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The role of European genetic admixture in the etiology of the insulin resistance syndrome in children- Are the effects mediated by fat accumulation?

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Abstract

Objective—To evaluate the contribution of European genetic admixture (EUADM) to the insulin resistance syndrome (IRS) in a multi-ethnic sample of children aged 7–12 years and if body fat affects this relationship.

Study design—Anthropometric measurements and blood pressure were assessed in 243 children. After an overnight fast, an intravenous glucose tolerance test was conducted, and measures of fasting insulin/glucose, lipids, insulin sensitivity (S_I), and acute insulin response to glucose (AIRg) were obtained. The proportion of EUADM was determined by maximum likelihood estimation using 140 ancestry informative markers. Participants were stratified into tertiles according to the proportion of EUADM for analyses. Subjects were categorized as lean or obese using percent fat cut-points (25% in boys, 30% in girls).

Results—Among lean subjects (72%), the tertile representing the greatest proportion of EUADM was associated with higher S_I ($p < 0.001$) and glucose ($p < 0.05$) and lower insulin ($p < 0.05$), AIRg ($p < 0.001$), HDL-C ($p = 0.05$), and blood pressure ($p < 0.05$). However, among obese subjects, EUADM was associated with only S_I ($p < 0.05$).

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The authors declare no conflicts of interest.

Conclusion—Our results suggest that population differences in the IRS likely have a genetic component. However, the influences of genetic background may be masked by obesity.

Keywords

obesity; metabolism; physiology genetic contribution

The insulin resistance syndrome (IRS), characterized by elevated insulin (without a compensatory decrease in glucose), abdominal obesity, abnormal lipid profile, and high blood pressure, increases the risk of type 2 diabetes (T2D) and cardiovascular disease (CVD). In adults, African- and Hispanic Americans are disproportionately burdened by CVD and T2D relative to European Americans. However, European Americans tend to have greater prevalence of IRS than other groups, raising the possibility that IRS may affect disease progression differently across populations and that such progression could be initiated at early stages of the life course. The most recent national estimates have shown that European and Hispanic Americans children are more likely to meet the criteria for IRS than African American children with estimates of 10.2%, 10.1% and 6.9%, respectively (1). Although it has been shown that the IRS and its sequelae represent a distinct but overlapping set of metabolic aberrations across racial/ethnic groups, the underlying physiological reason for these discrepancies are not fully understood.

The degree of ancestral genetic heterogeneity among populations differs and this variation may explain racial/ethnic disparities in chronic disease burden. In the US, European, African, and Amerindian groups intermixed to produce populations with a heterogeneous ancestral genetic background representative of these three parental populations. The genetic admixture approach has been used to investigate putative genetic factors contributing to racial/ethnic differences in physiological and metabolic traits. It also controls for the well documented confounding effects of population stratification that often limit the understanding of population differences in physiological and metabolic outcomes. Therefore, the use of genetic admixture may identify genetic aspects predisposing individuals to components associated with IRS and the progression to chronic diseases such as CVD and T2D.

The genetic contributions to metabolic outcomes are partly dependent on and modulated by physiological and environmental variables; e.g. increased levels of adiposity influence gene expression. Indeed, obese children and adolescents are at much greater risk of the metabolic perturbations associated with IRS. It is estimated that IRS is present in approximately one third to one half of obese children (2). Accounting for the interplay between genetic background and fat accumulation may provide insight into population differences in the IRS. The objective of this study was to evaluate the independent and interactive contributions of genetic admixture and fat accumulation to components of the IRS in a multi-ethnic sample of healthy children aged 7–12 years.

Methods

Participants were 243 (53% male) children aged 7–12 years recruited as a part of a cross-sectional study that aimed to identify racial and ethnic differences in insulin-related outcomes among healthy children. Children were categorized according to parental self-report as African American (AA; n=85), European American (EA; n=108), or Hispanic American (HA; n=52). The children were pubertal stage ≤ 3 as assessed by a pediatrician according to the criteria of Marshall and Tanner (3). Subjects were ineligible if they were previously diagnosed with any major illnesses since birth or taking any medications known to affect body composition, metabolism, cardiac function, etc. In addition, girls who had

begun menstruating were excluded. Before participating in the study. The children and parents provided informed assent and consent, respectively. The protocol was approved by the Institutional Review Board for human subjects at the University of Alabama at Birmingham (UAB). All measurements were performed at the General Clinical Research Center (GCRC) and the Department of Nutrition Sciences at UAB between 2004 and 2008.

