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Obesity and insulin sensitivity effects on cardiovascular risk factors: Comparisons of obese dysglycemic youth and adults

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OBESITY AND INSULIN SENSITIVITY EFFECTS ON CARDIOVASCULAR RISK FACTORS: COMPARISONS OF OBESE DYSGLYCEMIC YOUTH AND ADULTS:

The RISE Consortium*

Abstract

Background: Obesity and pubertal insulin resistance worsen cardiovascular (CV) risk factors in youth. It is unclear how the relationships of obesity and insulin resistance with CV risk compare to adults.

Subjects and Methods: We evaluated 66 pubertal youth (mean±SD: age 14.2±2.0 years, BMI 36.6±6.0 kg/m^2, HbA1c 38.5±6.1 mmol/mol) and 355 adults with comparable BMI (age 52.7±9.4 years, BMI 35.1±5.1 kg/m^2, HbA1c 39.8±4.2 mmol/mol) participating in a multicenter study. Insulin sensitivity was quantified using hyperglycemic clamps. Assessment of CV risk factors was standardized across sites. Regression analyses compared the impact of insulin sensitivity and CV risk factors between youth and adults.

Results: Obese pubertal youth were more insulin resistant than comparably obese adults ($p<0.001$), but with similar slopes for the inverse relationship between insulin sensitivity and obesity. The impact of obesity on CV risk factors was explained by insulin sensitivity (p=NS after adjustment for sensitivity). The two age groups did not differ in relationships between insulin sensitivity and diastolic blood pressure, total cholesterol, and LDL cholesterol, after adjusting for obesity. However, while systolic blood pressure (SBP) and HDL cholesterol exhibited the expected direct and inverse relationships respectively with insulin sensitivity in adults, these slopes were flat in youth across the range of insulin sensitivity ($p\leq0.05$ for group differences).

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* A complete list of the RISE Consortium Investigators can be found in the appendix.

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Author Contributions: Members of the RISE Consortium recruited participants and collected study data, and edited the manuscript. K.J.M. and S.C. proposed the analysis, interpreted data, wrote and edited the manuscript, which was also reviewed and edited by members of the writing group. The RISE Steering Committee reviewed and edited the manuscript and approved its submission. K.J.M. and S.L.E. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conclusions: Effects of obesity on CV risk factors were attributable to insulin sensitivity in both groups. The relationships between insulin sensitivity and CV risk factors were similar in obese youth and adult groups except for SBP and HDL cholesterol.

Clinical Trial Registration: The RISE consortium studies are registered through clinicaltrials.gov as (Adult Medication Study); (Adult Surgery Study); and (Pediatric Medication Study).

Keywords

adults; youth; impaired glucose tolerance; prediabetes; diabetes; insulin sensitivity; insulin resistance; glucose; cholesterol; triglyceride; cardiovascular; blood pressure; Insulin resistance; obesity; youth; adult; cardiovascular risk

INTRODUCTION

The rise in the incidence of obesity has fueled an epidemic of type 2 diabetes (T2D) in adults and a concerning increase in the prevalence of T2D in youth.[1–3] Obesity confers risk for cardiovascular (CV) disease in youth and adults.[4–6] Evidence suggests that insulin resistance is a key underlying driver of the obesity-associated increase in CV risk,[4,5,7,8] and insulin resistance and CV risk factors are inter-related in both youth and adults.[5,7,9–11] Healthy youth have lower insulin sensitivity than adults, reflecting transient physiological reductions during puberty.[12–15] However, it is unknown whether the combination of obesity-related and puberty-related reductions in insulin sensitivity exerts proportional effects on CV risk factors in youth. Exploring this question requires comparison against an obese non-pubertal population.

The Restoring Insulin Secretion (RISE) Consortium is a randomized multi-center clinical trial testing interventional approaches to preserve or improve β-cell function in youth and adults with impaired glucose tolerance or recently diagnosed T2D.[16] In all participants, we measured insulin sensitivity using glucose clamp methodology, and CV risk factors were measured using identical methods across age groups and study sites, including laboratory measurements performed at a central biochemical laboratory. Using these data, we set out to compare the adult and youth populations in the relationships of obesity and insulin resistance with CV risk factors.

METHODS

Participants

RISE baseline studies were performed in US academic centers from 2013 to 2017. Individuals were screened for study eligibility with a 75-gram oral glucose tolerance test (OGTT) and hemoglobin A1c (HbA1c). Youth aged 10–19 years with Tanner stage pubertal development II or greater were eligible for the RISE Pediatric Medication Study if they had a fasting plasma glucose ≥5.0 mmol/L plus 2-hour glucose ≥7.8 mmol/L and: (a) HbA1c ≤64 mmol/mol if drug naïve, (b) HbA1c ≤58.5 mmol/mol if on metformin for <3 months, or (c) ≤53 mmol/mol if on metformin for 3–6 months. Adults were eligible for the RISE Adult Medication Study if they had a fasting plasma glucose 5.3–6.9 mmol/L plus 2-hour glucose

≥7.8 mmol/L and HbA1c ≤53 mmol/mol. Adults were eligible for the RISE Adult Surgery Study (BetaFat) if they had a fasting glucose >5.0 mmol/L plus 2-hour glucose ≥7.8 mmol/L and HbA1C <53 mmol/mol. Adult participants were required to be naïve for glucose-lowering medications. Pediatric participants with any prior metformin exposure were excluded from the current analyses.

