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## Inter-relationships between the Severity of Metabolic Syndrome, Insulin and Adiponectin and their Relationship to Future Type 2 Diabetes and Cardiovascular Disease

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### Abstract

**Background**—The severity of the metabolic syndrome (MetS) is related to future incidence of type 2 diabetes (T2DM) and cardiovascular disease (CVD). However, the relationship between MetS severity and levels of fasting insulin and adiponectin—markers of insulin resistance—is unclear.

**Methods**—We used linear and logistic regression to analyze data from 711 participants of the Princeton Lipid Research Cohort with information regarding levels of insulin, adiponectin, and MetS severity during 1998–2003 (mean age 39.5y); 595 participants had MetS severity data from childhood (1973–1976, mean age 12.9y), and 417 had updated disease status from 2010–2014 (mean age 50.9y).

**Results**—Childhood MetS-Z-scores were positively associated with adult insulin levels ( $p < 0.001$ ) and negatively associated with adiponectin levels ( $p = 0.01$ ). In individual analyses, higher insulin levels and MetS-Z-score as adults were related to higher odds of incident diabetes

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**Author contributions:** Mark D. DeBoer, Matthew J. Gurka, Jessica G. Woo and John A. Morrison designed the study. Jessica G. Woo and John A. Morrison oversaw participant recruitment and data collection. Mark D. DeBoer and Matthew J. Gurka planned the analysis. Matthew J. Gurka performed the analysis. Mark D. DeBoer and Matthew J. Gurka wrote the manuscript. Mark D. DeBoer is the guarantor of this work and had full access to the data in the study and takes final responsibility for the decision to submit for publication. All authors have read and given final approval of the manuscript.

and CVD over the next 11.2y (all  $p < 0.001$ ), while lower adiponectin levels were only related to odds of future T2DM ( $p < 0.0001$ ). In a model including insulin, adiponectin and MetS-Z-score, adiponectin was not linked to future disease; both insulin ( $p = 0.027$ ) and MetS-Z-score ( $p = 0.002$ ) were related to risk of future T2DM, while only MetS-Z-score was related to future CVD ( $p < 0.001$ ).

**Conclusions**—The severity of MetS exhibits long-term links to levels of insulin and adiponectin, suggesting potential genetic and environmental influences on insulin resistance over time. As a long-term predictor of T2DM and CVD, the severity of MetS exhibited consistent independent correlations. This supports clinical utility in evaluating MetS severity as a predictor of risk for future disease.

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## Introduction

Insulin resistance is a complex pathophysiological process with clear influences of genetics, obesity and unhealthy lifestyle practices and with long-term sequelae including risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).<sup>1, 2</sup> On a molecular level, insulin resistance appears to result from underlying visceral adiposity, cellular dysfunction, oxidative stress, and low-grade inflammation, producing compensatory elevations in insulin levels and ultimately a rise in blood glucose.<sup>3, 4</sup> One apparent cause of insulin resistance is a low level of the adipokine adiponectin.<sup>5</sup> Adiponectin is produced by adipocytes in inverse proportion to the amount of fat stored. Hypoadiponectinemia appears to be in the causative pathway of insulin resistance in that genetic deletion of adiponectin<sup>5</sup> or its receptors<sup>6</sup> results in insulin resistance while administration of exogenous adiponectin restores signaling.<sup>5</sup> Lower levels of adiponectin have been linked to future risk for T2DM<sup>7</sup> and CVD,<sup>8, 9</sup> though in the case of CVD, not all studies have found this association.<sup>10</sup>

Insulin resistance is also associated with the presence of multiple CVD risk factors, which together are referred to as the metabolic syndrome (MetS). MetS has traditionally been defined by abnormalities in these individual components (central obesity, high blood pressure [BP], elevated triglycerides, low HDL-cholesterol and elevated fasting glucose).<sup>11</sup> However, these MetS criteria, such as those from the National Cholesterol Education Program Adult Treatment Panel III (ATP-III), can only identify the presence or absence of MetS and thus cannot follow for changes over time. Additionally, traditional MetS criteria exhibit racial/ethnic discrepancies in that African Americans are diagnosed at low rates with MetS despite having high rates of T2DM and CVD, suggesting that these criteria are missing risk detection among some African American individuals.<sup>12, 13</sup> We formulated a MetS Z-score that is sex- and race/ethnicity specific and estimates the severity of MetS within an individual.<sup>14, 15</sup> This score is associated with risk for future T2DM<sup>16</sup> and CVD.<sup>17</sup>