Participants completed two testing sessions. In the first session anthropometric measurements, pubertal status, and body composition were assessed and a dietary recall was obtained. In the second session (an overnight visit), a second 24-hour dietary recall was obtained. Participants were admitted to the GCRC in the late afternoon for an overnight visit. All participants were given the same meal and snack foods. After 2000h, only water and/or non-caloric decaffeinated beverages were permitted until after the morning testing. Upon completion of the overnight fast, fasting blood samples were obtained for markers of glucose/insulin homeostasis and DNA genotyping analysis and an intravenous glucose tolerance test was performed.

The same registered dietitian obtained anthropometric measurements on all children. Participants were weighed (Scale-tronix 6702W; Scale-tronix, Carol Stream, IL) to the nearest 0.1 kg in minimal clothing without shoes. Height was recorded without shoes using a digital stadiometer (Heightronic 235; Measurement Concepts, Snoqualmie, WA). BMI percentile was calculated using CDC growth charts (<http://apps.nccd.cdc.gov/dnpabmi/>). Waist circumference measures were obtained using a flexible tape measure (Gulick II; Country Technology, Inc., Gays Mills, WI) and were recorded to the nearest 0.1 cm.

Body composition was measured by dual-energy X-ray absorptiometry (DXA) using a GE Lunar Prodigy densitometer (GE LUNAR Radiation Corp., Madison, WI). Participants were scanned in light clothing, while lying flat on their backs with arms at their sides.

Following the overnight fast, a topical anesthetic (Emla cream, AstraZeneca, Wilmington, DE) was applied to the antecubital space of both arms, and flexible intravenous catheters were placed in both arms. Subsequently, an intravenous glucose tolerance test (IVGTT) was performed as previously described (4). The acute insulin response to glucose (AIRg), an approximation of first phase insulin secretion, was calculated as the incremental area under the curve for insulin during the first 10 minutes after glucose injection using trapezoidal methodology (5). Values for fasting insulin were obtained from the average of the two baseline values. Glucose and insulin values were entered into the MINMOD computer program for determination of insulin sensitivity (S_i) as described elsewhere (6). The disposition index (DI) was calculated as the product of S_i and AIRg.

Glucose and lipids were analyzed using a SIRRUS analyzer. Glucose was assayed by the glucose oxidase method (interassay CV 2.56%). Triglycerides were assessed with the glycerylphosphate (GPO) method. HDL-cholesterol (HDL) was analyzed using a two-reagent system involving stabilization of LDL, VLDL, and chylomicrons using cyclodextrin and dextran sulfate, and subsequent enzymatic-colorimetric detection of HDL.

Evening and morning blood pressure (Dinamap Pro 200 automated pediatric cuff, GE Medical Systems) was measured during the overnight inpatient stay. On each occasion, blood pressure was taken twice, 5 minutes apart, after 10 minutes of seated rest with legs uncrossed and feet flat on the floor. The evening measurements were taken at approximately 1800 h on the evening of the overnight stay. The morning measurements were taken shortly after awakening at approximately 0700 h of the overnight stay. The four evening and morning measurements were averaged to yield the final systolic blood pressure value.

Genotyping of the ancestry informative markers (AIMs) for the measurement of genetic admixture was performed at Prevention Genetics (www.preventiongenetics.com) using the Chemicon Amplifluor SNPs Genotyping System (Genome Research 11:163–169, 2001) coupled with ArrayTape technology (www.global-array.com) as described elsewhere (7). Briefly, a panel of 140 ancestry informative markers was used to estimate the genetic admixture proportion of each subject. The information from the AIMs was translated into estimates of African (AFADM), European admixture (EUADM), and Native American admixture (AMINADM) for each subject using maximum likelihood estimation based on the maximum likelihood algorithm described by Hanis et al. (8). The maximum likelihood method estimates the proportion of genetic ancestry for an individual, using a range of proportions from 0 to 1 and identifies the most probable value of admixture based on the observed genotypes.