In addition to the above features defining dysglycemia, youth were required to have body mass index (BMI) ≥85th percentile for age and sex and adults were required to have BMI ≥25 kg/m^2. Additional details on inclusion/exclusion criteria has been published.[16]

Sample sizes for the contributing studies were determined by the needs of the prospective parent study, based on β-cell function endpoints derived from the hyperglycemic clamp procedure. For the current analyses, we combined baseline data from all participants in the Adult Surgery Study (BetaFat; n=88) and Adult Medication Study (n=267) and compared them to baseline data from the 66 diabetes drug-naïve participants in the Pediatric Medication Study.

All participants gave written informed consent/assent, consistent with the Helsinki Declaration and the guidelines of each participating center's institutional review board.

Measurements

Anthropometric measurements were performed with participants wearing light clothing, and without shoes. Waist and hip circumferences were measured along a horizontal plane using a non-stretching fiberglass tape. Waist circumference was measured at the midpoint between the top of the iliac crest and the bottom of the costal margin in the mid-axillary line, and hip circumference encompassing the greater femoral trochanters. Height was measured using a calibrated stadiometer, with heels together, in a fully vertical position. Weight was measured using a calibrated electronic scale, zeroed before each measurement. All measurements were performed twice (three times if the first two values differed by over ~5%), reporting the average value. We performed parallel analyses using three different obesity terms calculated from these measures: BMI, waist-hip ratio, and waist-height ratio. Percentile distributions of BMI were derived from US representative populations.[17,18]

Blood pressure was measured with calibrated automated devices, using appropriately sized arm cuffs. Measurements were performed in a seated position with feet touching the floor or otherwise supported, after at least 5 minutes of rest in a quiet room, with outer clothing removed and sleeves rolled loosely to the shoulder. Two measurements were taken 5 minutes apart; the second measurement was used as the value of record. Participants were categorized as hypertensive using different approaches for the two age groups. For adults, we applied a threshold of BP >130/80 or current use of blood pressure lowering medication[19]; for youth we applied age, sex, and height appropriate 95th percentile cut-points [20], consistent with Stage 1 or higher hypertension described in the 2011 Expert Panel Guidelines,[21] or use of antihypertensive medication. Percentile distributions of blood pressures were derived from US representative populations.[17,22]

Insulin sensitivity was measured using the hyperglycemic clamp procedure,[23] which allows simultaneous quantification of insulin response and insulin sensitivity.[23–25] The glucose disposal rate (M) was calculated as the mean of the glucose infusion rate required to maintain the target glucose concentration of 11.1 mmol/L at 100, 110, and 120 minutes of the clamp. M was expressed per kg body weight, corrected for urinary glucose loss, and divided by the mean insulin concentration at these same time points (I).[26–28] This calculated M/I term was used as the measurement of insulin sensitivity.

Assays

All biochemical measurements were performed in a single central laboratory (Northwest Lipids Laboratory, University of Washington, Seattle WA). Glucose was measured by the glucose hexokinase method using Roche reagent on a Roche c501 autoanalyzer. The observed inter-assay coefficient of variation (CV) on quality control samples for glucose was ≤2.0%. Cholesterol and triglyceride concentrations were measured enzymatically using Roche reagents on a Cobas c501 autoanalyzer. Cholesterol in HDL was measured on plasma supernatants obtained after precipitation of apoB-containing lipoproteins. The inter-assay CV was consistently <2.0% for cholesterol and <3.0% for triglycerides (TG) and HDL. Insulin was measured by a two-site immuno-enzymometric assay performed on a TOSOH 2000 autoanalyzer, using automated dilution methods to ensure all measurements were made on the linear portion of the assay curve. The assay calibrator is traceable to the WHO IRP 66/304 reference standard. The assay has a sensitivity level of 0.5 uU/mL and is linear up to 330 uU/mL. A set of high, medium, and low insulin level control samples are included in each analytical batch to monitor the assay performance. The inter assay CVs for low, medium, and high level control samples are 7.0%, 5.0%, and 4.5% respectively. This assay was evaluated in 2007 during the ADA Insulin Assay Standardization project and was considered a top performer in terms of specificity, sensitivity, and precision. The evaluation of the specificity provided the following results: cross-reactivity with human C-peptide: 0%; intact proinsulin: 2.3%; proinsulin split (32,33): 2.6%; proinsulin Des (64,65): 39.8%. In healthy adults, Des 64,65 proinsulin constitutes <6% of the total proinsulin and therefore a 39.8% cross reactivity is insignificant. The accuracy of the assay is monitored by quarterly exchange of samples with the reference laboratory at the University of Missouri [29]. Percentile distributions of lipid values were derived from a US representative population.[17]

Statistical Analysis

The SAS analysis system (SAS Institute, Cary, NC) and R (The R Foundation) were used for statistical analyses. Descriptive statistics included percentages, mean±SD, or geometric means (95% confidence intervals) for non-normally distributed data, and were compared between adults and youth using Chi-square tests or Students t-tests. Insulin, insulin sensitivity (M/I), and TG were log-transformed prior to data analysis. Nominal p-values are presented. P-values <0.05 were considered statistically significant, with no adjustments made for multiple comparisons in this secondary analysis.

