Age-Related Patterns of the Clustering of Cardiovascular Risk Variables of Syndrome X From Childhood to Young Adulthood in a Population Made up of Black and White Subjects

The Bogalusa Heart Study

Wei Chen, Weihang Bao, Shahana Begum, Abdalla Elkasabany, Sathanur R. Srinivasan, and Gerald S. Berenson

The age-related patterns of clustering of cardiovascular risk variables of Syndrome X from childhood to adulthood were examined in a community-based sample of black and white children (aged 5–10 years, *n* = 2,389), adolescents (aged 11–17 years, *n* = 3,371), and young adults (aged 18–37 years, *n* = 2,115). In the analysis of clustering, insulin resistance index, BMI, triglycerides/HDL cholesterol ratio, and mean arterial pressure were used either as categorical variables (age-, race- and sex-specific values >75th percentiles) to calculate risk ratios (observed frequency/expected frequency) or as continuous variables (normal scores based on ranks) to compute intraclass correlations. In the total sample, the risk ratio for clustering of adverse levels of all 4 variables was 9.8 for whites (*P* < 0.01) versus 7.4 for blacks (*P* < 0.01); the intraclass correlation was 0.33 for whites (*P* < 0.001) versus 0.26 for blacks (*P* < 0.001). Both the risk ratio and intraclass correlation were significantly higher in whites than in blacks in the total sample. The intraclass correlations of the 4 variables were significant (*P* < 0.001) in all race and age-groups, and they were higher during preadolescence and adulthood than during adolescence. Furthermore, unlike risk ratios, intraclass correlations showed a continuous increase with age during adulthood. When BMI was adjusted, the intraclass correlations involving the other 3 variables were reduced by ~50%, and the age-related pattern was no longer evident. These results suggest that the degree of clustering of risk variables of Syndrome X varies with age from childhood to adulthood and is likely influenced by the age-related changes in obesity and the attendant insulin resistance. *Diabetes* 49:1042–1048, 2000

From the Tulane Center for Cardiovascular Health, School of Public Health and Tropical Medicine, Tulane University Medical Center, New Orleans, Louisiana.

Address correspondence and reprint requests to Gerald S. Berenson, MD, Tulane Center for Cardiovascular Health, 1501 Canal St., 14th Fl., New Orleans, LA 70112. E-mail: berenson@mailhost.tcs.tulane.edu.

Received for publication 11 May 1999 and accepted in revised form 6 March 2000.

CDC, Centers for Disease Control and Prevention; ICC, intraclass correlation coefficient; IRI, insulin resistance index; O/E, observed to expected numbers; TG, triglyceride.

Dyslipidemia, hypertension, hyperinsulinemia, and obesity have been recognized as potent risk factors for coronary heart disease in adults (1–3). These risk factors have also been found to be associated with early atherosclerotic lesions in youth (4,5). Further, the extent of coronary atherosclerosis in youth increased markedly with the number of multiple risk factors (6). Coexistence of the above cardiovascular risk variables often occurs in both children (7–10) and adults (7,8,11–13). Such a condition has been termed Syndrome X (14), deadly quartet (15), insulin resistance syndrome (11,16), and multiple metabolic syndrome (17).

Although the clustering of cardiovascular risk factors related to Syndrome X has been found to occur at a very early age (7–10) and persist from childhood into adulthood (8), very little is known about the age-related trend in clustering of risk variables during this period. The Bogalusa Heart Study, a long-term community-based investigation of cardiovascular disease risk factors in black and white children and young adults (18–20), provided a unique opportunity to examine the age-related trend in clustering of risk variables during this period. The objective of the present study was to determine the age-related patterns in the magnitude of clustering of cardiovascular risk variables of Syndrome X during the periods of childhood and young adulthood.

RESEARCH DESIGN AND METHODS

Study subjects. The Bogalusa Heart Study is a long-term epidemiological study of cardiovascular risk factors in children and young adults in a biracial community (65% white, 35% black) of Bogalusa, Louisiana. A total of 16,060 observations were made of children, adolescents, and young adults, aged 5–37 years, who participated in 1 or more of the 5 cross-sectional surveys conducted between 1981 and 1996. The sample size of each cross-sectional study ranged from 2,571 to 3,430. For individuals with multiple examinations, the most recent measurement was chosen for the current analysis. After removing 1,440 individuals with nonfasting blood samples, with hypertension, taking antihypertensive medications, and missing values for study variables, the final sample size for the current analyses was 7,873 (64.2% white, 35.8% black). The sample size of each race/age-group was adequate for the current analysis.

