{\text{par}}, \text{Ins } Z_{\text{par}})/6$$

$$CS5_{\text{parent}} = \text{sum}(\text{Waist } Z_{\text{par}}, \text{SBP } Z_{\text{par}}, \text{HDL } Z_{\text{par}}, \text{Trig } Z_{\text{par}}, \text{Gluc } Z_{\text{par}}, \text{Ins } Z_{\text{par}})/5$$

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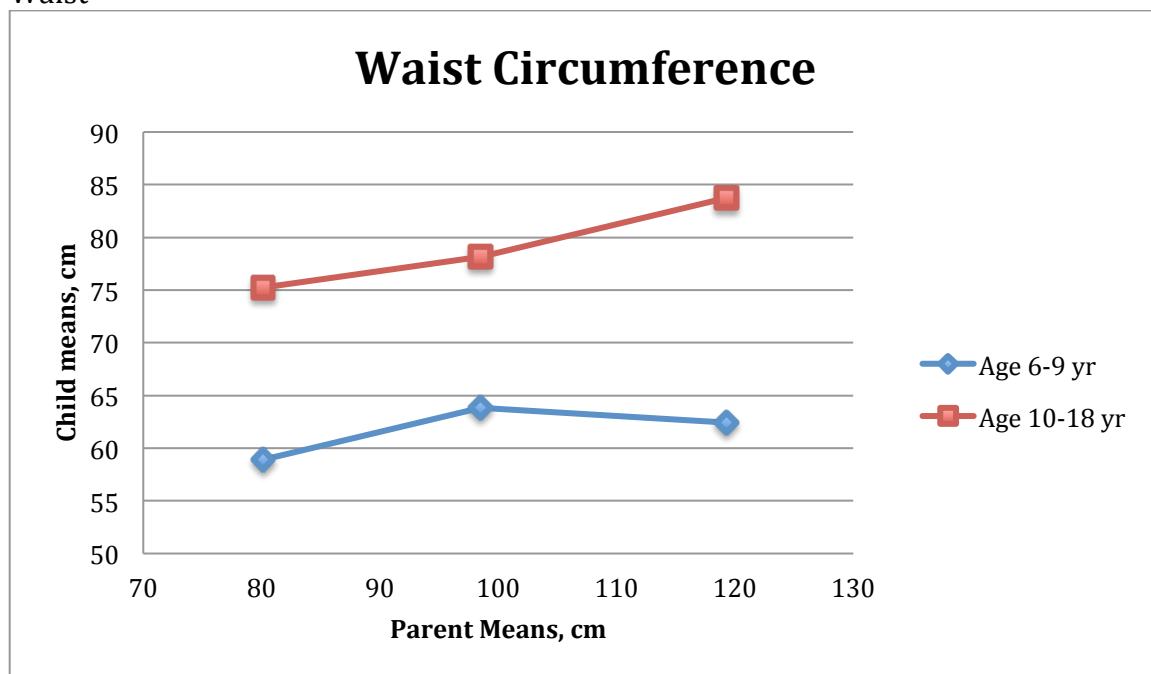
\* This score was used to calculate parent-child cluster score correlation coefficients for "all children." †Because HDL is a protective factor, the HDL Z scores used to calculate the cluster scores are the actual Z scores multiplied by negative 1. Trig = triglycerides

## APPENDIX B

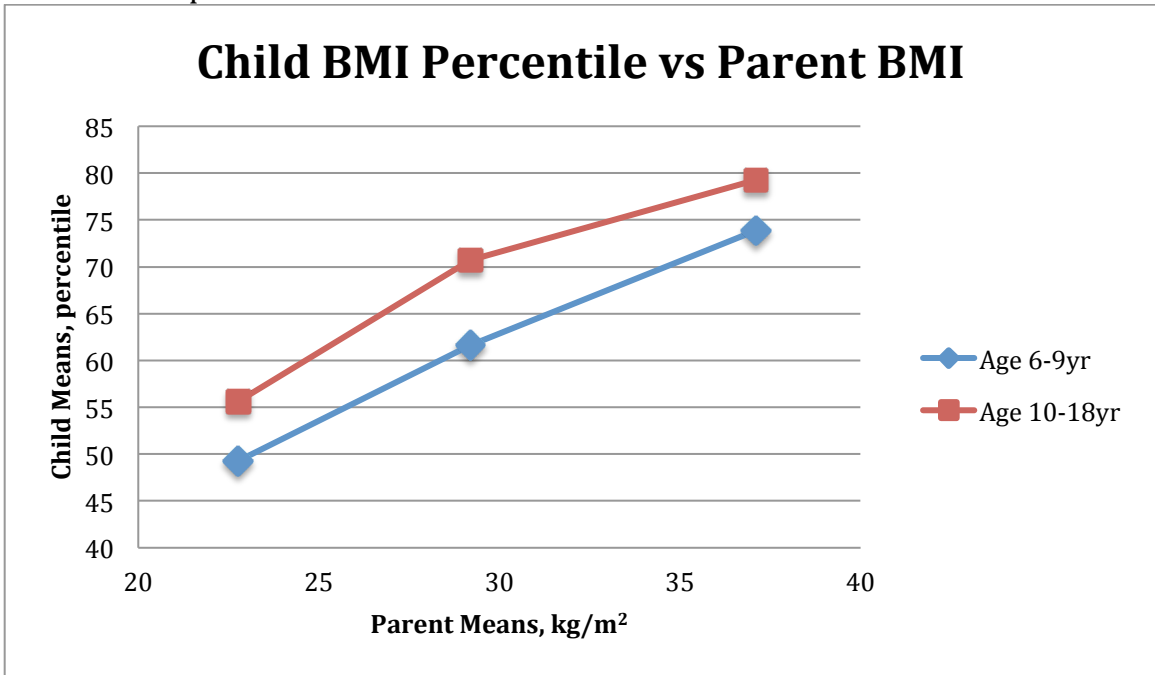
### Complete Set Of Charts Depicting Trends Of Means Within Parent Tertiles For Each Risk Factor

Each chart portrays the mean parent risk factor value (x-axis) and mean child risk factor value (y-axis), within each parent tertile for each individual risk factor. Children are grouped with their parents, irrespective of their own risk factor value. The markers represent subjects within the first (left marker), second (middle marker) and third (right-most marker) tertiles, respectively.

