Insulin Resistance and Cardiovascular Disease Risk Factors in Children of Parents With the Insulin Resistance (Metabolic) Syndrome

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OBJECTIVE — To evaluate whether children of parents with the insulin resistance syndrome (IRS) themselves have greater insulin resistance and unfavorable patterns of cardiovascular disease (CVD) risk factors.

RESEARCH DESIGN AND METHODS — This cross-sectional study included 220 white and 36 black children aged 11–15 years identified through a school-based blood pressure screening program, along with 378 of their parents. Measures of insulin resistance (glucose disposal per minute per kilogram of lean body mass in a euglycemic-hyperinsulinemic clamp [M_{lbm}] and fasting insulin), adiposity, and other CVD risk factors were compared in children with and without a parental history of IRS, defined according to the National Cholesterol Education Program Adult Treatment Panel III consensus definition.

RESULTS — Compared with children in whom neither parent had IRS, children who had at least one parent with the syndrome had statistically significantly lower mean M_{lbm} (12.1 vs. 13.6 $mg \cdot kg^{-1} \cdot min^{-1}$; $P = 0.04$) and higher fasting insulin (geometric means 99 vs. 76 pmol/l; $P = 0.01$) after adjustment for sex, race, age, and Tanner stage. Mean BMI, waist circumference, waist-to-hip ratio, triceps and subscapular skinfolds, and percentage of body fat were also significantly higher in children of an affected parent, but there were no significant differences in lipid or blood pressure levels between the two groups.

CONCLUSIONS — Insulin resistance and obesity may be the earliest manifestations of IRS in children with a parental history of the syndrome.

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The insulin resistance syndrome (IRS), a cluster of traits including hyperinsulinemia, dyslipidemia, hypertension, and obesity, is associated with increased risk of cardiovascular disease (CVD) and all-cause mortality (1). The etiology of IRS is likely multifactorial, involving both genetic and environmental factors as well as their interactions. Impaired insulin-mediated glucose uptake and adiposity have been hypothesized to be the common underlying factors leading to development of the syndrome.

The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recently published a consensus definition of IRS (also termed the metabolic syndrome) based on abnormalities in three or more of five component traits (waist circumference, blood pressure, fasting glucose, HDL, and triglycerides) (2). According to National Health and Nutrition Examination Survey III (NHANES III) data (3), an estimated 22% of U.S. adults (~47 million total) met this definition for IRS in 1988–1994. Although the prevalence of IRS was highest in the 60- to 69-year age-group, it was also 5–10% among those aged 20–29 years, suggesting that IRS may develop before adulthood in some high-risk individuals. Children with a parental history of IRS may represent one such high-risk group because of genetic and environmental factors shared within families. Twin and family studies have found substantial familial aggregation for IRS as well as for each of the component traits (4–7).

To our knowledge, there have been no comprehensive studies during adolescence relating IRS in parents to insulin resistance in their children. The data for the present study were obtained from a cohort of 11- to 15-year-old children and their parents participating in a longitudinal evaluation of the effect of insulin resistance during childhood on development of type 2 diabetes and young adult cardiovascular risk. Although the prevalence of overt IRS, as defined for adults (2), is low during childhood, we hypothesized that children of parents with IRS would have greater insulin resistance and elevated CVD risk factors compared with children of parents without IRS. Confirming this association is of clinical importance because of the expectation that children will increasingly resemble their parents as they progress from childhood to adulthood.

RESEARCH DESIGN AND METHODS

— The University of Minnesota Institutional Review Board approved the project. The children in this study were recruited after blood pressure screening of 12,043 fifth- through eighth-grade Minneapolis Public School students

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Abbreviations: ATP-III, National Cholesterol Education Program Adult Treatment Panel III; CVD, cardiovascular disease; IRS, insulin resistance syndrome; WHR, waist-to-hip ratio.

(3,819 black, 4,216 white, 4,008 other; 6,035 boys, 6,008 girls). Details of the recruitment have previously been published (8). Participants were randomly selected with stratification according to sex, race (black and non-Hispanic white), and systolic blood pressure percentile (half from the upper 25 percentiles and half from the lower 75 percentiles to enrich the study population with potentially higher risk children).