Diet composition was determined by two 24-hour diet recalls using the multiple pass method with cup and bowl sizes provided to help gauge portion sizes. Recalls were always performed in person in the presence of at least one parent. One recall was performed at each visit. A trained dietitian coded and analyzed dietary intake data using Nutrition Data System for Research software version 2006, (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) a dietary analysis program designed for the collection and analyses of 24-hour dietary recalls. The average of the individual daily intakes for each nutrient was used in subsequent analyses.

The MTI Actigraph accelerometer (Actigraph GT1M – Standard Model 198-0100-02, ActiGraph LLC, Pensacola, FL) was used to measure physical activity levels and patterns for 7 days prior to participant's inpatient visit at the GCRC. Epoch length was set at one minute and data expressed as counts per minute (counts min⁻¹). Children were instructed to wear the monitor on an elastic belt at the waist, removing only for sleeping, bathing and swimming. Actigraph monitors have previously demonstrated a high degree of inter-instrument reliability. Daily and total counts per minute were summed and averaged as minutes spent in light, moderate, hard or very hard activity, as determined by the software accompanying the device. Sedentary time was also computed.

Scientific evaluation of the uniqueness of population-based differences is challenging, in particular because in many contexts, delineation between biology and environment in the variable "race/ethnicity" is not clearly defined. Further, race/ethnicity changes according to historical periods, social structure, and as individuals become more admixed. In our analysis, statistical models include race/ethnicity (dummy coded) as a control variable for social and cultural characteristics.

Direct observation for the assessment of pubertal stage by a pediatrician, the 'gold standard' for differentiating among the 5 stages of maturity (9;10), was utilized. The staging based on the criteria of Marshall and Tanner (11;12) is according to both breast and pubic hair development in girls and genitalia and pubic hair development in boys. One composite number is assigned for Tanner staging, representing the higher of the two values defined by breast/genitalia and pubic hair (13).

Socioeconomic status (SES) was measured with the Hollingshead 4-factor index of social class (14), which combines the educational attainment and occupational prestige for the number of working parents in the child's family. Scores ranged from 8 to 66, with the higher scores indicating higher theoretical social status.

EUADM was analyzed to determine the distribution and subsequently divided into tertiles based on the distribution of admixture in the sample. EUADM was selected, because in this sample, relative to African or Amerindian admixture, EUADM displays the greatest

variation. Differences in descriptive statistics by tertile of admixture were examined using ANOVA with Duncan's post-hoc analysis. Two multiple linear regression models were analyzed. The first model tested contributions of European admixture in the overall sample. The models were adjusted for total fat mass, height, age, pubertal stage, sex, ethnicity (dummy coded), and SES.

The second model evaluated the contribution of EUADM to components of the IRS stratified by cut-points for percentage fat. Although specific cut-off points do not exist, it has been suggested that the percent body fat in girls not to exceed 30% and that of boys not to exceed 25% (15). We used these suggestions to divide the groups into high and low body fat percent groups (i.e. coded as 0 for lean ($\leq 25\%$ or 30% fat in boys and girls, respectively) and 1 for obese ($>25\%$ or 30% fat in boys and girls, respectively). Models stratified by percent fat cut-points were adjusted for height, age, sex, pubertal stage, ethnicity (dummy coded) and SES.

To conform to the assumptions of linear regression, all statistical models were evaluated for residual normality and logarithmic transformations were performed when appropriate. All data were analyzed using SAS 9.1 software (SAS Institute, Cary, NC).

Results

European admixture estimates for the entire sample ranged from 0 to 1.0, with European admixture 0.96, 0.14, and 0.35 for EA (n=108), AA (n=85), HA (n=52), respectively. Figure 1 (available at www.jpeds.com) illustrates the relationship between self-reported race/ethnicity and European admixture. Based on the sample distribution for European admixture, tertiles 1 (T1; n=86), 2 (T2; n=76), and 3 (T3; n=82) were defined as 1.0 to 0.941, 0.94 to 0.21, and 0.2 to 0.0, respectively. Participant characteristics (n=243; 53% male) are presented in Table I. Participants in T1 reported a greater SES than those in T2 and T3. Participants in T2 had a greater total fat mass and percent body fat than those in T1 and T3. Participants in T3 had greater pubertal maturation than those in T1. Neither total caloric intake, macronutrient intake, nor objectively measured total daily physical activity differed by tertile (data not shown).