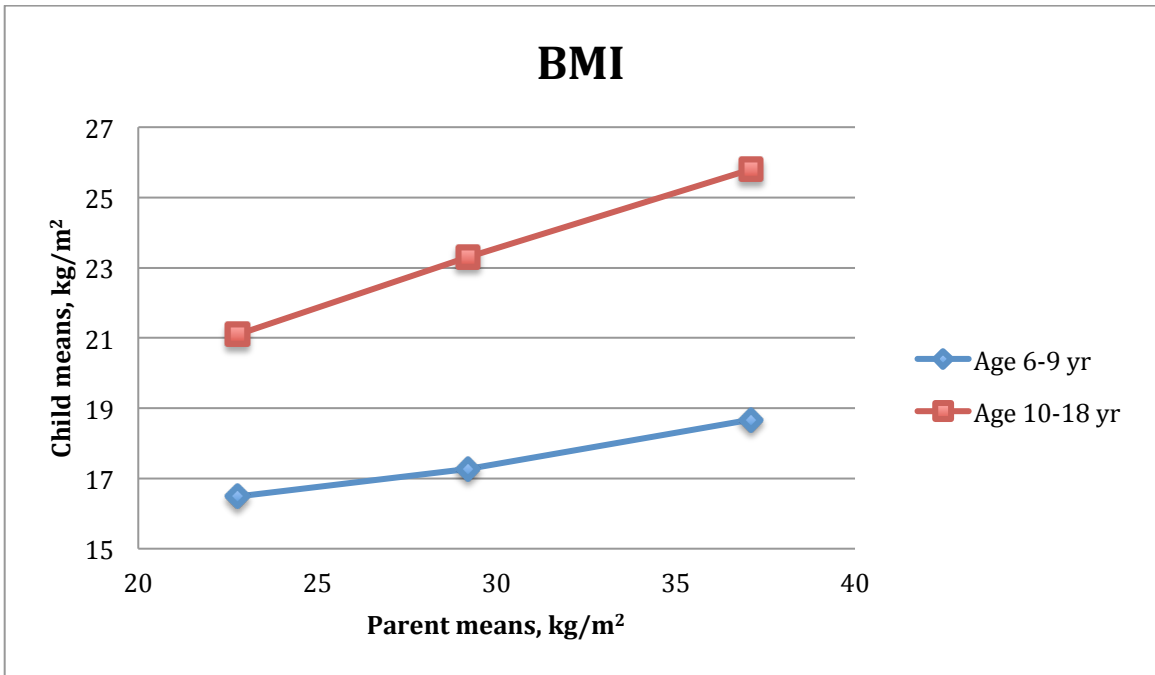
Waist



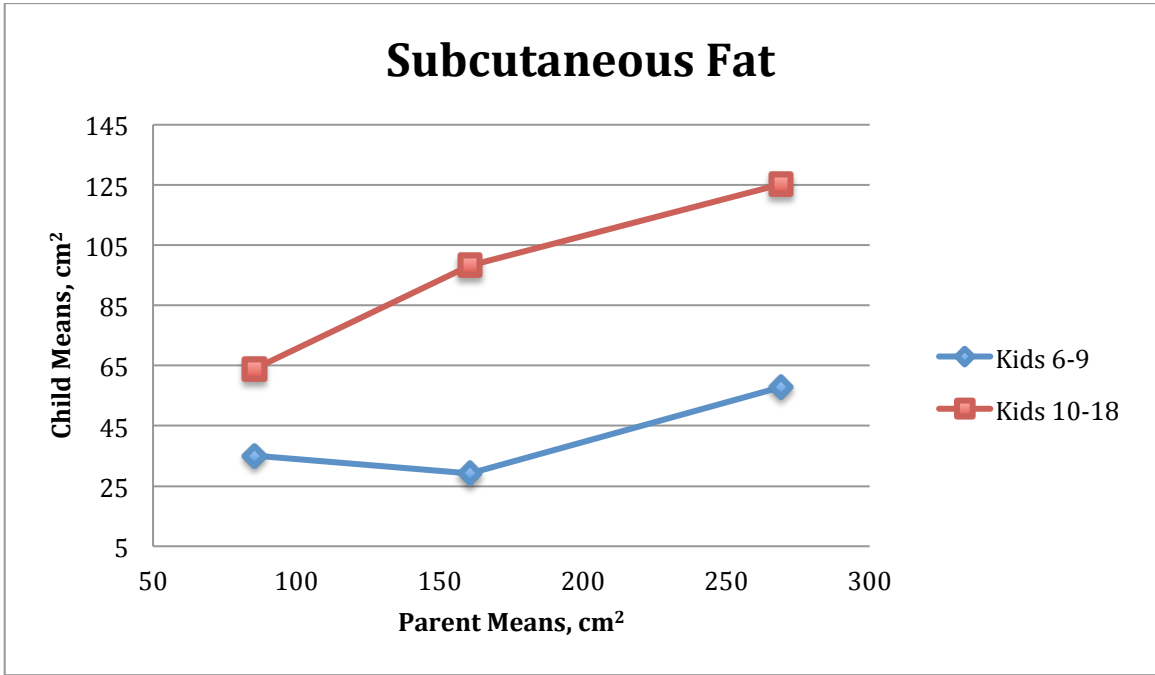
BMI and BMI percentile



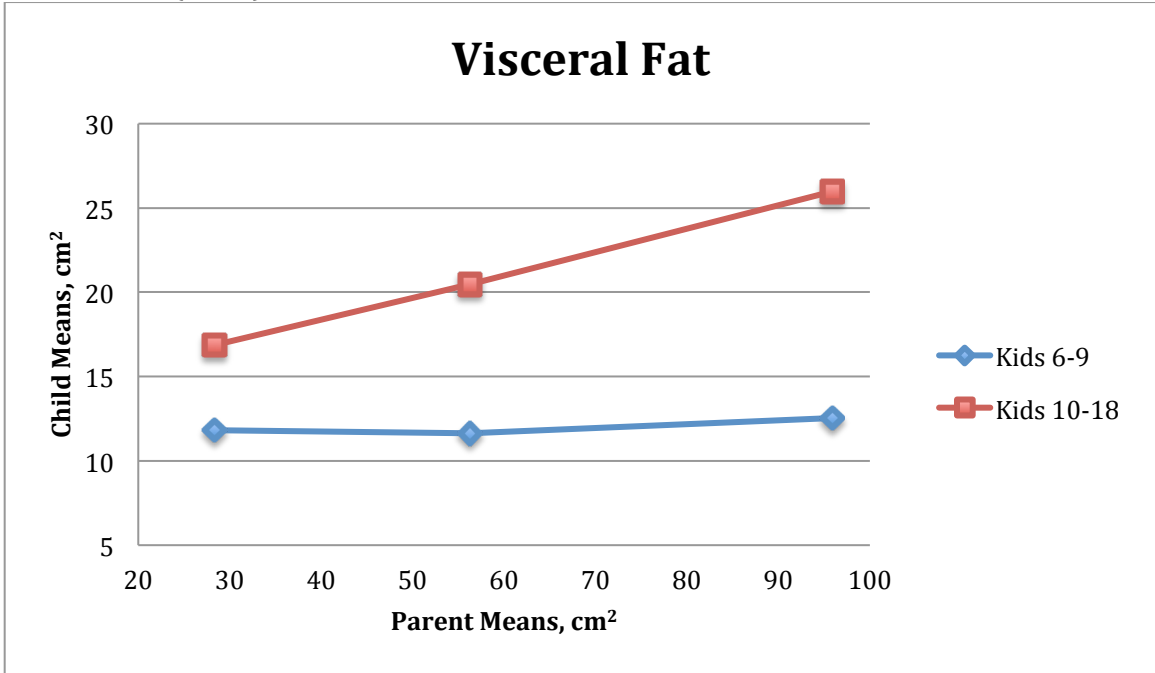