Of 2,915 students who received a recruitment letter, 537 attended an information meeting (held in groups of 20–30 children and their parents). Informed consent was obtained from 401 children and their parents. The screening blood pressure of this group did not differ from that of the children choosing not to participate. Of the 401 children who agreed to participate in the study, 25 subsequently refused to attend the clinic, 2 were found to be ineligible for participation because of chronic illness, and 17 were unable to complete a euglycemic-hyperinsulinemic clamp study because of technical difficulties with venipuncture and catheter placement in the clinical research center. A total of 357 children completed the euglycemic-hyperinsulinemic clamp studies.

Clinical and laboratory measurements in children

At the initial clinic visit (1996–1997), the children underwent a physical examination. Anthropometric measurements for height, weight, waist and hip circumferences, and skinfolds were made using conventional methodology, as previously described (8). Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer with subjects in the seated position; the averages of the two measurements (systolic and fifth-phase Korotkoff diastolic) were used in the analyses. Tanner stage for boys was determined according to pubic hair development; for girls, the most development between breast and pubic hair was used to determine Tanner stage. Data from all participants were combined based on the relation of insulin sensitivity to Tanner stage, as previously reported in this cohort (9). We have confirmed that insulin resistance increases significantly between Tanner stages 1 and 2, remains stable through Tanner stages 2, 3, and 4, and decreases significantly at Tanner stage 5. Despite these changes, the inverse association between insulin sensitivity and BMI was statistically significant at each of the Tanner stages and was not significantly different between any of the stages.

The euglycemic-hyperinsulinemic clamp studies were conducted in the University of Minnesota Clinical Research Center, as previously described (8). Blood samples for serum insulin levels were obtained at baseline (−10, −5, and 0 min before the start of the insulin infusion) and at steady state during the clamp (+140, +160, and +180 min). Plasma glucose was also measured at baseline (−10, −5, and 0 min) and every 5 min during the clamp. The insulin infusion was started at time 0 and continued at a rate of 1 mU · kg^{-1} · min^{-1} for 3 h. An infusion of 20% glucose was started at time 0 and was adjusted, based on plasma glucose levels, to maintain euglycemia, that is, plasma glucose at 5.6 mmol/l. Insulin sensitivity was determined from the amount of glucose required to maintain euglycemia over the final 40 min of the euglycemic-hyperinsulinemic clamp study and was expressed as M_{lbm} (i.e., glucose disposal in milligrams per kilogram lean body mass, or fat-free mass, per minute), with body fat and fat-free mass calculated by the method of Slaughter et al. (10).

Blood samples were analyzed for glucose immediately at the bedside with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). The insulin samples were collected on ice and centrifuged within 20 min. Insulin levels were determined by radioimmunoassay (Diagnostic Products, Los Angeles, CA). The average of the three baseline measurements was used in the analyses. Blood samples for serum lipids were analyzed in the University of Minnesota laboratory, as previously described (8).

Clinical and laboratory measurements in parents

Parents completed a clinical examination during 1998–2002 that included anthropometrics, fasting lipid, insulin, and glucose determinations, and blood pressure measurements. Protocols were identical to those used for their children. Current use of antihypertensive, antidiabetic, and lipid-lowering medications was ascertained through a medication inventory.

Statistical methods

Parents were classified as affected or unaffected with IRS based on the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) consensus definition (2), which requires three or more of the following abnormalities: *1*) abdominal obesity = waist circumference >102 cm in men or 88 cm in women; *2*) elevated blood pressure ≥130/85 mmHg; *3*) hypertriglyceridemia ≥1.69 mmol/l; *4*) low HDL <1.03 mmol/l in men or 1.29 mmol/l in women; and *5*) elevated fasting glucose ≥6.1 mmol/l.