As indicated in Table II, there were also differences in cardiometabolic outcomes across tertiles. Participants in T1 had a greater S_I and lower fasting insulin than those in T2 and T3. Individuals in T2 had higher triglycerides than those in T3. Subjects in T3 had higher AIRg, HDL, DI, and lower glucose than those in T1 and T2. Diet and physical activity did not differ by tertile and were not included in subsequent multiple linear regression analyses.

Figure 2 illustrates group-wise comparisons when stratified according by percent fat cut-point. Among lean children (n=178), individuals in T1 (n=66) had higher S_I , glucose and triglycerides and lower AIRg fasting insulin, blood pressure and HDL than those in T3 (n=65). However among obese individuals, children in T2 (n=29) had lower blood pressure than those in T1 (n=21) and T3 (n=17), but otherwise, there were no differences in IRS risk factors.

In multiple regression analysis, EUADM was associated with all IRS risk factors (except HDL) ($p<0.05$) after adjusting for age, sex, pubertal stage, total fat mass, ethnicity and SES as covariates, such that European admixture was positively associated with S_I , glucose and waist circumference and inversely associated with AIRg, DI, fasting insulin, TG, and blood pressure. When stratified by percent fat, European admixture was positively associated with S_I ($p<0.001$) and fasting glucose ($p<0.05$), and inversely associated with AIRg ($p<0.001$), DI ($p<0.01$), fasting insulin ($p<0.05$), HDL ($p=0.05$), and systolic blood pressure ($p<0.05$). However, among obese participants, European admixture was only associated with S_I

($p < 0.05$). Race/ethnicity was not significantly associated with any IRS risk factors and was subsequently removed from final models.

Discussion

The pathophysiologic mechanisms related to the IRS are likely initiated in childhood. However, differences in the genetic architecture of individuals may differentially influence pathways associated with these mechanisms and contribute to disparate disease progression among individuals. Our results demonstrate that greater European admixture (T1) was associated with better glucose homeostasis but a poorer lipid profile. The fact that these relationships were only identified among lean individuals suggests that excessive fat accumulation may mask the genetic contribution to risk factors associated with the IRS.

The observation of a differential association dependent of fat categorization is not surprising. Although fat accumulation is consistently associated with impaired glucose metabolism (16–20), racial/ethnic differences in glucose homeostasis documented in lean individuals have not consistently been observed in samples of obese individuals (16;17;19;21). Our findings support the notion that fat accumulation could represent an effect modification underlying population differences on IRS outcomes. It is possible that the detrimental effects of fat accumulation on metabolism may be at least partially dependent on genetic background and/or that the cut-point (e.g. 30% body fat) for fat accumulation does not equally represent health status across populations. For example, excessive fat accumulation has also been shown to worsen the progression to T2D (22); however, our previous data in adult women suggests that ancestral genetic background may differentially impact the relationship between fat accumulation ‘thresholds’ and health such that a greater body fat is more tolerable in some individuals (23–25). The extent to which the interaction(s) between fat accumulation genetic background, and inherent metabolic phenotypes in childhood reflects racial/ethnic differences in chronic disease progression warrants further study.

Insulin homeostasis and excess adiposity are also intricately involved in lipid homeostasis. Moreover, heritability estimates are high for all lipid traits and population differences in lipid profile have been consistently documented (31–33). Our findings among children, as well as studies in adults have shown a negative correlation between European admixture and HDL and a positive association between triglycerides and European admixture (31;33). These findings imply that among individuals with a lower degree of European admixture, triglycerides are cleared from the circulation even in the presence of impaired insulin homeostasis, thereby maintaining a normal lipid profile. Although European admixture was chosen due to the greatest variation among the sample, upon further analysis into etiology of the observed relationships, models were run with African and Amerindian admixture tertiles rather than European. Among lean individuals only, there was an inverse relationship between fasting glucose and triglyceride concentration and individuals with greater African admixture (T1); whereas no relationship was observed using Amerindian tertiles (data not shown). It is possible that in this sample, the variation of Amerindian admixture may not have been wide enough for a relationship to be observed. Future investigations are necessary to fully understand the mechanisms through which genes (and gene variants), body composition, and insulin dynamics influence the lipid profile and how the associations differ according to ancestral genetic background.