ATP-III MetS is linked to insulin resistance as assessed by fasting insulin and the homeostasis model of insulin resistance (HOMA),<sup>18</sup> and is also associated with lower elevated levels of adiponectin.<sup>19</sup> Moreover, adiponectin and MetS exhibit reciprocal predictive properties over short time periods.<sup>20, 21</sup> However, the relationship between levels of adiponectin and insulin with the severity of MetS is not clear, nor is the long-term durability of this relationship or whether independent relationships exist between these

factors and risk of future disease. The goal of this analysis was to evaluate how MetS severity correlates with adiponectin and fasting insulin and to determine whether MetS severity offers additional risk assessment to adiponectin and insulin in predicting future CVD and T2DM. We evaluated this using data from the Princeton Lipid Cohort, a cohort of white and black participants with data spanning approximately 40 years, giving a picture of long-term interrelationships between markers of insulin resistance and disease risk.

## Methods

Participants were originally recruited as part of the Cincinnati Clinic of the National Heart Lung and Blood Institute Lipid Research Clinic (LRC) Prevalence Program (1972–1978), a multistage survey of lipids and other CVD risk factors.<sup>22, 23</sup> In 1973–1976, the LRC enrolled students in grades 1–12 in the Princeton School District and a random sample of their parents. The Institutional Review Boards of NHLBI, the University of Cincinnati, West Virginia University and the University of Virginia approved the study and/or its analysis. The Princeton Follow-up Study (PFS, 2000–2004) was a 25–30-year follow-up of these student and parent-participants to prospectively assess changes in CVD risk factors from childhood into the 4<sup>th</sup>–5<sup>th</sup> decades of life<sup>24</sup>. PFS eligibility required participation in LRC visits where lipoproteins were measured and participation of a first-degree relative at those same visits. The Princeton Health Update (PHU, 2010–2014) was performed 8–14 years after the PFS to assess updated disease status of PFS participants. Data were obtained by telephoning or mailing participants and first-degree relatives using a standardized questionnaire and by examining death certificates from the National Death Index for cause of death.

## Clinical Measures

In both the LRC and PFS studies, data were collected via standard protocols,<sup>22–24</sup> including measures of height and weight in LRC<sup>25</sup> and height, weight, and waist circumference (WC) in PFS.<sup>24</sup> WC was measured in PFS at the level of the umbilicus following normal expiration. In the LRC and PFS, BP was measured on a participant's right arm with a standard sphygmomanometer after sitting for 5 minutes. In LRC and PFS fasting blood was drawn and tested for lipid profiles in LRC–Centers for Disease Control and Prevention (CDC) standardized laboratories. In the LRC, glucose was measured on the ABA-100 by a hexokinase method. In the PFS, glucose was measured on the Dade Dimension Xpand (Dade Behring, Deerfield, IL), by the hexokinase-glucose-6-phosphate-dehydrogenase method. Insulin and adiponectin were measured at PFS by electrochemiluminescence immunoassay (ECLIA) using an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN) and ELISA (Millepore, St. Charles, MO) techniques, respectively, according to manufacturer directions. Diabetes was classified based on self-report at all three studies. In both PFS and PHU, CVD was classified as self-reported myocardial infarction, coronary artery bypass, other heart surgery, coronary revascularization procedure (angioplasty, stent placement) or stroke.

Traditional MetS was defined using the ATP-III criteria for adults;<sup>11</sup> participants had to meet 3 of the following 5 criteria: concentration of triglycerides  $\geq 1.69$  mmol/L (150 mg/dL),

HDL-C <1.04 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women, WC 102cm for males and 88cm for females, glucose concentration 5.55 mmol/L (100 mg/dL), and systolic BP 130 mmHg or diastolic BP 85 mmHg. MetS in childhood was defined using a modification of these criteria<sup>24, 26</sup> in which participants had to meet 3 of the following: concentration of triglycerides 110 mg/dL, HDL-C 40 mg/dL, BMI 90<sup>th</sup> percentile, glucose 100 mg/dL and systolic or diastolic BP 90th percentile (age, height, and sex-specific).<sup>27</sup>