Parents currently being treated for hypertension or diabetes were included in the elevated blood pressure and glucose categories, respectively. Children were classified as having an affected parent if at least one parent had IRS. Children were classified as not having an affected parent if both parents did not have IRS. Children with one unaffected parent and one parent unavailable for measurement were placed in a separate category. Contingency tables and ANCOVA were used to compare prevalences or mean levels of demographic, clinical, and laboratory variables in parents with or without IRS as well as in children of parents with or without IRS. Similar methods were used to compare children with or without an obese parent (BMI ≥30 kg/m^2).

Table 1—*Prevalence of IRS component traits in parents*

IRS traits	Mothers	Fathers
n	221	157
Abdominal obesity (%)	45	35
Elevated blood pressure (%)	20	34
Hypertriglyceridemia (%)	24	40
Low HDL (%)	47	47
Elevated fasting glucose (%)	16	29
Three or more traits (%)	25	32

Table 2—*Demographic, anthropmetric, and laboratory data in parents with (IRS+) and without (IRS−) IRS*

	Mothers		Fathers	
	IRS+	IRS−	IRS+	IRS−
n	53	168	51	106
Age (years)	47.4 ± 0.8	45.4 ± 0.4	49.0 ± 0.8	48.4 ± 0.5
Race (% black)	11	11	6	10
Fasting insulin (pmol/l)*†	123 ± 7	74 ± 2	133 ± 8	73 ± 3
Fasting glucose (mmol/l)*	6.05 ± 0.10	5.28 ± 0.06	7.26 ± 0.28	5.42 ± 0.19
Height (cm)*	164.2 ± 0.8	165.7 ± 0.5	178.1 ± 1.1	178.2 ± 0.8
Weight (kg)*	94.6 ± 2.1	73.3 ± 1.2	105.8 ± 2.4	85.4 ± 1.7
BMI (kg/m^2)*	35.0 ± 0.7	26.7 ± 0.4	33.4 ± 0.7	26.8 ± 0.5
Waist (cm)*	104.1 ± 1.8	83.5 ± 1.0	112.2 ± 1.7	94.1 ± 1.2
WHR*	0.86 ± 0.01	0.79 ± 0.01	0.97 ± 0.01	0.90 ± 0.01
Triceps skinfold (mm)*	39.0 ± 1.3	29.5 ± 0.7	28.1 ± 1.4	20.4 ± 1.0
Subscapular skinfold (mm)*	33.8 ± 1.4	21.4 ± 0.8	29.9 ± 1.4	18.3 ± 1.0
Total cholesterol (mmol/l)*	5.37 ± 0.12	4.85 ± 0.07	5.28 ± 0.16	4.98 ± 0.11
LDL (mmol/l)*	3.28 ± 0.11	2.91 ± 0.06	3.09 ± 0.13	3.17 ± 0.09
HDL (mmol/l)*	1.11 ± 0.05	1.46 ± 0.03	0.88 ± 0.04	1.17 ± 0.03
Triglycerides (mmol/l)*†	1.87 ± 0.12	0.93 ± 0.03	2.27 ± 0.16	1.22 ± 0.06
Systolic blood pressure (mmHg)*	122.7 ± 1.8	112.7 ± 1.0	127.8 ± 1.8	117.8 ± 1.3
Diastolic blood pressure (mmHg)*	75.4 ± 1.4	68.9 ± 0.8	77.9 ± 1.3	72.6 ± 0.9

Data are means ± SE unless otherwise indicated. *Adjusted for age and race; †geometric mean.

RESULTS — Of the 357 children in the cohort, 256 had at least one parent who completed a clinic examination. After excluding parents who did not participate or could not be located ($n = 126$) and those examined but with missing data on one or more IRS component traits ($n = 8$), a total of 378 parents (221 mothers and 157 fathers) were available for this analysis, including 122 spouse pairs. The mean age of the mothers was 45.9 years (range 31–61); the mean age of the fathers was 48.6 years (32–64). The IRS (i.e., abnormalities in three or more component traits) was diagnosed in 53 (25%) of the mothers and in 51 (32%) of the fathers (Table 1). The prevalence of abnormalities for component traits of IRS ranged from 16 to 47% in mothers and from 29 to 47% in fathers (Table 1); low HDL was the most common disorder in both sexes. After adjusting for age and race, mean fasting insulin, blood pressure, and most anthropometric and lipid variables were higher in parents with IRS than in those without IRS (Table 2).