The racial/ethnic differences in blood pressure attributable to genetic background, though complicated, are also of considerable interest. It is known that African Americans have higher rates of hypertension than their European and Hispanic American counterparts, even in childhood. We report an inverse relationship between European admixture and blood

pressure, such that lower European admixture (T3) is associated with higher blood pressure in lean individuals. However, the relationship becomes curvilinear in the obese participants such that high and low European admixture is associated with increased blood pressure; yet, individuals in T2 have lower blood pressure. Our results are in concordance with Tang et al (34) who reported no relationship between admixture variables and blood pressure among Mexican Americans when analyzed by the whole group or when stratified by normo- or hypertensive groups. Interestingly, using African admixture we observed that African admixture was positive associated with systolic blood pressure, regardless of fat accumulation; whereas there was no relationship using tertiles of Amerindian admixture (data not shown). It is evident that a relationship exists between blood pressure and genetic background; however, population differences in blood pressure may not operate the same throughout the distribution of adiposity, suggesting the need for further research to elucidate potential mechanisms.

The vast majority of the literature to determine the etiology of racial/ethnic differences in health disparities relies on an individual's self-assignment into a racial/ethnic group. One of the concerns of these studies is the confounding effect due to racial categorization and its contribution to the etiology of a disease. By using genetic admixture, we characterized the genetic factors underlying racial classification and their contribution, if any, to the genetic admixture-phenotype associations. To the best of our knowledge, this was the first study to investigate the independent role of genetic admixture and adiposity on the insulin resistance syndrome in the pediatric population. There are, however, some limitations. A cross-sectional study prevents inference of long-term relationships over the pubertal transition. Longitudinal data will be required to determine the long-term contribution of individual adiposity and genetic background on later metabolic health. Further, the relatively small sample included only participants from a discrete geographic area, limiting the generalizability of findings to other regions of the U.S. The analysis conducted according to tertiles of European admixture is somewhat limiting particularly considering, the individuals in T2 were primarily of South and Central-American Indian heritage and individuals in T3 had a greater proportion of African heritage. The differential makeup between these groups may serve as an explanation for some of the differences in insulin and lipid homeostasis as well as blood pressure. Future studies would benefit by including individuals from other geographic regions, thereby, heterogeneity in genetic admixture component.

Disentangling the mechanisms underlying population based variation in IRS is proving to be exceedingly difficult; however, advances in the identification of genetic, metabolic and environmental contributors provide some insight into understanding the etiology of IRS and population disparities, allowing for more accurate risk prediction, and informed intervention strategies. Future investigations are necessary to fully understand the mechanisms through which the genetic architecture, body composition and risk factors for the insulin resistance syndrome impact future disease risks and how the associations differ according to ancestral genetic background.

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Figure 1. Relationship between self-identified race/ethnicity and European Admixture. A) European American (1); b) African American (2); c) Hispanic American (3). X-axis represents maximum likelihood estimate of European genetic admixture 0 to 100.

Figure 2.

Risk factors associated with the insulin resistance syndrome by tertile European genetic admixture. Gray bars represent lean children and black bars represent obese children. Lean (T1, n=66; T2, n=47; T3, n=65); Obese (T1, n=21; T2, n=29; T3, n=17).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 1

Descriptive Statistics by Tertile European Admixture (mean± SE unless otherwise indicated)