BMI



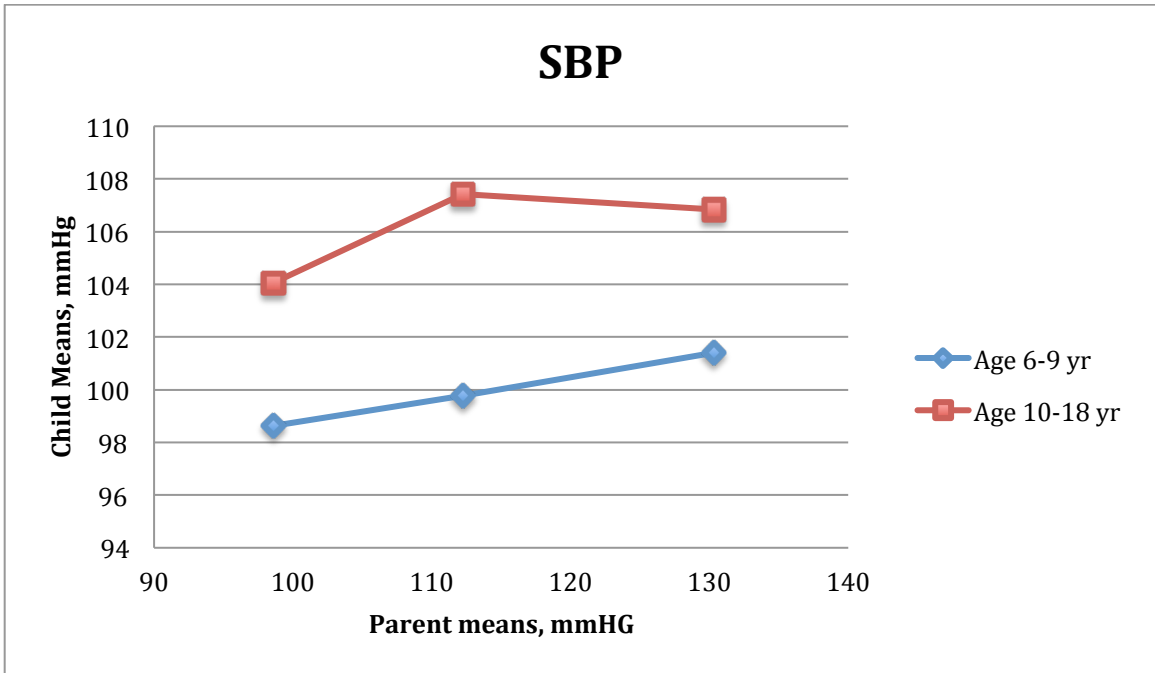
Subcutaneous Fat



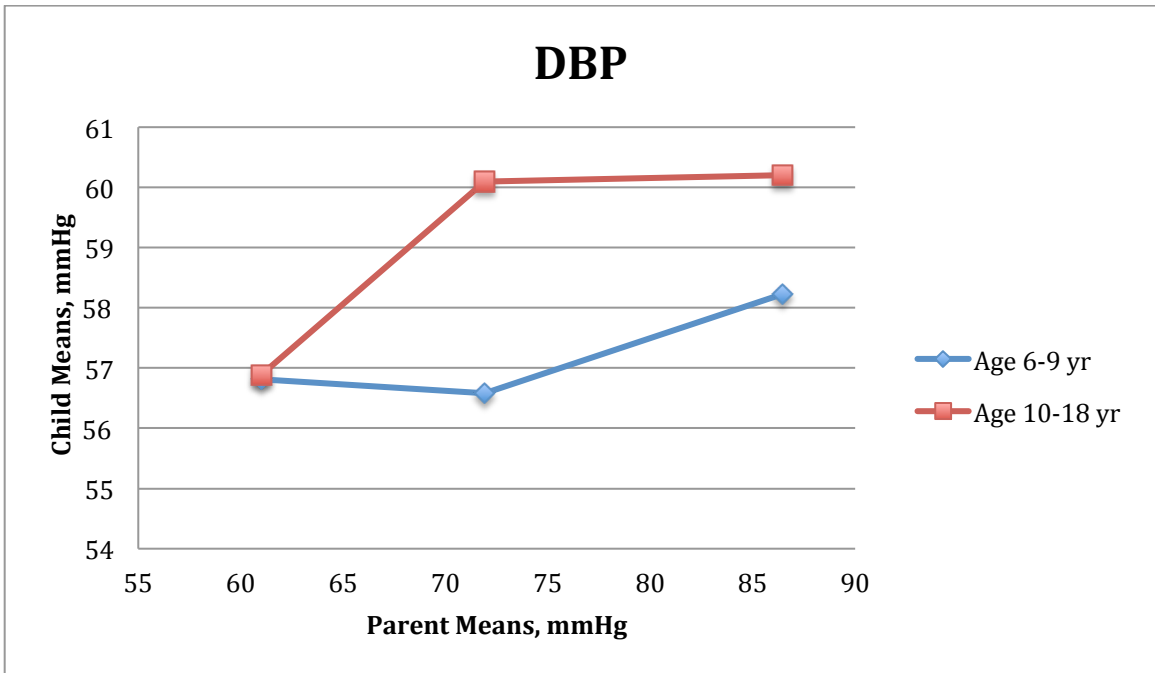
Visceral Fat (CTIN)