For comparisons between groups in the relationships between body size and insulin sensitivity, we used linear regression models to evaluate the relationship between BMI and log-transformed M/I. Analyses were also performed using alternate measures of adiposity,

namely waist/hip ratio and waist/height ratio. We evaluated whether youth differed from adults by including age group as an indicator variable and by including an interaction term between age group and obesity terms.

For analyses comparing CV risk factors between groups, we used linear regression, evaluating the relationships of each CV risk factor variable with age group, degree of obesity, and insulin sensitivity. These are presented as Model 1 (relationships with obesity), Model 2 (relationships with insulin sensitivity, log(M/I)), and Model 3 (relationships with both obesity and insulin sensitivity, mutually adjusted). All analyses were also adjusted for age group, sex, race, and use of confounding medication(s) in adults (blood pressure lowering agents for the BP variables; lipid lowering agents for the lipid variables). Sensitivity analyses were performed excluding participants taking potentially confounding medications.

For each evaluated relationship, a model was first constructed incorporating a test of whether the relationship being evaluated differed between the age groups (e.g. an obesity-by-age group interaction); if the p value for this interaction was <0.05, the model incorporating this term was used to describe the determinants of that dependent variable. Otherwise this interaction was removed and the resulting model was used.

RESULTS

Demographic, metabolic, and CV risk factor characteristics comparing youth and adults are presented in Table 1. Participants were all obese, with BMI of 36.6±6.0 kg/m^2 in youth and 35.1±5.1 kg/m^2 in adults (p=0.035). Because of differences in height, these modestly different absolute BMI values represent a much greater degree of obesity in youth than adults (p<0.001; Table 1). Waist/hip and waist/height ratios were numerically comparable and not statistically different between groups (Table 1).

Youth exhibited significantly lower insulin sensitivity (M/I) than comparably obese adults (Table 1). The absolute glucose disposal rates were ~20% higher in youth than adults, and >100% higher insulin concentrations were achieved in response to hyperglycemia. Thus, the ratio of M/I reflects reduced insulin action in target tissues (Table 1). Within the youth cohort, insulin sensitivity was not different across Tanner stages (p=0.76), and did not differ by sex (p=0.52). Blood pressure was numerically lower in youth and fewer achieved age-specific criteria for hypertension. Similarly, youth had lower lipid concentrations. However, evaluated against population distributions across the lifespan, we found higher percentile-ranked blood pressures for youth than adults and lower percentile-ranked HDL values for youth than adults. Triglyceride/HDL ratios were similar between groups.

Relationships of Obesity and Insulin Sensitivity: Comparison of Youth and Adults

Relationships between obesity and insulin sensitivity are presented in Figure 1. Raw data are presented in the figure; statistical evaluations were adjusted for sex and race/ethnicity. The lower insulin sensitivity in youth (Table 1) was evident as a difference (offset) between the groups, where youth exhibited lower insulin sensitivity for any given measure of BMI or adiposity. This offset was uniform across the distribution of the obesity measures, resulting

in similar slopes of the obesity/insulin sensitivity relationship for the two groups (Figure 1) (p=0.45 for BMI-by-age group interaction). Waist/hip and waist/height ratios were also strongly inversely related to insulin sensitivity, with parallel offset slopes between groups.

The slopes of relationship between obesity measures and insulin sensitivity were not different by Tanner stage in this cohort (interaction p values 0.74 – 0.90). Grouping Tanner stages to better match the sample sizes between groups did not alter this observation.

Comparison of Relationships in Youth and Adults between Insulin Sensitivity and CV Risk Factors After Accounting for Effects of Obesity

Relationships of BMI or insulin sensitivity (M/I) with selected CV risk factors are presented in Figure 2. The sex- and race/ethnicity-adjusted regression models for all evaluated CV risk factors are presented in Table 2 (using BMI as the obesity term) and in Supplemental Tables 1 and 2 (using waist/hip ratio and waist/height ratio as the obesity terms, respectively). In all these analyses, the apparent relationships between obesity and CVD risk factors lost significance in models that included both obesity and insulin sensitivity.

The groups differed in reported use of blood pressure lowering medications (47.0% adults vs 3.0% youth, p<0.001) and statin medications (38.3% vs 1.5%, p<0.001). The models presented in Table 2 and Supplemental Tables 1 and 2 included adjustment for these exposures. Blood pressure medication status was not significantly related to systolic blood pressure (SBP) or diastolic blood pressure (DBP). Use of lipid-lowering medications was significantly related to total and LDL cholesterol (p<0.001), but not to HDL, triglycerides, or TG/HDL ratios. The main analyses presented below included all participants, with an adjustment for medication exposure; sensitivity analyses were also performed excluding the patients with medication exposures, presented separately below.

Blood Pressure—Blood pressures were lower in youth than adults (Table 1); nevertheless these represented a right-shifted distribution of values relative to population norms (50^{th} to 90^{th} percentiles for blood pressure in youth versus a tighter distribution around the 50^{th} percentile range for adults [22,30]). In adjusted univariate analyses, BMI was significantly and directly related to SBP (Figure 2A; Table 2, Model 1), and M/I was inversely related to SBP (Figure 2B; Table 2, Model 2). The slopes of the relationship of M/I with SBP were not statistically different between age groups (Figure 2B, p=0.053). When evaluated together in the adjusted analysis (Table 2, Model 3), M/I remained significantly associated with SBP, but BMI did not. The relationship of M/I with SBP adjusted for BMI approached, but did not meet, significance when comparing youth and adults (p=0.057). Excluding participants treated with blood pressure-lowering medications revealed a significant between-group difference in the relationship of M/I with SBP, in Model 2 and Model 3 (Supplemental Table 2; p=0.008 comparing slopes between groups, with a flat slope in youth and an inverse relationship in adults). In similar analyses, M/I was inversely related to DBP (Table 2); this relationship did not differ between youth and adults (p=0.88; Table 2).