	Total (n=243)	Tertile 1 (n=86)	Tertile 2 (n=75)	Tertile 3 (n=82)
Age (yrs)	9.6±0.1	9.7±0.2	9.6±0.2	9.7±0.2
SR EA Ethnic (%)	35.5	80.6	19.4	0
Sex (% male)	53	54	40	59
Height (cm)	139.5±0.6	140.4±1.2	140.6±1.2	140.7±1.1
Weight (kg)	36.6±0.5	36.0±1.0	38.0±1.1	36.5±0.9
Tanner	1.4±0.1	1.3±0.1^a	1.5±0.1^{ab}	1.7±0.1^a
BMI percentile	66.3±1.5	61.1±3.0^a	69.5±2.9^b	63.9±2.9^a
Waist	64.3±0.5	63.6±1.0	66.0±1.1	63.1±0.8
Total Body Fat (kg)	8.9±0.3	8.5±0.6^a	10.3±0.7^b	7.6±0.6^a
Percent Body Fat	23.4±0.5	22.6±0.9	26.4±1.0	20.4±1.1
Lean Body Mass (kg)	25.6±0.3	25.6±0.5	25.6±0.6	26.6±0.6
SES	38.7±0.8	48.8±1.1^a	34.3±1.7^b	35.5±1.2^b
EURADM	0.54±0.02	0.98±0.0^a	0.52±0.03^b	0.12±0.01^c
AFADM	0.32±0.02	0.01±0.0^a	0.19±0.03^b	0.74±0.03^c
AMINADM	14.0±0.02	0.01±0.0^a	0.29±0.03^b	0.14±0.03^c
Total Caloric Intake	1886.5±26.6	1886.9±44.4	1847.3±47.9	1933.8±60.3
Daily Physical Activity	286.4±3.3	287.8±5.7	279.1±6.5	291.9±7.6

^{a-c}Superscripts indicate significant differences between tertiles, P<0.05

SR EA= Self-Reported European American; SES= socioeconomic status; EURADM= European Admixture

Table 2

Association of cardiometabolic risk factors by tertile of European genetic admixture.

	Total (n=243)	Tertile 1 (n=86)	Tertile 2 (n=75)	Tertile 3 (n=82)
SI	5.8±0.2	6.8+0.3^a	5.3+0.3^b	4.6+0.3^b
AIKg	947.9±46.3	607.4+46.8^a	850.3+73.6^a	1256.6+100.0^b
DI	4148.0±150.0	3688.1+252.6^a	3660.8+229.7^a	4537.7+277.4^b
Fasting glucose	97.8±0.4	97.5+0.7^a	98.2+0.7^a	95.4+0.7^b
Fasting Insulin	12.7±0.4	11.0+0.5^a	13.1+0.7^b	13.8+0.8^b
Triglycerides	66.5±2.1	68.3+3.6^{ab}	70.9+4.3^a	58.7+3.4^b
HDL	50.2±0.7	47.5+1.2^a	48.1+1.5^a	53.7+3.5^b
Systolic BP	103.3±0.6	102.5+1.2	102.3+1.1	105.3+1.2

^{a-c} superscript indicate significant differences between tertiles, p<0.05

SI= insulin sensitivity index; AIKg= acute insulin response to glucose; DI = disposition index; HDL= high density lipoprotein cholesterol

Table 3

Multiple linear regression analysis* identifying the association (or lack) between European admixture (EUADM) and cardiometabolic outcomes lean and obese children.

	Overall (n=245)		Lean (n=178)		Obese (n=67)	
	mean	p-value	mean	p-value	mean	p-value
SI	5.9+2.3	<0.001	6.2+2.4	<0.001	4.1+1.8	0.04
AIRg	804.7+414	<0.001	731.0+385	<0.001	997.2	0.09
DI	3816+1946	<0.01	3920+1914	<0.01	3549+1994	0.81
Fasting Glucose	97.4+5.5	<0.01	96.8+5.5	<0.05	98.8+6.0	0.21
Fasting Insulin	12.2+3.9	<0.01	10.8+3.4	<0.05	16.1+4.7	0.14
HDL	49.0+10.3	0.06	50.8+10.5	0.05	44.4+9.8	0.63
Triglycerides	63.0+26.0	<0.01	59.7+25.7	<0.01	72.0+27.5	0.94
Waist	63.5+6.7	<0.05	60.7+4.2	0.14	71.8+6.6	0.38
Systolic BP	103.4+10.0	<0.05	102.3+9.9	<0.05	105.9+10.5	0.76

* All models adjusted for age, sex, Tanner stage, total body fat, and Socioeconomic Status (SES). Acute Insulin Response to Glucose (AIRg) models also adjusted for Insulin Sensitivity (SI); High Density Lipoprotein (HDL) models also adjusted for Triglyceride (TG).