SBP

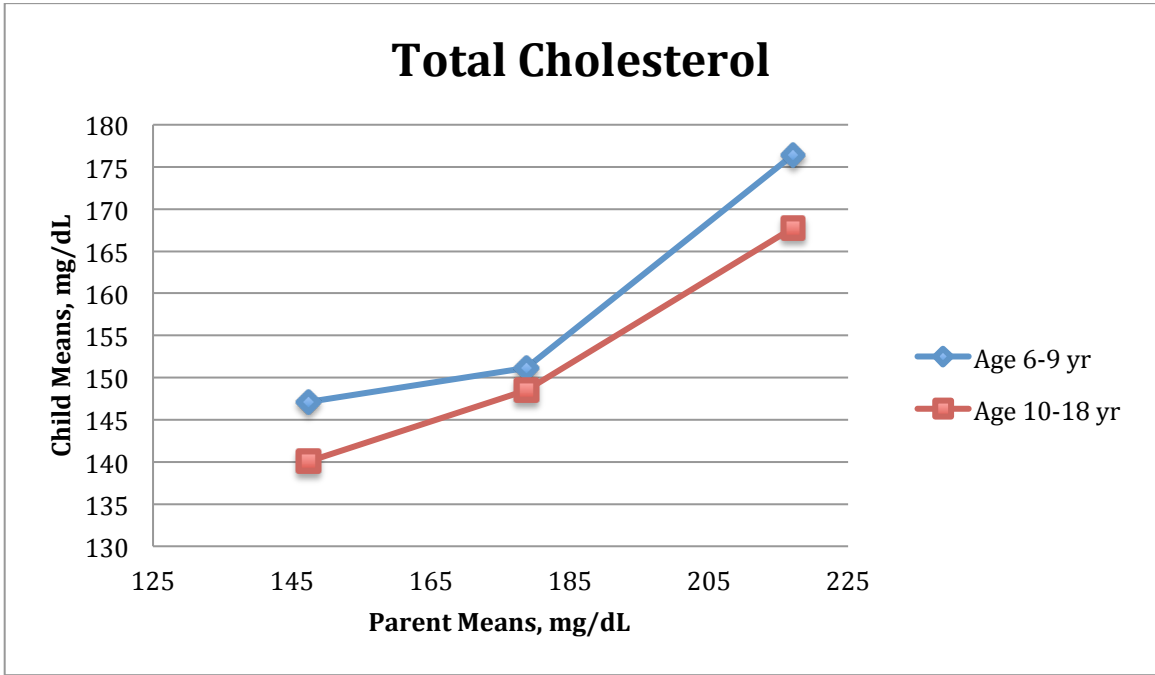


DBP

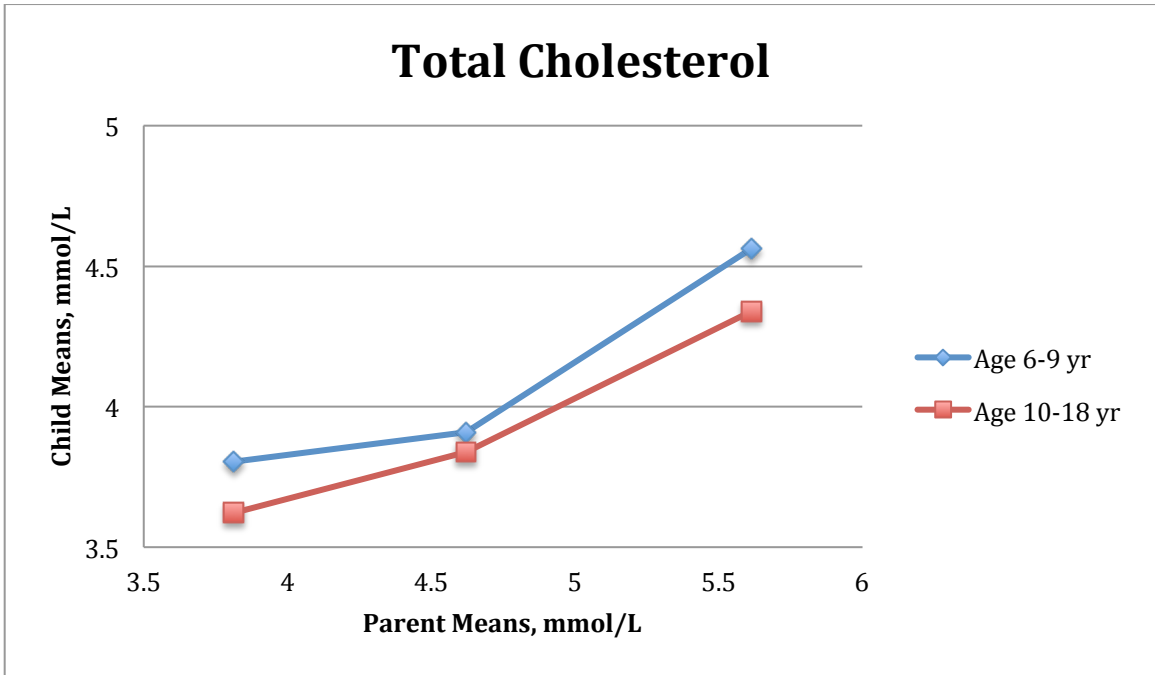




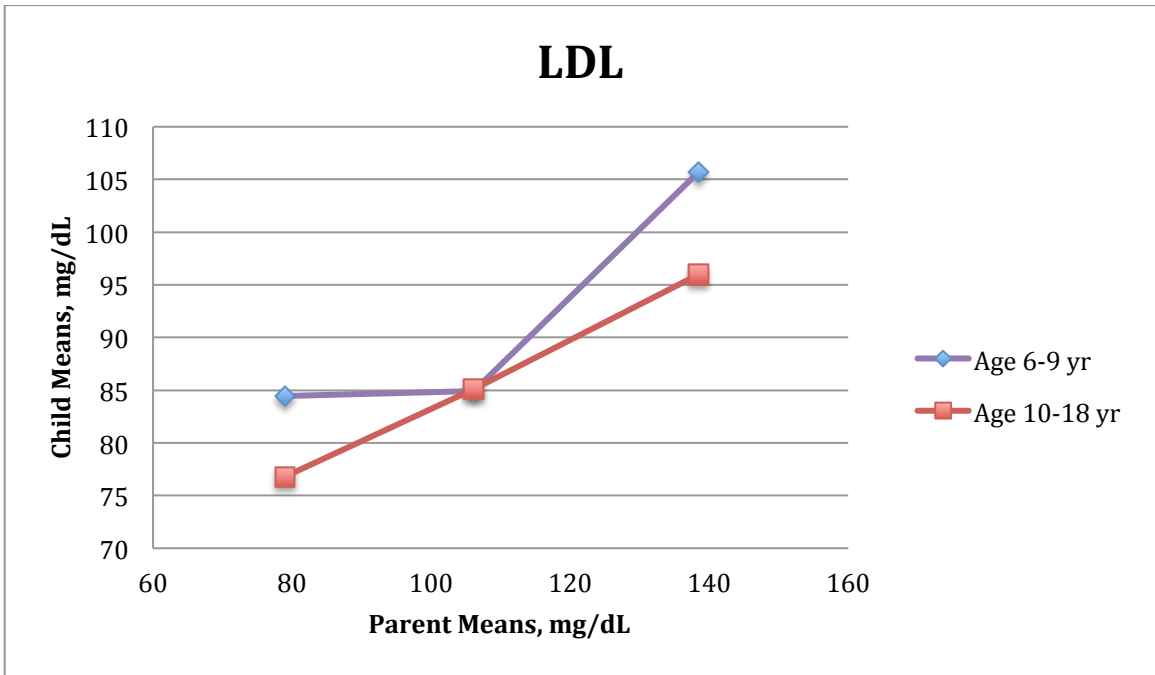
Total Cholesterol