MetS severity Z-score was calculated for adolescents at their LRC visit and then again as adults during their PFS visit using formulas published elsewhere.<sup>14, 28</sup> Briefly, these scores were formed using confirmatory factor analysis of the 5 traditional components of MetS (as above) to determine the weighted contribution of each of these components to a latent MetS “factor” on a sex- and race/ethnicity-specific basis. Confirmatory factor analysis was performed on data from the National Health and Nutrition Examination Survey (NHANES) for adolescents age 12–19 years<sup>14</sup> and adults age 20–64 years,<sup>28</sup> with both adolescents and adults divided into six sub-groups based on sex and the following self-identified race/ethnicities: non-Hispanic white, non-Hispanic black and Hispanic. For each of these six population sub-groups, loading coefficients for the 5 MetS components were determined toward a single MetS factor. The loading coefficients were then used to generate equations to calculate a standardized MetS severity score for each sub-group (<http://mets.health-outcomes-policy.ufl.edu/calculator/>). These MetS severity scores are Z-scores (ranging from negative infinity to positive infinity) of relative MetS severity on a sex- and race/ethnicity-specific basis and are highly correlated to other surrogate markers of MetS risk, including hsCRP, uric acid and the homeostasis model of insulin resistance.<sup>14, 28</sup> In calculating these scores in the present study, individual measures of participants from LRC and PHS were entered into these equations to calculate MetS severity as children and adults, respectively. For the LRC visit, BP was missing for 185 participants; for these individuals, systolic BP was estimated to be the 50<sup>th</sup> percentile of normal based on published equations for sex, age, and height percentile.<sup>27</sup>

### Statistical analysis

All statistical analyses were performed using SAS 9.4. Due to their skewed distributions, the natural log transformation for both insulin and adiponectin was used in all analyses for consistency. Linear regression was used to estimate and compare age-adjusted mean levels of both ln(insulin) and ln(adiponectin) between white and black males and females. Pearson’s r correlation was calculated to estimate linear associations between MetS severity Z-scores and both insulin and adiponectin at PFS. A series of linear models were fit to the natural log-transformed values of fasting insulin and adiponectin at the PFS visit, comparing the predictive value of MetS as traditionally defined and MetS severity Z-score, both at the LRC and PFS visits, using R<sup>2</sup> values as the metric of comparison. This also included evaluating predictors of the change in MetS score between LRC and PFS visits, as had been performed previously for the traditional MetS criteria.<sup>24</sup> Finally, logistic models were fit estimating odds of incident diabetes/CVD at at PHU (excluding those individuals who reported disease at PFS). These models included insulin, adiponectin, and the MetS severity

Z-score, with separate models for each of these PFS predictors and their combinations. Collinearity was assessed in these models by examination of variance inflation factors.

## Results

### Participant characteristics

We evaluated data from 711 participants of PFS with adequate data regarding MetS severity, insulin and adiponectin for cross-sectional analyses (Table 1). This included 595 participants with adequate data regarding childhood MetS severity (for analysis of childhood MetS-adult insulin/adiponectin) and 417 participants with health outcomes data from PHU (for analysis of insulin/adiponectin/MetS z-score on future adult disease). The remainder of participants in the analytic cohort was lost to follow-up. At PFS and PHU respectively, 5.4% and 14.4% of individuals had T2DM and 1.4% and 7.1% had CVD. By PHU, 1.7% of cohort members accounted for had died.

### Inter-relationships between levels of adiponectin and insulin and MetS severity Z-score

**Cross-sectional associations**—Figure 1 displays cross-sectional associations between MetS severity scores and levels of adiponectin and insulin. MetS severity scores displayed a strong inverse correlation with levels of adiponectin (Pearson's  $r=-0.47$ ,  $p<0.001$ ) and a strong correlation with insulin (Pearson's  $r=0.62$ ,  $p<0.001$ ). Adiponectin and insulin levels displayed a strong inverse association (Pearson's  $r=-0.44$ ,  $p<0.001$ ).