Lipid Profile—Total and LDL cholesterol were lower in youth than in adults (Table 1). These represent concentrations in the 25^{th} to 50^{th} percentile range for both groups.[17] BMI and the other evaluated measures of adiposity were not associated with these cholesterol

subsets (Figure 2 and Table 2), (Supplemental Tables 1 and 2). M/I was directly related to total cholesterol, but not LDL cholesterol (Table 2, Model 2). In the mutually adjusted analyses, the same pattern of relationships was seen (Table 2). There were no age group differences in these relationships.

HDL cholesterol and triglycerides were lower in youth, but the TG/HDL ratio did not differ between age groups (Table 1). The observed HDL values represent concentrations in the 5th to 25th percentile range for youth and 25th to 50th percentile range for adults.[17] BMI and measures of adiposity were unrelated to triglyceride concentrations, but M/I was significantly inversely related to triglycerides (Figure 2 and Table 2), without a difference in this relationship between age groups. In the mutually adjusted analyses (Table 2, Model 3), the relationship between M/I and triglycerides persisted, with lower triglycerides concentrations in youth than adults at all levels of insulin sensitivity. BMI was inversely related to HDL in both age groups (Figure 2; Table 2). The relationship of M/I with HDL was significantly different between age groups (p=0.014), with a strong positive relationship seen in adults and an essentially flat relationship at low HDL concentrations in youth (Figure 2; Table 2). In the mutually adjusted model (Table 2, Model 3), the relationship with obesity was lost, but the age group difference in the relationship with M/I persisted. BMI was not associated with the TG/HDL ratio in Model 1, but M/I was related to TG/HDL in Model 2 and approached significance for a group difference in the relationship between M/I and TG/HDL in Model 3 (p=0.051 comparing age groups). After excluding participants treated with lipid-lowering agents (Supplemental Table 3), the magnitude of the between-group differences in total and LDL cholesterol was greater, but overall the relationships among BMI, M/I, and lipid variables, and the between-group differences were unchanged. Therefore, the age groups differed in the relationship of M/I with HDL, with low values of HDL across the range of insulin sensitivity in youth. The statistically borderline group differences in TG/HDL ratios were driven by this effect of HDL.

Parallel analyses using waist/hip ratio or waist/height ratio as the obesity measure revealed similar results overall (Supplemental Tables 1 and 2). Modest differences were seen in the relationships with total cholesterol (significant in the univariate models with waist/hip and waist/height ratios, non-significant in the individual model with BMI), with triglycerides (significantly associated with waist/hip and waist/height ratios in univariate models but not in the mutually adjusted models), and with HDL (TG/HDL ratio associations with waist/hip ratio and waist/height ratio in Model 3 analyses approaching, but not achieving, statistical significance). Nevertheless, these analyses were most notable for how little difference was introduced by using these alternate measures of adiposity.

DISCUSSION

In the obese, dysglycemic youth and adults in RISE, insulin sensitivity was related to CV risk factors after adjusting for obesity. Despite lower insulin sensitivity in youth overall and at any degree obesity, the magnitude of the associations between insulin sensitivity and CV risk factors was similar in youth and adults. The main exception was HDL cholesterol, where the relationship of decreasing insulin sensitivity with decreasing HDL was seen in adults, but among youth, the HDL cholesterol concentration was low across the range of

insulin sensitivity and unrelated to insulin sensitivity. A difference between groups was seen in the relationship of insulin sensitivity with systolic blood pressure (SBP) after excluding participants treated with blood pressure lowering medications, such that in youth the SBP was elevated relative to population norms but unrelated to insulin sensitivity.

Obesity and Insulin Sensitivity in Youth and Adults

Youth had lower insulin sensitivity compared with adults (Table 1, Figure 1). Many factors could underlie the lower insulin sensitivity in youth, including differences in fat or lean body mass, genetics, diet and other environmental factors, or socioeconomic status. Physiologic pubertal insulin resistance may contribute importantly to this difference [9,13,15,31], and previous studies describe a further reduction in insulin sensitivity in obese pubertal children compared to non-obese pubertal children [9,12–14,32–37]. However the nature of the dual contributions of obesity and puberty to reduced insulin sensitivity is unclear. The current observations are contributory, in that we observed a parallel inverse relationships between obesity and insulin sensitivity in youth and adults (Figure 1) with a uniform difference or 'offset' between the groups. In other words, there was a whole-group difference in sensitivity that uniformly lowered insulin sensitivity in youth across the range of obesity, without altering the slope of the obesity-sensitivity relationship.

Relationships with CV Risk Factors

Insulin resistance is known to be associated with an adverse cardiometabolic risk factor profile,[10,11,31,35,38–40] and both obesity and insulin resistance appear to contribute independently to CV risk in representative populations of youth.[5,10,15,21,38,41–49] In our obese dysglycemic adult and youth cohorts, the dominant associations with CV risk factors were from insulin sensitivity without a separate effect of obesity. However, systolic blood pressure and HDL-lipoproteins exhibited differences in these relationships between youth and adults.