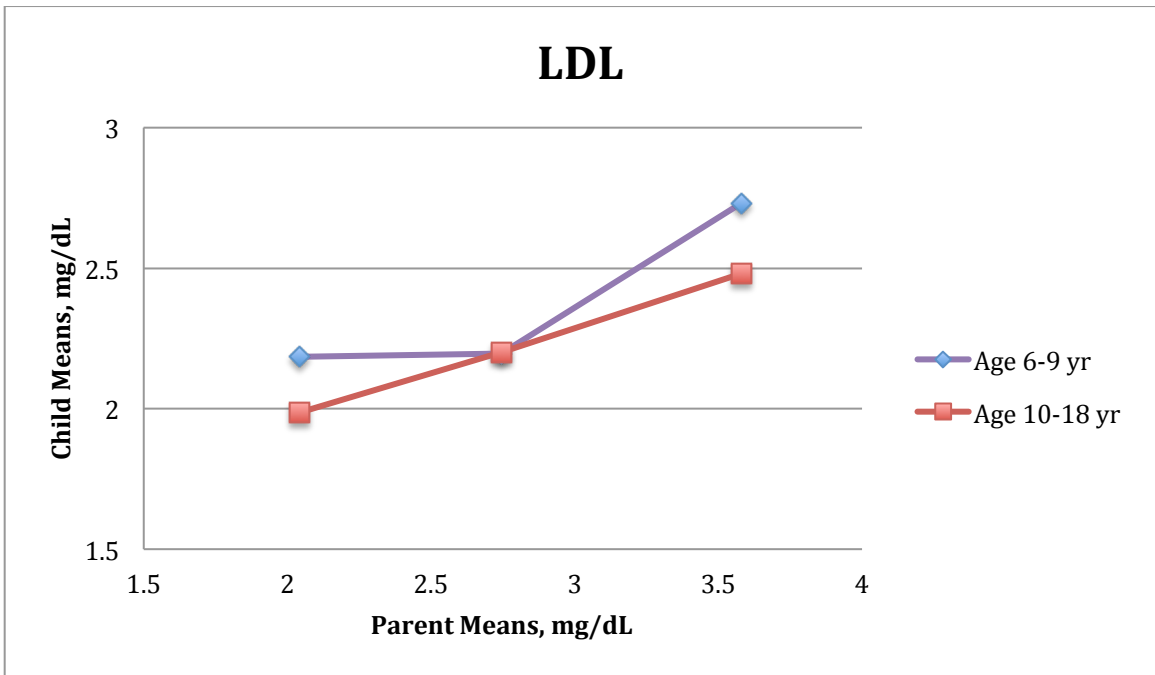
Total Cholesterol in SI units



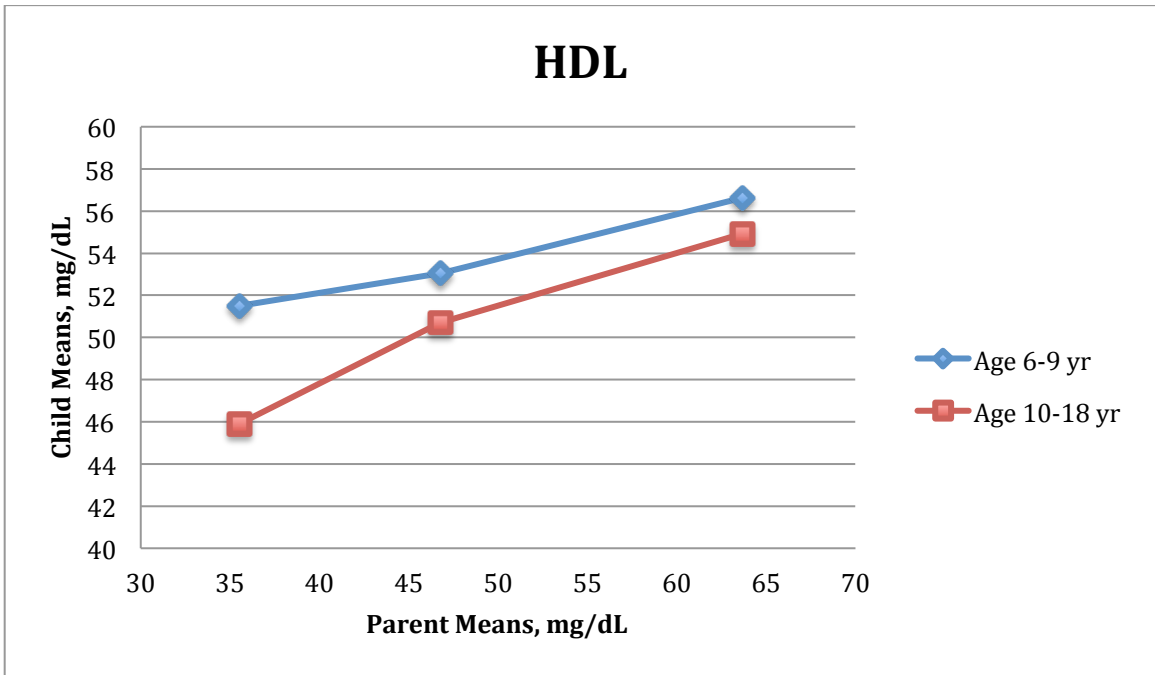
LDL



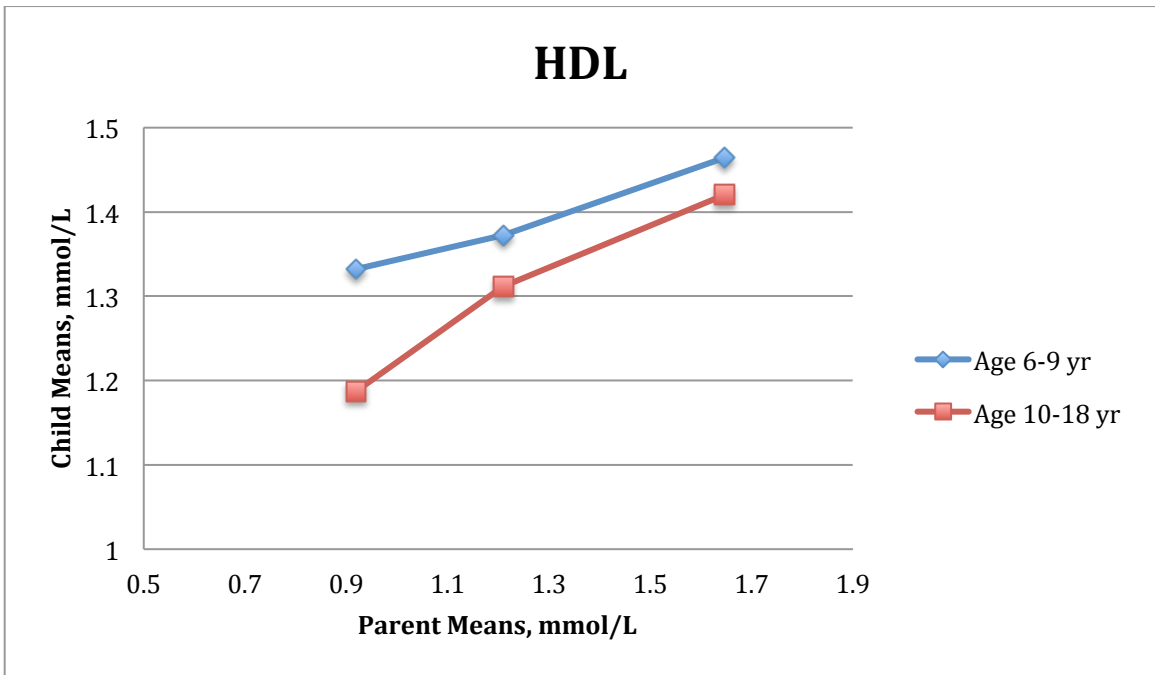