**MetS severity score correlations from childhood**—As reported previously, there was a high degree of correlation in MetS severity score between childhood at LRC and mid-adulthood at PFS.<sup>16</sup> Childhood MetS scores correlated with adult levels of adiponectin (Pearson's  $r=-0.11$ ,  $p=0.01$ ) and insulin (Pearson's  $r=0.26$ ,  $p<0.01$ )(Figure 2). Using linear regression (Table 2), MetS severity score in childhood was positively associated with adult levels of insulin ( $p<0.01$ ) and negatively associated with adult levels of adiponectin ( $p<0.01$ ); the same was true of MetS in childhood using traditional criteria ( $p<0.01$  and  $p<0.05$ , respectively)(Models 1,2).<sup>24</sup> Similarly, in adulthood, both MetS severity and MetS by traditional criteria were positively associated with insulin ( $p<0.01$ ) and negatively associated with adiponectin ( $p<0.01$ )(Models 3,4). Finally, in a model that included MetS severity score at LRC and the *change* in this score from childhood to adulthood, both childhood MetS severity score and the change in score were highly associated with insulin and negatively associated with adiponectin ( $p<0.01$ )(Model 5).

### Insulin, adiponectin and MetS severity predicting T2DM and CVD

Odds of future disease by PHU based on levels of insulin, adiponectin and MetS Z-score are shown in Table 3. Higher levels of insulin (Model 1) were significantly linked to odds of future T2DM and CVD (for each unit increase in log of insulin, the odds increased eight-fold for T2DM ( $p<0.0001$ ) and three-fold for CVD ( $p=0.0009$ ) while lower levels of adiponectin (Model 2) were only linked to odds of future T2DM (for each increasing unit of log of adiponectin: OR=0.25,  $p<0.0001$ ) and not CVD. In this cohort MetS Z-score (Model 3) was linked to both future T2DM and CVD (OR=5.6,  $p<0.0001$  and 3.5,  $p<0.0001$ , respectively). In models that included both insulin and MetS Z (Model 4), both measures

were linked to future T2DM (insulin OR=3.4,  $p=0.0120$ ; MetS Z OR=3.4,  $p=0.0012$ ) while only MetS Z was linked to future CVD (OR=3.4,  $p=0.0002$ ). In a model including adiponectin and MetS Z-score (Model 5), only MetS Z-score was linked to future disease (T2DM: 5.0,  $p<0.0001$ ; CVD: 4.4,  $p<0.0001$ ). Finally, in a model that included all 3 measures (Model 6), adiponectin was not linked to future disease, while both insulin and MetS Z-score were linked to future T2DM (3.0,  $p=0.0269$  and 3.4,  $p=0.0019$ , respectively) and only MetS Z-score was linked to future CVD (4.0,  $p<0.0001$ ). In each of these models, VIF's were  $<2$ , reassuring against excess collinearity in the analyses.

## Discussion

Obesity-associated insulin resistance can be an important forerunner to future risk of both T2DM and CVD.<sup>29</sup> We evaluated three measures related to insulin resistance for inter-relationships and for potential independent associations with future disease. As hypothesized, we found that a linear estimate of MetS severity had a strong cross-sectional association with fasting insulin and an inverse correlation with adiponectin. What was more surprising was that these associations persisted when assessing childhood measures of MetS severity with adult levels of insulin and adiponectin 26 years later. Nevertheless, despite these strong inter-correlations, the severity of MetS exhibited independent associations with future T2DM and CVD. This suggests that MetS severity may capture additional risk beyond what is associated with insulin resistance as estimated by fasting insulin and adiponectin. While MetS as a concept has been criticized as not being more than the sum of its parts,<sup>30, 31</sup> these data support that as an overall assessment of long-term risk, this MetS severity score may help to integrate risk associated with the aggregate of individual components. Because this score can be followed within individuals over time,<sup>32</sup> it may provide a means of following for risk reductions in response to treatments. This is particularly true should the score be able to be calculated automatically from MetS-related data in the electronic medical record.

MetS appears to be produced by genetic factors and multiple underlying pathophysiological processes including cellular dysfunction, oxidative stress, and low-grade inflammation—processes that are also associated with insulin resistance.<sup>3, 4, 33</sup> The MetS severity scores that we evaluated here had previously been shown within individuals to be associated with surrogates for these underlying processes, including uric acid and hsCRP.<sup>14, 28</sup> Low levels of adiponectin have also been evaluated as an assessment for the underlying processes behind MetS, with potential utility in distinguishing “healthy obese” individuals without cardiovascular risk factors from those with MetS-related risk factors.<sup>34, 35</sup> The present findings of correlations between MetS severity scores in childhood and fasting insulin and adiponectin in adulthood suggest either durability of these underlying processes or that genetic susceptibility is manifest already in childhood. The long-term nature of these risks is further supported by the ability of these MetS severity scores in childhood to identify risk for future T2DM<sup>16</sup> and CVD,<sup>17</sup> as reported previously from this cohort. However, even more important than childhood MetS severity in predicting future insulin and adiponectin was the change in MetS severity over time (Table 2), potentially as a reflection of the worsening of underlying pathophysiological processes in the interim.