Systolic Blood Pressure—In our primary analysis the association of insulin sensitivity with SBP differed modestly between adults and youth (Figure 2B) and in youth with marked obesity, reduced insulin sensitivity, and elevated age-adjusted blood pressure there was no relationship between obesity or insulin sensitivity and SBP. The epidemiologic literature suggests concurrent relationships of obesity and insulin sensitivity with blood pressure.[40,46,50–53] However, the RISE youth cohort represents one extreme of the spectrum, comprised almost entirely of individuals at or above the 95th percentile for BMI. Our observations are consistent with the epidemiologic literature in that the associated blood pressures are elevated compared to age-specific norms, but we do not see the expected relationships with obesity or insulin sensitivity measures. The flat relationships in the RISE youth seem likely to represent a ceiling effect of obesity, insulin resistance, or both as a determinant of SBP in our cohort of youth.

These observations may have implications for future blood pressure and cardiovascular risk. In a representative population of youth, Sinaiko and colleagues evaluated relationships between blood pressure and insulin sensitivity at age 13 and then reassessed them at age 19.[46] Insulin sensitivity increased yet blood pressures rose in that interval; blood pressure at

age 19 was determined by the change in BMI and by insulin sensitivity at age 13. In contrast, adult blood pressure was not determined by the change in insulin sensitivity over the interval. Sex and race/ethnicity appear to be important factors in this transition.[50,54] Prospective studies of individuals at the extremes of obesity or insulin sensitivity have not been reported and, therefore, it is unknown whether our results portend more adverse adult blood pressure outcomes in populations resembling the RISE youth cohort.

Plasma Lipids—Consistent with epidemiologic evaluations in representative populations,[46,55–58] we saw lower total and LDL cholesterol concentrations in youth; the relationships with insulin sensitivity reflected this difference between age groups but revealed similar slopes between age groups. We interpret these results as demonstrating a similar underlying relationship of insulin sensitivity with total and LDL cholesterol between groups.

Insulin sensitivity is more strongly associated with triglyceride and HDL cholesterol concentrations compared with LDL concentrations.[58–60] The current data show that the relationship of insulin sensitivity with triglycerides was similar in youth and adults. However, relationships of insulin sensitivity with HDL cholesterol differed. In adults, we saw the expected direct relationship (lower insulin sensitivity with lower HDL), whereas in youth HDL was not dependent on insulin sensitivity. Notably, in youth the HDL concentrations were low across the range of insulin sensitivity. As with the SBP relationship, we interpret this as likely representing a ceiling effect of obesity, insulin sensitivity, or both on HDL concentrations in youth.

In epidemiologic studies evaluating obesity/insulin resistance and lipid concentrations, an inverse association has generally been found in children as in adults.[11,46,55,56] Other examples include mutual associations among insulin sensitivity, sex hormone-binding globulin, sex hormones, and HDL found in a cross-sectional study of school age children not pre-selected for obesity or dysglycemia,[55] and an inverse association of HDL cholesterol with socioeconomic status and adiposity described in children in Turkey.[57] Measured insulin sensitivity is quite low in the RISE populations, but still exhibits a sufficient range that underlying relationships are evident with other CV risk factors. Nevertheless, one interpretation of the current findings is that a ‘ceiling effect’ is at play, where the maximal reduction in HDL is reached at all levels of insulin sensitivity present in the youth cohort, with no opportunity for further reduction in this low range of insulin sensitivity.

Strengths and Limitations

The strengths of our study include cohorts of youth and adults with comparable BMI and dysglycemia, and the application of identical measurements in both groups, including glucose clamp methodology for direct measurement of insulin sensitivity[23] and standardized, high-quality measures of CV risk factors, with all biochemical assays performed in a single laboratory. These features allow comparisons between adults and youth never previously reported. Limitations include the use of a clinical trial population with pre-specified enrollment criteria, with consequent restrictions on the range of BMI and glucose tolerance. Further, in these individuals we measured BMI and central adiposity using anthropometrics, but did not directly assess total body fat or intra-abdominal fat

depots, for example using dual energy x-ray absorptiometry or CT scans. We expressed insulin sensitivity measures per kg body weight, rather than per kg fat-free mass as is often done. The relationship of BMI with direct measures of adiposity may differ between youth and adults [61,62], perhaps owing to different relationships with height [63], which may have affected the outcomes. However, confidence in our results is supported by our observations of parallel relationships among CV risk factors and central obesity assessed using waist/height and waist/hip ratios. Although many adults were treated with blood pressure and cholesterol lowering medications, we adjusted for this in the main analyses and also performed sensitivity analyses excluding treated participants. The features of the youth that distinguish them from the adults include the pubertal state plus other features, which we cannot separate in exploring obesity-independent differences in insulin sensitivity and associations with CV risk factors in the current analyses.