The mean age of the children was 12.9 years (range 11–15). Most of the children were white (86%). Only eight children (3.1%) met the ATP-III definition of IRS. Of the 256 children with one or both parents in the study, 91 (36%) had at least one parent with IRS, 60 (23%) had neither parent with IRS, and 105 (41%) were unclassifiable because they had one parent without IRS and one parent with missing data. Demographic data, body measurements, and laboratory data for the first two groups are presented in Table 3. Children with a parent affected with IRS had greater evidence for insulin resistance, with significantly lower mean M_{lbm} and higher fasting insulin after adjustment for sex, race, age, and Tanner stage. Children with an affected parent were also generally fatter, as indicated by significantly higher mean BMI, waist circumference, waist-to-hip ratio (WHR), triceps and subscapular skinfolds, and percentage of body fat. Differences in M_{lbm} and fasting insulin by parental IRS status were attenuated by 23 and 27%, respectively, upon additional adjustment for measures of adiposity (BMI and WHR) in the children and were no longer statistically significant ($P = 0.11$ and $P = 0.07$, respectively). With the exception of waist circumference, none of the specific IRS component traits (blood pressure, triglycerides, HDL, and glucose) was significantly different between the two groups of children, although a higher percentage of children with an affected parent had three or more IRS traits above the trait-specific sex- and age-specific 75th percentile (16 vs. 7%, OR 2.58, 95% CI 0.81–8.26). Children with an unclassifiable parental IRS status had mean values for M_{lbm}, fasting insulin, BMI, waist, WHR, triceps and subscapular skinfolds, and percentage of body fat that were intermediate between those for children with at least one affected parent and children with two unaffected parents (data not shown). For example, adjusted mean M_{lbm} was 12.3 mg · kg^{-1} · min^{-1} in children with one unaffected and one missing parent, compared with 12.1 and 13.6 mg · kg^{-1} · min^{-1} in children with at least one affected parent and two unaffected parents, respectively.

Similar patterns were not observed when children were instead classified according to their parents' obesity status (Table 4). Although children with at least one obese parent were generally fatter than children with no obese parents, there were no differences in mean M_{lbm}, fasting insulin, or other CVD risk factors between the two groups. Cross-classification of children according to parental IRS and parental obesity indicated only partial overlap between the groups: 50% of children had both parental IRS and parental obesity, 8% had parental IRS but not parental obesity, 8% had parental obesity but not parental IRS, and 34% had neither parental IRS nor parental obesity.

CONCLUSIONS — The results of this study show that adolescent children of parents with IRS, defined by the ATP-

Table 3—*Demographic, anthropometric, and laboratory data in children of parents with and without IRS*

	Parental status for IRS§		
	Present	Absent	*P* value
n	91	60	
Age (years)	13.0 ± 0.1	12.7 ± 0.1	0.09
Sex (% women)	43	40	0.37
Race (% black)	11	7	0.14
Three or more IRS traits >75th percentile (%)*	16	7	0.10
M_{lbm} ($mg \cdot kg^{-1} \cdot min^{-1}$)†	12.1 ± 0.4	13.6 ± 0.5	0.04
Fasting Insulin (pmol/l)†‡	99 ± 6	76 ± 6	0.01
Fasting glucose (mmol/l)†	5.61 ± 0.04	5.53 ± 0.05	0.27
Height (cm)†	161.2 ± 0.8	162.8 ± 0.9	0.21
Weight (kg)†	59.2 ± 1.4	54.9 ± 1.8	0.07
BMI (kg/m^2)†	22.6 ± 0.5	20.6 ± 0.6	0.01
Waist (cm)†	79.6 ± 1.1	74.2 ± 1.4	<0.01
WHR†	0.84 ± 0.01	0.81 ± 0.01	0.01
Triceps skinfold (mm)†	23.4 ± 1.0	20.1 ± 1.2	0.04
Subscapular skinfold (mm)†	14.0 ± 0.7	11.4 ± 0.9	0.04
Body fat (%)†	29.3 ± 1.1	25.7 ± 1.3	0.03
Total cholesterol (mmol/l)†	4.00 ± 0.08	3.80 ± 0.10	0.13
LDL (mmol/l)†	2.38 ± 0.07	2.16 ± 0.09	0.06
HDL (mg/dl)†	1.12 ± 0.02	1.17 ± 0.03	0.16
Triglycerides (mmol/l)†‡	0.98 ± 0.05	0.90 ± 0.06	0.46
Systolic blood pressure (mmHg)†	107.7 ± 0.9	107.7 ± 1.2	0.99
Diastolic blood pressure (mmHg)†	54.4 ± 1.3	55.7 ± 1.6	0.54