Previous studies have reported mixed relationships between insulin and adiponectin in their relationship to future disease. While higher levels of fasting insulin weakly correlate with risk of future T2DM<sup>36</sup> and CVD,<sup>37</sup> as a clinical measure, fasting insulin is typically replaced by other measures of islet cell function such as oral glucose tolerance tests and related indices of insulin secretion and resistance,<sup>38</sup> Insulin levels as a marker of risk are further complicated by non-standardized assay variability, making it difficult to compare between assays. Adiponectin levels correlate consistently better with risk of future T2DM than of future CVD. A meta-analysis of 13 longitudinal studies of 15,000 patients with follow-up periods of 1–12 years revealed that the relative risk of future T2DM was 0.72 for every 1-log rise in adiponectin levels. Regarding adiponectin and future CVD, however, data are mixed,<sup>8–10</sup> with a meta-analysis of 16 studies comprising almost 24,000 patients with follow-up of 6–20 years demonstrating that a 10 ug/mL increase in adiponectin conferred a non-significant relative risk of 0.91 (0.8, 1.03) for future coronary heart disease.<sup>10</sup> Our findings are thus in line with prior studies on these measures as risk factors. Interestingly, in our combined analysis of these predictors of future T2DM (Model 6), we found tighter independent associations of fasting insulin than adiponectin. The cause of this is unclear, though it may be that the MetS severity score was able to account for much of the risk conferred by adiponectin. In our combined analysis of CVD risk using all three factors, neither adiponectin nor insulin was associated with future CVD risk.

The identification of risk underscores the potential importance of targeting intensive lifestyle therapy to reduce risk in individuals exhibiting early abnormalities in metabolic parameters prior to progression to T2DM or CVD.<sup>39</sup> While uncertain, discovery of future disease risk could be used as a motivator to change among adolescents.<sup>24</sup> One potential use of a MetS severity score is to follow the score within individuals over time to assess for response to therapy, including lifestyle modification.<sup>32</sup> Given the increase in odds of disease with interval increases in MetS Z-score over time,<sup>16, 17</sup> there is potential that reductions in MetS severity score could lower long-term risk.

This study had several limitations. Our analysis was based on outcomes (incidence of T2DM and CVD) that had occurred in only 22 and 19 individuals, respectively, by PHU, thus limiting our ability to statistically assess for sex and race differences. For the PHU study, follow-up was incomplete, and we relied on self-report of outcomes, without adjudication or in-person assessments of MetS severity status. This study was performed in a long-term cohort of white and African Americans in the Cincinnati area, potentially limiting generalizability to individuals from other areas and different racial/ethnic backgrounds. Finally, we measured total adiponectin instead of HMW adiponectin, which is the most metabolically active form.<sup>40</sup> However, prior studies assessing both forms in the same cohort have demonstrated similar correlations of total adiponectin and HMW adiponectin as a predictor of T2DM.<sup>41</sup> However, the study also had several strengths, including long-term follow-up in a biracial cohort originally studied as children in the 1970's.

In conclusion, we found that the severity of MetS exhibits tight long-term correlations with adiponectin and insulin but confers independent associations with future T2DM and CVD. This score may be useful in identifying individuals at higher risk for future disease who could be targeted for interventions to reduce risk. Future research will be needed to clarify

which underlying processes are associated with each of these markers and to set thresholds of MetS severity that are particularly associated with elevated risk of disease.