LDL in SI units



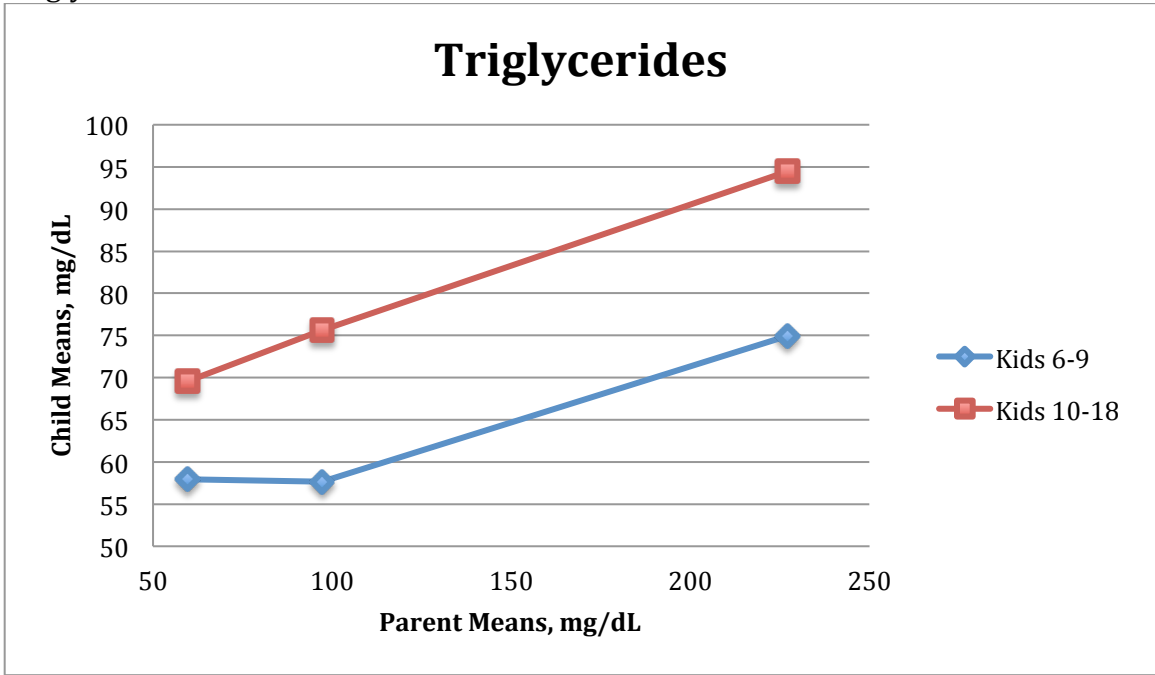
HDL



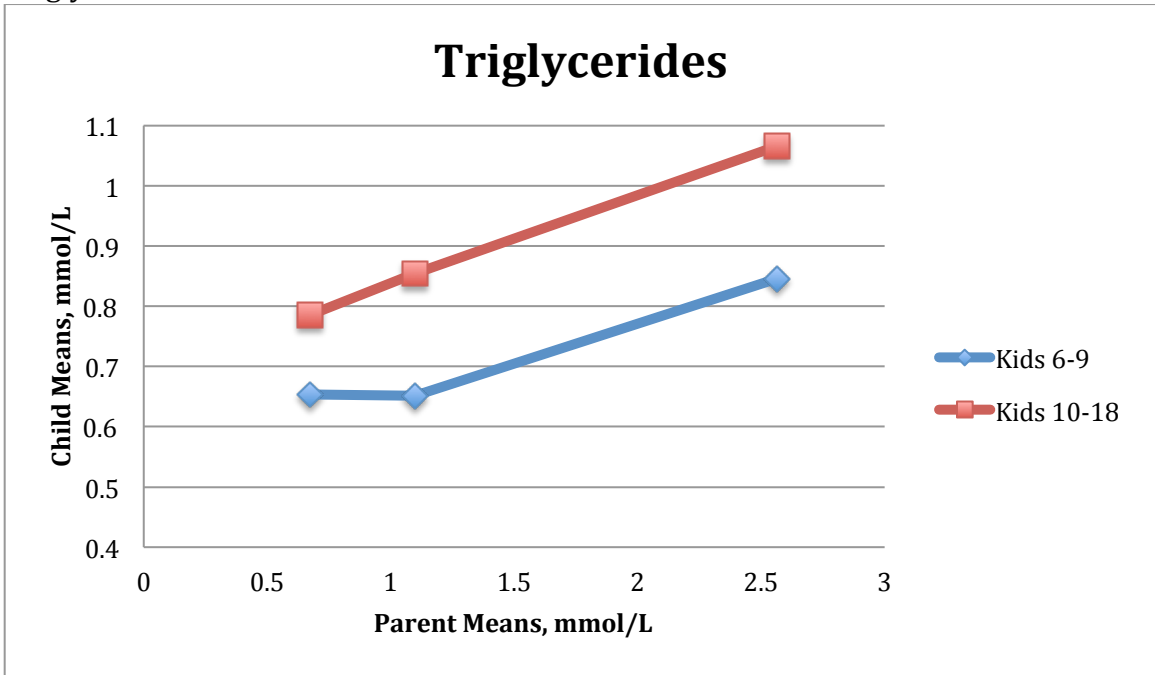
HDL in SI units



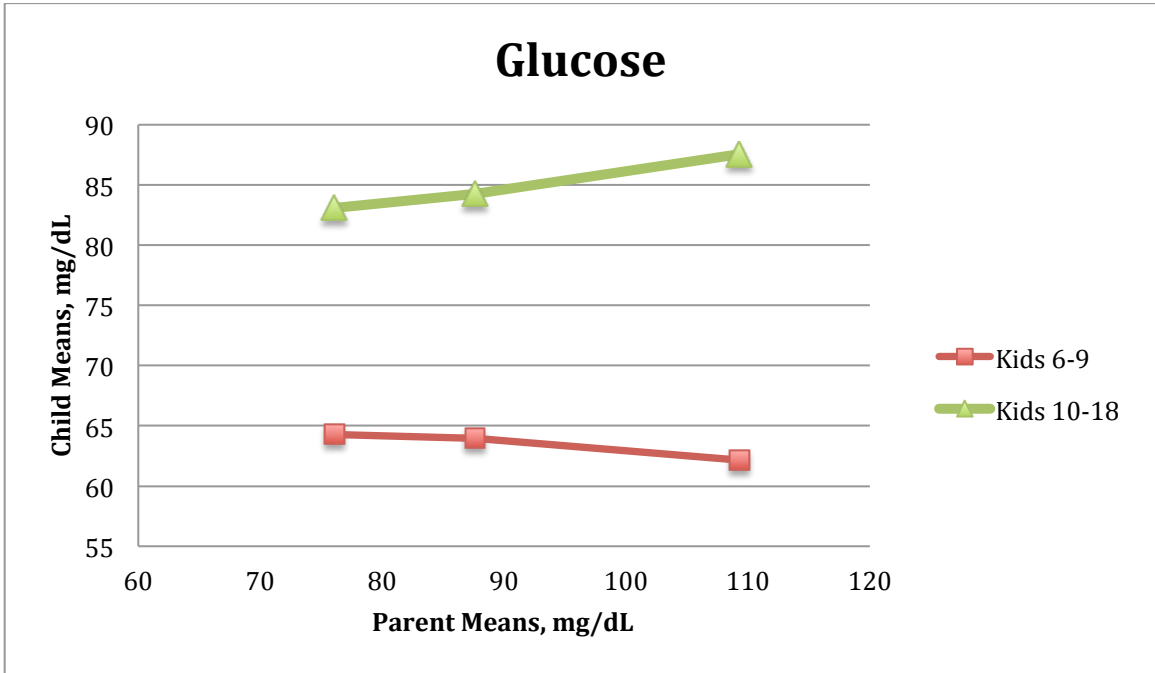