Conclusions

In the RISE cohorts, we observed significantly lower insulin sensitivity in youth compared to adults across the spectrum of obesity. Overall, the relationships between insulin sensitivity and CV risk factors were similar in adults and youth, and insulin sensitivity accounted for the associations between obesity on CV risk factors in both groups. Systolic blood pressure and HDL cholesterol were exceptions, with flat relationships of these measures with insulin sensitivity in youth, which we interpret as a ceiling effect of insulin sensitivity on these parameters in youth. These direct comparisons provide evidence that poor insulin sensitivity in obese dysglycemic youth has “adult-like” impact on CV risk. The implications of this are sobering, given the relatively young age of the RISE Pediatric cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI
body mass index

CV
cardiovascular

DBP
diastolic blood pressure

HDL
high-density lipoprotein

LDL
low-density lipoprotein

M/I insulin sensitivity
measured as glucose disposal rate (M) divided by insulin concentrations (I)

RISE
Restoring Insulin Secretion consortium

SBP
systolic blood pressure

TG
triglycerides

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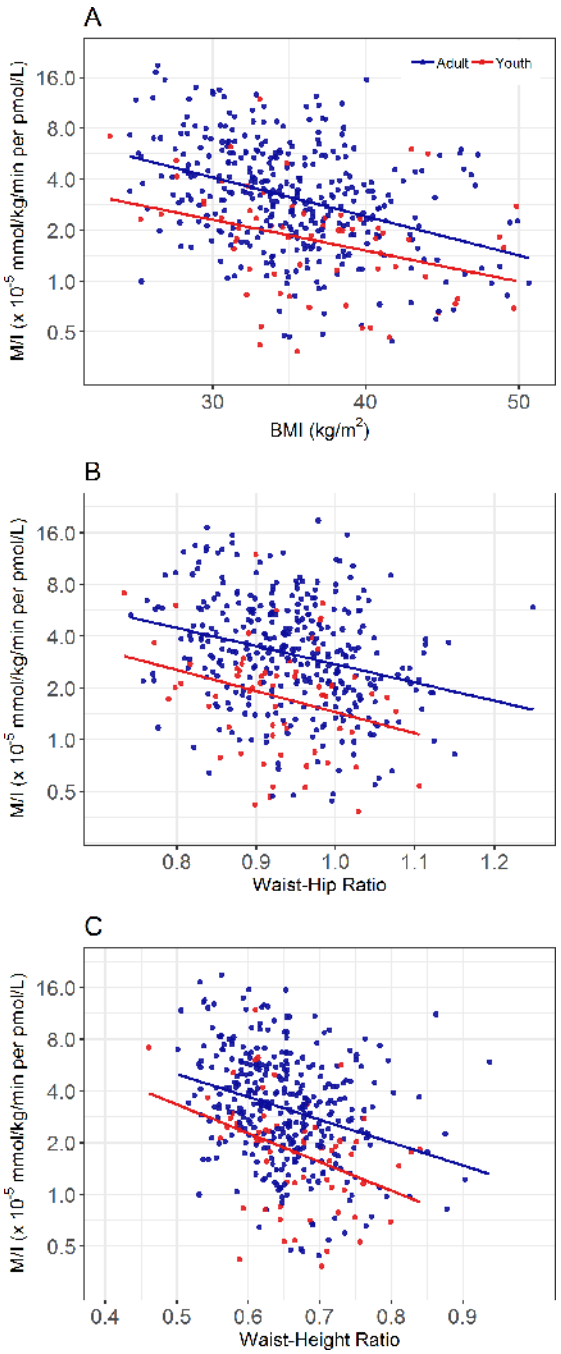

Figure 1.

Relationship of insulin sensitivity to BMI (Panel A), to waist/hip ratio (panel B) and waist/height ratio (panel C). Youth are presented in red and adults in blue. Insulin sensitivity (M/I, the clamp glucose disposal rate divided by the steady-state insulin concentration) is presented on a log scale. The slopes relating insulin sensitivity to obesity measures were all significant ($p<0.001$) and the group differences were all significant ($p<0.001$). The slopes did not differ by group ($p=0.452 – 0.676$). BMI, body mass index.