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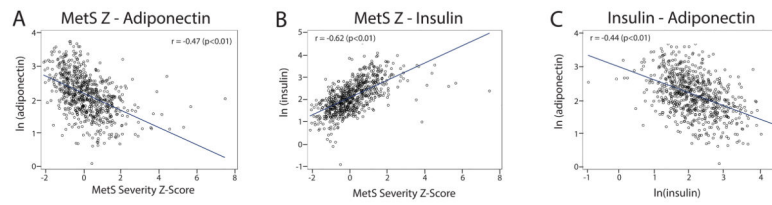
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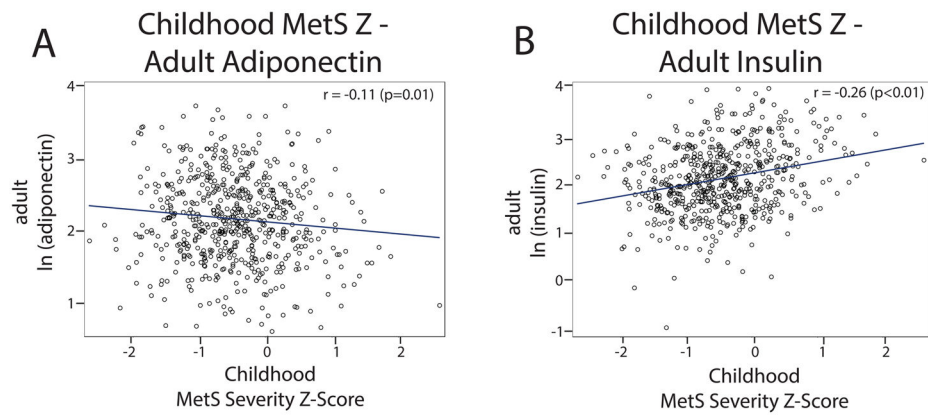


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**Figure 1. Inter-relationships between MetS severity score, adiponectin and fasting insulin**  
Scatterplots from Princeton Follow-up Study data (mean age 38 years) reveal correlations between adult MetS severity scores and log adiponectin (A) and log insulin (B) and between log insulin and log adiponectin (C).



**Figure 2. Correlations between childhood MetS severity scores with adult adiponectin and insulin**

Scatterplots from childhood MetS severity scores from Princeton Lipid Research Clinic (mean age 13 years) with adult log adiponectin (A) and log insulin (B) from Princeton Follow-up Study (mean age 38 years).

**Table 1**  
**Descriptive Statistics**

Primary sample: those with valid MetS severity scores, fasting insulin and adiponectin at the PFS Visit (n = 711). From those 711 participants, the LRC column provides data at the LRC (child) visit for the n = 595 participants < 20 years old and who had valid MetS severity scores at the time. The PHU column provides data on those 417 individuals from the 711 who were followed up during the 2010–2014 period.

	Primary Analysis Sample (n = 711)		
	LRC Visit 1973–1976	PFS Visit 1998–2003	PHU Contact 2010–2014
N	595	711	417
Mean (SD):			
Age (years)	12.9 (3.3)	39.5 (4.7)	50.9 (4.9)
BMI (kg/m <sup>2</sup> )	20.0 (4.3)	28.8 (6.8)	--
Waist (cm)	--	97.5 (16.9)	--
Glucose (mg/dL)	85.4 (8.2)	90.6 (27.7)	--
HDL-C (mg/dL)	54.5 (12.1)	45.3 (14.3)	--
Triglycerides (mg/dL)	74.7 (38.3)	136.7 (115.5)	--
Systolic blood pressure (mm Hg)	102.8 (12.7)	121.0 (15.2)	--
Diastolic blood pressure (mm Hg)	63.1 (11.3)	79.8 (11.1)	--
Metabolic syndrome severity score (z-score)	-0.5 (0.8)	0.1 (1.1)	--
Fasting insulin	--	10.9 (9.0)	--
Adiponectin		10.4 (6.8)	--
Frequency (Percent):			
Male	259 (43.5%)	316 (44.4%)	174 (41.7%)
White	418 (70.3%)	502 (70.6%)	321 (77.0%)
Overweight*	71 (11.9%)	231 (32.5%)	--
Obese*	57 (9.6%)	247 (34.8%)	--
Metabolic syndrome	22 (3.7%)	231 (32.5%)	--
High Insulin ( > 16)	--	132 (18.6%)	--
T2DM**	--	37 (5.4%)	60 (14.4%)
Myocardial Infarction**	--	6 (0.9%)	15 (3.7%)
Stroke**	--	3 (0.4%)	11 (2.8%)
Angioplasty, Stent, Bypass, or other Heart Surgery**	--	1 (0.1%)	14 (3.5%)
Cardiovascular Disease**		10 (1.4%)	29 (7.1%)
Deceased**	--	0	7 (1.7%)

\* Overweight = BMI > 85<sup>th</sup> percentile for LRC, > 25 for PFS; Obese = BMI > 95<sup>th</sup> percentile for LRC, > 30 for PFS

\*\* Cumulative frequencies by the designated visit

**Table 2**  
**Relationship between MetS severity and levels of fasting insulin and adiponectin**

Linear regression of Ln(Insulin) and Ln(Adiponectin) measured at PFS as a function of MetS or MetS Severity during childhood (LRC, 1973–1976) and adulthood (PFS 1998–2003) (only using the n = 595 participants with LRC data).