Triglycerides



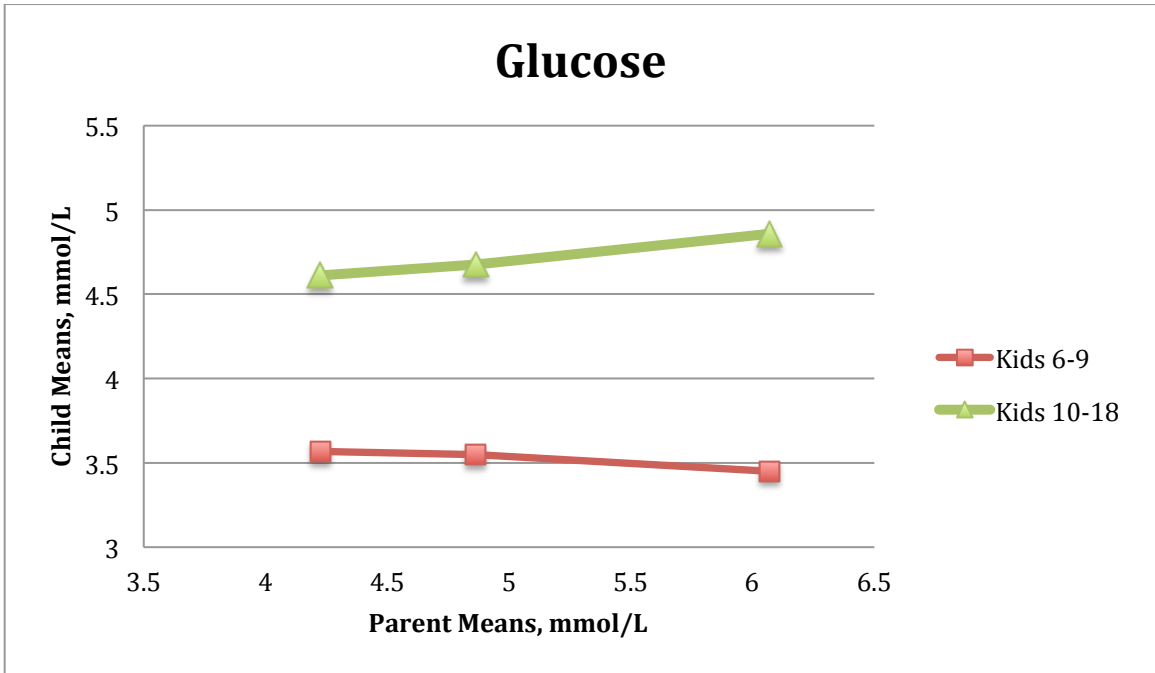
Triglycerides in SI units



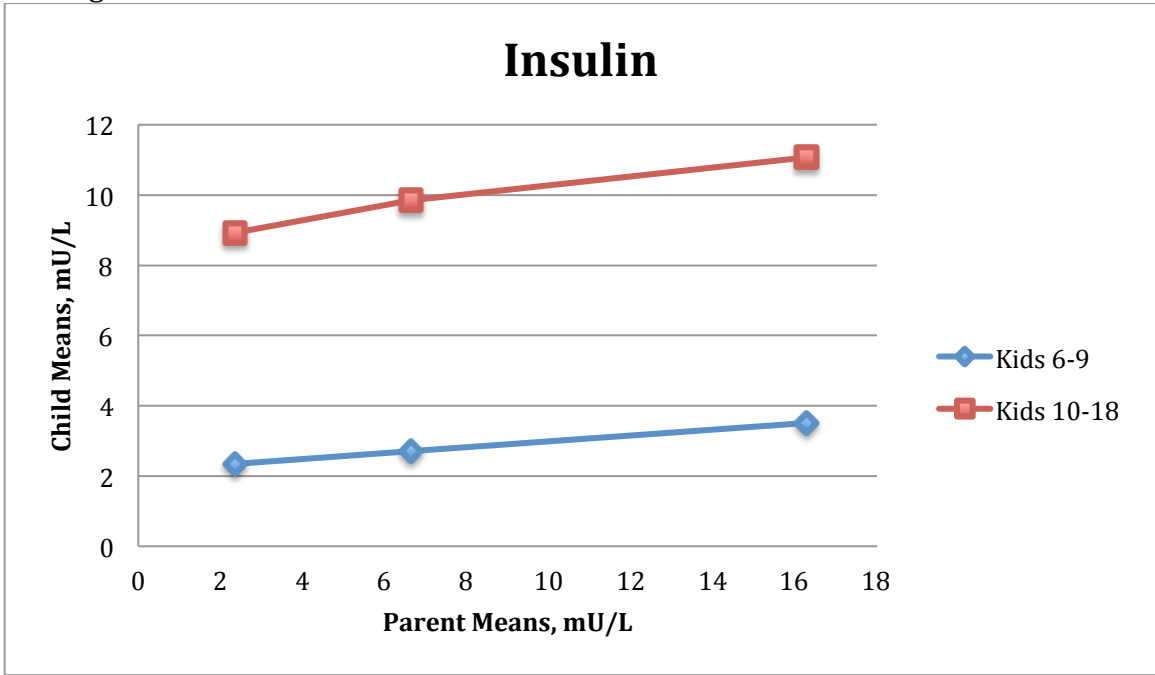
Glucose



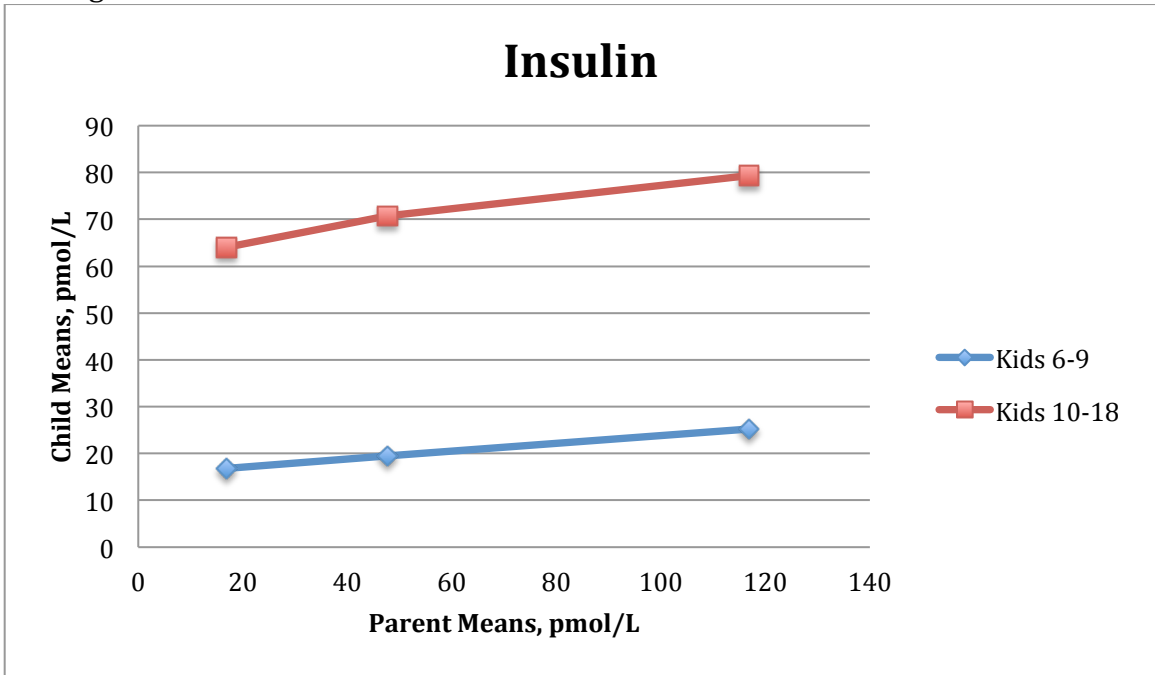