Data are means ± SE. *Number of IRS traits (waist circumference, systolic blood pressure, triglycerides, low HDL, glucose) above the sex- and age-specific 75th percentile in children; †adjusted for sex, race, age, and Tanner stage; ‡geometric mean; §a total of 256 children had at least one parent participate in the study. Parental status for IRS was classified as *present* if both parents were affected ($n = 13$ children), one parent was affected and the other parent was unaffected ($n = 49$), or one parent was affected and the status of the other parent was unknown ($n = 29$). Parental status for IRS was classified as *absent* if both parents were unaffected ($n = 60$). Parental status for IRS was *unclassifiable* if one parent was unaffected and the status of the other parent was unknown ($n = 105$, data not shown in table).

III (2), have significantly greater body fatness and insulin resistance as measured by the euglycemic-hyperinsulinemic clamp. Thus, parental IRS is a predictor of insulin resistance in childhood, despite the absence in children of differences in the conventional IRS criteria currently used for diagnosis in adults. By contrast, there were no differences in insulin resistance between children with or without an obese parent, despite significant differences in adiposity between these same children.

Studies of the development of IRS in childhood are of potential importance, not only because of the current high prevalence of IRS in adults (3), but also because of the steadily increasing prevalence of obesity (11), the high prevalence of impaired glucose tolerance in obese children and adolescents (12), and the increasing incidence of type 2 diabetes in children (13). Children of parents with IRS are at high risk of developing IRS themselves because of genetic and shared environmental factors (4–7). In addition, individuals with a parental or family history of individual traits, such as hypertension or diabetes, are also more likely to develop IRS (14,15) or insulin resistance (16). Although the prevalence of IRS as classified by contemporary adult definitions is low in children and young adults compared with middle-aged and older adults (3), the quantitative traits that comprise IRS have been found to cluster in both children (17) and adults. This suggests that initiation of the syndrome may occur relatively early in life. Indeed, a previous study found that patterns of clustering of fasting insulin, lipids, blood pressure, and BMI were similar in parents and their children aged 5–17 years (18), supporting a familial basis for the syndrome. The present study provides a critical additional piece of evidence by showing the association between parental IRS and childhood insulin resistance itself.

Individual components of IRS as well as various composite indexes of IRS traits have been found to track moderately well through childhood, adolescence, and early adulthood (19–22). However, it is possible that associations between parental IRS components, insulin resistance, and other components in children may be partially obscured during puberty because of the transient increase in insulin resistance that occurs as part of normal development. Intra-individual clustering of selected elements of IRS (homeostasis model assessment insulin resistance index, BMI, triglyceride-to-HDL ratio, and mean arterial pressure) in the Bogalusa Heart Study was stronger in the prepubertal years (5–10 years) or young adulthood (18–37 years) than in adolescence (11–17 years) (23). Previous studies in our cohort have shown that insulin resistance increased during puberty before decreasing again at Tanner stage 5, but there were no differences in the pattern of association between BMI and insulin resistance across the five Tanner stages (9). An alternative explanation for the finding that the associations between parents and children were only modest in strength may be the relatively young age of the children. Thus, it is expected that parent-child intra-individual clustering of components of IRS will strengthen as these children mature and enter early adulthood. This is supported by data from adult studies in which greater overall obesity, abdominal obesity, and fasting insulin have been found to be strong and independent predictors of the later development of IRS (24).