	Ln(Fasting Insulin)		Ln(Adiponectin)	
	Parameter Estimate (SE)	p-value	Parameter Estimate (SE)	p-value
<u>Baseline (LRC) Models</u>				
Model 1: Pediatric ATP-III MetS at LRC				
Intercept	2.10 (0.03)	< 0.001	2.17 (0.02)	< 0.001
MetS at LRC	0.41 (0.15)	0.007	−0.24 (0.13)	0.069
<i>R-squared</i>	0.01		0.01	
Model 2: MetS severity at LRC				
Intercept	2.23 (0.03)	< 0.001	2.13 (0.03)	< 0.001
MetS z-score at LRC	0.24 (0.04)	< 0.001	−0.08 (0.03)	0.010
<i>R-squared</i>	0.07		0.01	
<u>PFS-Only Models</u>				
Model 3: ATP-III MetS at PFS				
Intercept	1.88 (0.03)	< 0.001	2.32 (0.03)	< 0.001
MetS at PFS	0.79 (0.05)	< 0.001	−0.51 (0.05)	< 0.001
<i>R-squared</i>	0.28		0.15	
Model 4: MetS severity at PFS				
Intercept	2.09 (0.02)	< 0.001	2.19 (0.02)	< 0.001
MetS z-score at PFS	0.38 (0.02)	< 0.001	−0.24 (0.02)	< 0.001
<i>R-squared</i>	0.38		0.20	
<u>Models over both Time Periods</u>				
Model 5: MetS severity over time				
Intercept	2.09 (0.03)	< 0.001	2.23 (0.03)	< 0.001
MetS z-score at LRC	0.38 (0.03)	< 0.001	−0.18 (0.03)	< 0.001
Change in MetS z-score (PFS-LRC)	0.38 (0.02)	< 0.001	−0.27 (0.02)	< 0.001
<i>R-squared</i>	0.38		0.21	

**Table 3**

Odds of Future Disease Using Insulin and Adiponectin, with and without MetS z-score.

	Incident Disease by PHU Visit:			
	Incident Diabetes (n = 22)		Incident CVD (n = 19)	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Model 1				
Ln(Insulin) at PFS	8.40 (3.76, 18.73)	<0.001	3.44 (1.66, 7.12)	<0.001
<i>ROC AUC</i>	<i>0.85</i>		<i>0.75</i>	
Model 2				
Ln(Adiponectin) at PFS	0.25 (0.11, 0.53)	<0.001	0.68 (0.32, 1.44)	0.318
<i>ROC AUC</i>	<i>0.72</i>		<i>0.57</i>	
Model 3				
MetS Z-score at PFS	5.60 (2.98, 10.56)	<0.001	3.51 (2.08, 5.93)	<0.001
<i>ROC AUC</i>	<i>0.87</i>		<i>0.82</i>	
Model 4				
Ln(Insulin) at PFS	3.42 (1.31, 8.92)	0.012	1.14 (0.43, 3.03)	0.786
MetS Z-score at PFS	3.45 (1.63, 7.30)	0.001	3.35 (1.79, 6.26)	<0.001
<i>ROC AUC</i>	<i>0.89</i>		<i>0.82</i>	
Model 5				
Ln(Adiponectin) at PFS	0.47 (0.18, 1.24)	0.128	2.37 (0.86, 6.57)	0.097
MetS Z-score at PFS	5.00 (2.56, 9.77)	<0.001	4.39 (2.41, 8.00)	<0.001
<i>ROC AUC</i>	<i>0.87</i>		<i>0.82</i>	
Model 6				
Ln(Insulin) at PFS	3.04 (1.14, 8.13)	0.027	1.39 (0.49, 3.93)	0.539
Ln(Adiponectin) at PFS	0.63 (0.23, 1.71)	0.362	2.52 (0.90, 7.06)	0.080
MetS Z-score at PFS	3.35 (1.56, 7.18)	0.002	3.97 (2.02, 7.79)	<0.001
<i>ROC AUC</i>	<i>0.89</i>		<i>0.82</i>	