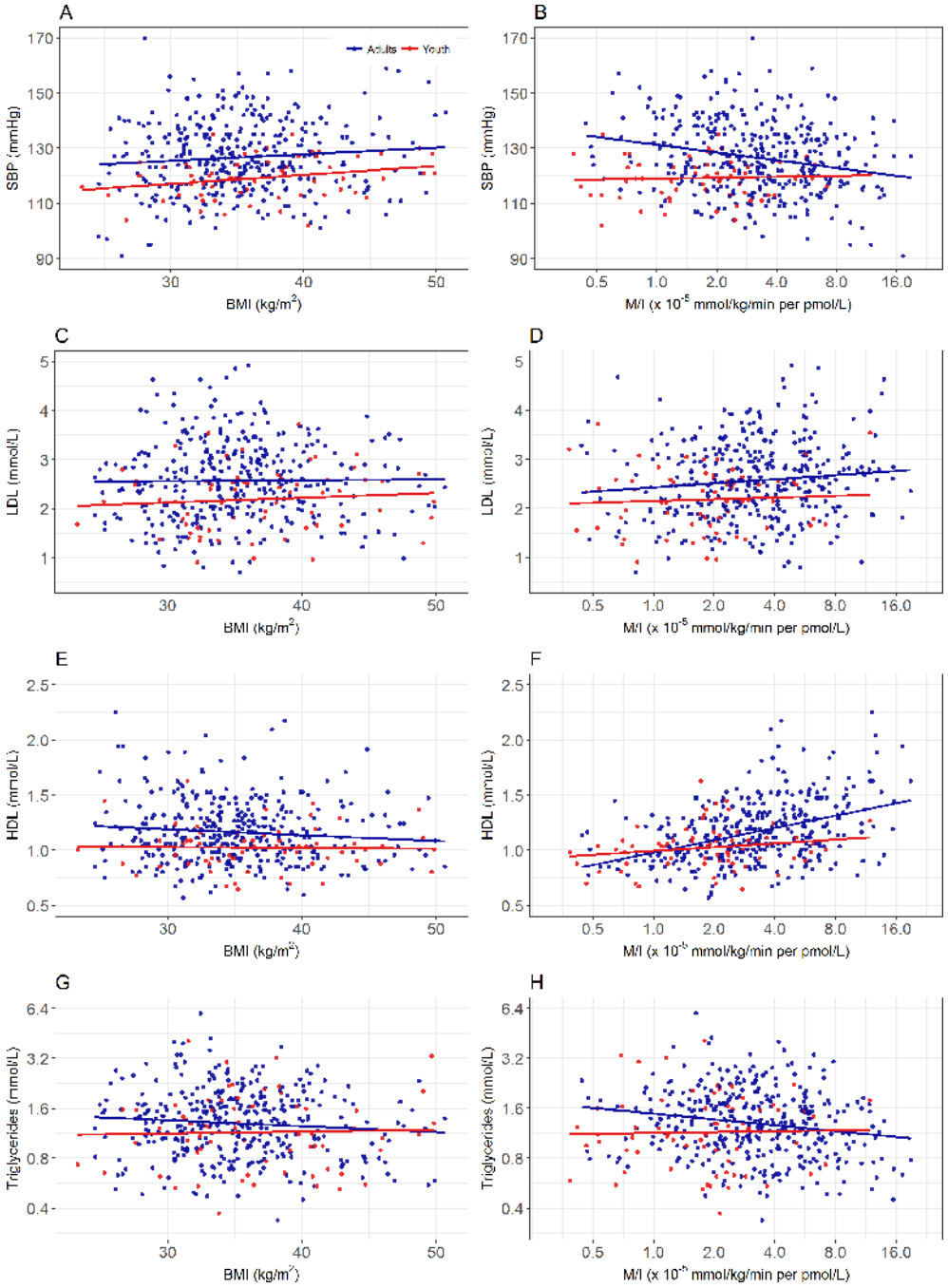

Figure 2.

Body Mass Index and Insulin Sensitivity as Determinants of CV Risk Factors in Youth and Adults. Youth are presented in red and adults in blue. Insulin sensitivity (M/I, the clamp glucose disposal rate divided by the steady-state insulin concentration) and triglycerides are presented on a log scale. The underlying statistical analyses are presented in Table 2. The slopes were significantly different between age groups only for M/I versus HDL cholesterol (p=0.014); M/I versus SBP approached but did not reach significance (p=0.053). BMI, body

mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Table 1.

Baseline characteristics of the study population.

	Youth	Adult	P value
Demographics	N=66	N=355	
Age (years)	14.2 ± 2.0	52.7 ± 9.4	<0.001
Sex			0.005
Female	47 (71.2%)	183 (51.5%)	
Male	19 (28.8%)	172 (48.5%)	
Race/ethnicity			<0.001
White	19 (28.8%)	166 (46.9%)	
Black	14 (21.2%)	97 (27.4%)	
Hispanic	25 (37.9%)	68 (19.2%)	
Mixed/Other	8 (12.1%)	23 (6.5%)	
Anthropometrics			
Weight (kg)	98.9 ± 22.6	100.8 ± 18.2	0.454
Height (cm)	163.7 ± 9	169.2 ± 9.7	<0.001
Waist circumference (cm)	109 ± 14.2	110.4 ± 12.7	0.448
Hip circumference (cm)	117.6 ± 13.9	117.1 ± 10.8	0.776
BMI (kg/m^2)	36.6 ± 6.0	35.1 ± 5.1	0.035
BMI Percentile			<0.001
>25 to 50	0 (0.0%)	28 (7.9%)	
>50 to 75	0 (0.0%)	85 (23.9%)	
>75 to 85	1 (1.5%)	78 (22%)	
>85 to 90	0 (0.0%)	60 (16.9%)	
>90 to 95	1 (1.5%)	58 (16.3%)	
>95	64 (97.0%)	46 (13.0%)	
Waist to Hip Ratio	0.93 ± 0.08	0.94 ± 0.08	0.176
Waist to Height Ratio	0.66 ± 0.07	0.65 ± 0.07	0.206
Tanner Stages (II/III/IV/V) (n)	4/10/12/40	-	
Baseline Metabolic Measures			
HbA1c (mmol/mol) (%)	38.54 ± 6.11 5.68 ± 0.56	39.6 ± 4.4 5.78 ± 0.40	0.080
Fasting glucose (mmol/L)	5.9 ± 0.9	6.2 ± 0.7	<0.001
2 hour glucose (mmol/L)	9.89 ± 2.5	10.15 ± 2.4	0.404
IGT/T2D (n)	53/13	251/104	0.147
Steady State Glucose Disposal Rate (M; mmol/kg/min)	0.025 ± 0.010	0.021±0.010	0.007
Steady State Insulin concentration (I; pmol/L)	1370.3 (298.6, 6288.0)	610.7 (147.4, 2530.4)	<0.001
Insulin Sensitivity (M/I x 10^{-5} mmol/kg/min per pmol/L)	1.69 (0.37, 7.69)	3.13 (0.76, 12.87)	<0.001
Baseline CVD Variables			
Systolic BP (mm Hg)	119.3 ± 7.4	126.6 ± 13.0	<0.001