The finding that children with a parental history of IRS had greater body fatness raises the possibility that the association between parental IRS and insulin resistance may simply be due to greater adiposity in these children. Indeed, additional adjustment for measures of adiposity in the children partially attenuated the association between parental IRS and both M_{lbm} and fasting insulin in the children, suggesting that familial aggregation of adiposity may account for these associations to some degree. Nevertheless, the fact that parental IRS but not parental obesity was associated with measures of insulin resistance in the offspring suggests that there may be additional genetic or environmental factors contribut-

Table 4—*Demographic, anthropometric, and laboratory data in children of parents with and without obesity*

	Parental status for obesity§		
	Present	Absent	*P* value
n	108	62	
Age (years)	12.8 ± 0.1	12.9 ± 0.1	0.58
Sex (% women)	42	37	0.56
Race (% black)	18	3	<0.01
Three or more IRS traits >75th percentile (%)*	11	10	0.75
M_{lbm} (mg · kg^{-1} · min^{-1})†	12.9 ± 0.4	12.6 ± 0.6	0.73
Fasting insulin (pmol/l)†‡	87 ± 5	89 ± 7	0.82
Fasting glucose (mmol/l)†	5.60 ± 0.04	5.58 ± 0.05	0.68
Height (cm)†	160.9 ± 0.7	162.7 ± 1.0	0.14
Weight (kg)†	58.5 ± 1.3	55.2 ± 1.7	0.14
BMI (kg/m^2)†	22.4 ± 0.4	20.7 ± 0.6	0.02
Waist (cm)†	78.4 ± 1.0	75.1 ± 1.4	0.06
WHR†	0.83 ± 0.01	0.83 ± 0.01	0.71
Triceps skinfold (mm)†	23.2 ± 0.9	19.5 ± 1.3	0.02
Subscapular skinfold (mm)†	13.7 ± 0.7	11.7 ± 0.9	0.09
Body fat (%)†	29.1 ± 1.0	25.0 ± 1.3	0.01
Total cholesterol (mmol/l)†	3.95 ± 0.07	3.79 ± 0.10	0.20
LDL (mmol/l)†	2.34 ± 0.06	2.15 ± 0.09	0.08
HDL (mg/dl)†	1.15 ± 0.02	1.14 ± 0.03	0.69
Triglycerides (mmol/l)†‡	0.86 ± 0.04	0.93 ± 0.06	0.36
Systolic blood pressure (mmHg)†	107.5 ± 0.8	108.0 ± 1.1	0.74
Diastolic blood pressure (mmHg)†	55.4 ± 1.2	55.9 ± 1.6	0.81

Data are means ± SE unless otherwise indicated. *Number of IRS traits (waist circumference, systolic blood pressure, triglycerides, low HDL, glucose) above the sex- and age-specific 75th percentile in children; †adjusted for sex, race, age, and Tanner stage; ‡geometric mean; §a total of 256 children had at least one parent participate in the study. Parental status for obesity was classified as *present* if both parents were affected (BMI 30 kg/m^2; n = 24 children), one parent was affected and the other parent was unaffected (n = 39), or one parent was affected and the status of the other parent was unknown (n = 45). Parental status for obesity was classified as *absent* if both parents were unaffected (n = 62). Parental status for obesity was *unclassifiable* if one parent was unaffected and the status of the other parent was unknown (n = 86, data not shown in table).

ing to the early development of insulin resistance in these children that cannot be directly attributed to a general predisposition to obesity.

In the present study, adolescent children who had at least one parent with IRS were more insulin resistant and had greater adiposity than children with two unaffected parents. By contrast, other components of IRS (dyslipidemia, blood pressure, and fasting glucose) were not significantly different. Because obesity tracks into adulthood and predicts the development of other components of IRS, a substantial proportion of these children are likely to develop IRS themselves, particularly given recent secular trends in obesity among children and adults (11,25). This high-risk group of children may particularly benefit from interventions designed to establish healthy diet and exercise patterns that would carry forward into adulthood.

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