Glucose in SI units



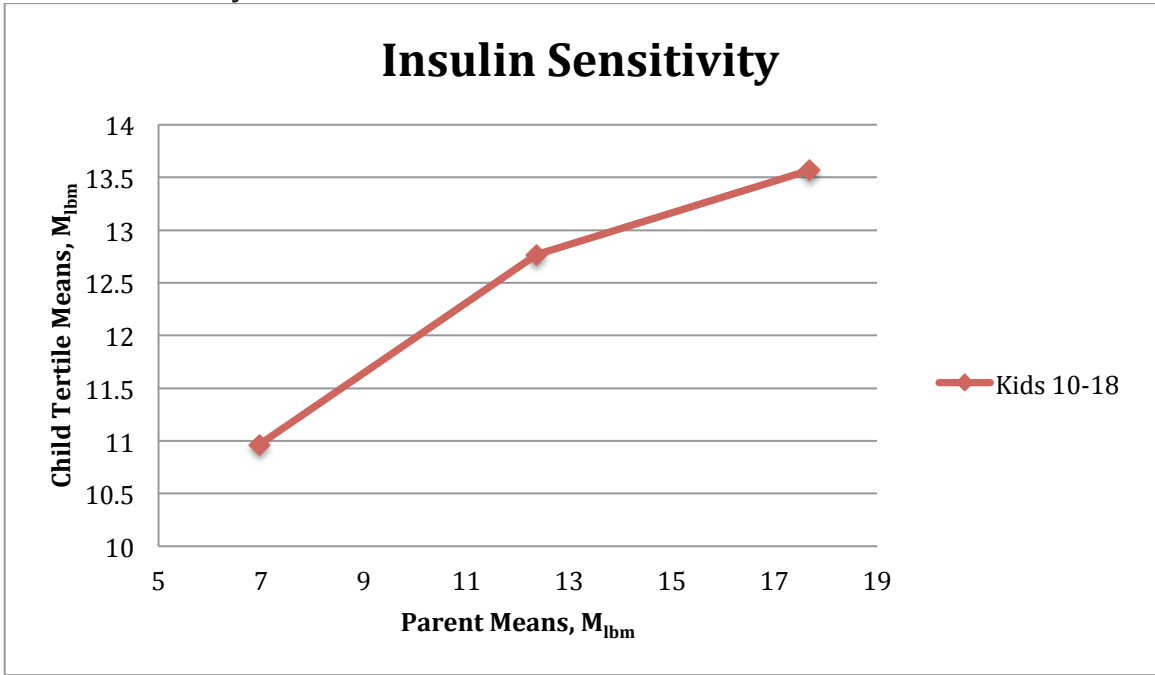
Fasting Insulin



Fasting Insulin in SI units



Insulin sensitivity



Cluster Scores