	Youth	Adult	P value
Diastolic BP (mm Hg)	67.8 ± 7.3	77.1 ± 10.0	<0.001
Hypertension	13 (19.7%)	257 (72.4%)	<0.001
Total cholesterol (mmol/L)	3.8 ± 0.7	4.4 ± 0.9	<0.001
LDL cholesterol (mmol/L)	2.2 ± 0.7	2.6 ± 0.8	<0.001
HDL cholesterol (mmol/L)	1.0 ± 0.2	1.2 ± 0.3	<0.001
TG (mmol/L)	1.15 (0.42, 3.12)	1.30 (0.53, 3.20)	0.047
TG/HDL ratio (mmol/mmol)	1.14 (0.36, 3.59)	1.15 (0.37, 3.57)	0.985

Note. Data are presented as number (percent of total), arithmetic mean ± SD for normally distributed data, or geometric means (5th, 95th % Confidence Interval) for non-normally distributed data. BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; M/I, glucose disposal rate divided by insulin concentrations;T2D, type 2 diabetes mellitus; TG, triglyceride.

Table 2.

Regression modeling evaluating Body Mass Index and insulin sensitivity as determinants of cardiovascular risks

Outcome variable	Model	Variable	Estimate	SE	p	Group Interaction p
SBP (mmHg)	**1**	**Age Group**	−5.709	1.720	0.001	0.913
		BMI	+0.289	0.113	0.011	
	2	**Age Group**	−7.234	1.798	<0.001	0.054
		Log (M/I)	−2.812	0.815	<0.001	
	3	**Age Group**	−7.216	1.796	<0.001	0.057
		Log (M/I)	−2.362	0.876	0.007	
		BMI	+0.168	0.121	0.166	
DBP (mmHg)	**1**	**Age Group**	−7.672	1.342	<0.001	0.825
		BMI	−0.012	0.088	0.889	
	2	**Age Group**	−8.809	1.403	<0.001	0.848
		Log (M/I)	−1.519	0.636	0.016	
	3	**Age Group**	−8.820	1.403	<0.001	0.864
		Log (M/I)	−1.799	0.684	0.009	
		BMI	−0.104	0.094	0.270	
Total Cholesterol (mmol/L)	**1**	**Age Group**	−0.737	0.123	<0.001	0.082
		BMI	−0.012	0.008	0.135	
	2	**Age Group**	−0.655	0.128	<0.001	0.455
		Log (M/I)	+0.143	0.059	0.015	
	3	**Age Group**	−0.659	0.128	<0.001	0.4613
		Log (M/I)	+0.128	0.064	0.045	
		BMI	−0.006	0.009	0.533	
LDL Cholesterol (mmol/L)	**1**	**Age Group**	−0.545	0.105	<0.001	0.245
		BMI	−0.005	0.007	0.472	
	2	**Age Group**	−0.496	0.110	<0.001	0.612
		Log (M/I)	+0.081	0.051	0.109	
	3	**Age Group**	−0.497	0.110	<0.001	0.614
		Log (M/I)	+0.079	0.055	0.151	
		BMI	−0.001	0.008	0.906	
HDL Cholesterol (mmol/L)	**1**	**Age Group**	−0.143	0.035	<0.001	0.132
		BMI	−0.006	0.002	0.008	
	2	**Age Group**	−0.001	0.044	0.986	
		Log (M/I)	+0.144	0.018	<0.001	

Outcome variable	Model	Variable	Estimate	SE	p	Group Interaction p
		Group*Log(M/I)	−0.102	0.041	0.014	0.014
	3	**Age Group**	−0.001	0.044	0.995	
		Log (M/I)	+0.146	0.019	<0.001	
		BMI	+0.001	0.002	0.822	
		Group*Log(M/I)	−0.102	0.041	0.014	0.014
Log(Triglycerides) (mmol/L)	**1**	**Age Group**	−0.114	0.064	0.073	0.506
		BMI	−0.006	0.002	0.919	
	2	**Age Group**	−0.186	0.066	0.005	0.176
		Log (M/I)	−0.106	0.030	<0.001	
	3	**Age Group**	−0.191	0.066	0.004	0.167
		Log (M/I)	−0.126	0.033	<0.001	
		BMI	−0.007	0.005	0.118	
Log(TG/HDL ratio) (mmol/mmol)	**1**	**Age Group**	0.010	0.0778	0.895	0.991
		BMI	0.005	0.0052	0.373	
	2	**Age Group**	−0.124	0.080	0.113	0.054
		Log (M/I)	−0.210	0.036	<0.001	
	3	**Age Group**	−0.130	0.078	0.098	0.051
		Log (M/I)	−0.231	0.039	<0.001	
		BMI	−0.008	0.0054	0.157	

Note. All models were adjusted for sex, race/ethnicity and relevant medication use (antihypertensives for blood pressure variables; statins for lipid variables). The interaction of age group and insulin sensitivity (Group*Log(M/I)) was evaluated in Models 2 and 3; these interactions were significant for HDL cholesterol, indicating that the relationship with insulin sensitivity differed between adults and adolescents. Adolescents were coded as 1 and adults as 0; otherwise the slope terms are presented per 1 mmHg for BP or per 1 mmol/L for lipid values. BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M/I, glucose disposal rate divided by insulin concentrations; SBP, systolic blood pressure; TG, triglyceride.