General examinations. All examinations followed the same protocols, and procedures for the general examination were described elsewhere (18). Subjects were instructed to fast for 12–14 h before the screening, and compliance with fasting was determined by interview on the morning of examination. Ante-

cubital venous blood was collected to obtain serum and plasma. Height and weight were measured twice to ±0.1 cm and to ±0.1 kg, respectively. As a measure of obesity, BMI (weight in kilograms divided by the square of the height in meters) was used. Blood pressure levels were measured in replicate on the right arm of subjects in a relaxed, sitting position by 2 randomly assigned nurses. The fourth Korotkoff phase was used to determine diastolic blood pressure. Means of replicate readings were used in all analyses. Mean arterial pressure (diastolic blood pressure + one-third pulse pressure) was used as a measure of adverse hemodynamic status.

Serum lipids, insulin, and glucose. From 1982 to 1986, total cholesterol and triglycerides (TGs) were measured using chemical procedures in a Technicon Auto Analyzer II (Technicon Instruments, Tarrytown, NY) according to the Laboratory Manual of the Lipid Research Clinics Program (21). Since 1986, these variables have been determined by enzymatic procedures (22,23) on the Abbott VP instrument (Abbott Laboratories, North Chicago). Serum lipoprotein cholesterols were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (24). Both chemical and enzymatic procedures met the performance requirements of the lipid standardization program of the Centers for Disease Control and Prevention (CDC) (Atlanta, GA). The laboratory has been monitored for precision and accuracy of lipid measurements by the agency's surveillance program since 1973. Measurements on CDC-assigned quality control samples showed no consistent bias over time within or between surveys. Intraclass correlation coefficients (ICCs) (a measure of reproducibility of the entire process from blood collection to data processing) between the blind duplicate values ranged from 0.97 to 0.99 for TG and from 0.92 to 0.98 for HDL cholesterol. The ratio of TG to HDL cholesterol was used as a measure of dyslipidemia because the combination of high TG and low HDL cholesterol levels characterizes the dyslipidemia in Syndrome X (14). Furthermore, an elevated ratio of TG to HDL cholesterol has been associated with the presence of atherogenic small dense LDL particles (25).

A commercial radioimmunoassay kit (Padebas Pharmacia, Piscataway, NJ) was used for measuring plasma immunoreactive insulin. This insulin assay has 41% cross-reactivity with proinsulin, which is disproportionately low in nondiabetics, and <0.2% cross-reactivity with C-peptide. The detection limit of insulin level was 2.0 μU/ml. Plasma glucose was measured by an enzymatic method using the Beckman Instant Glucose Analyzer (Beckman Instruments, Palo Alto, CA). ICCs between the blind duplicate values ranged from 0.94 to 0.98 for insulin and 0.86 to 0.98 for glucose. Insulin resistance index (IRI) was calculated according to the homeostasis model assessment formula: IRI = fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5. This model is considered useful to assess insulin resistance in epidemiological studies (26).

Statistical analysis. All data analyses were performed using Statistical Analysis System (SAS) (27). In the analyses, IRI, BMI, TG/HDL cholesterol ratio, and mean arterial pressure were used as cardiovascular risk variables related to Syndrome X. Because data collection spanned over 15 years, adjustment was made for year of measurement of risk variables using Z-transformation [(original – mean)/SD] in each year before performing all the subsequent analyses.

The risk ratio of observed number to expected number (O/E) was applied to estimate the clustering of adverse levels of cardiovascular risk variables. Because the acceptable cutoff points for IRI, TG/HDL cholesterol ratio, and mean arterial pressure are not available, disorders were defined as values above the 75th percentiles (specific for race, sex, and age). The expected prevalence was calculated by multiplying together all 4 individual prevalence rates of each disorder, which were expected to be 25% each. Significance tests for O/E ratios were performed using the generalized 1-sample binomial test when $E \geq 5$, and the significance of O/E ratios was assessed based on the Poisson distribution when $E < 5$ (28).

Intraclass correlation based on ranks was, for the first time, introduced in the present study as another statistical approach to evaluate the degree of clustering of 2 or more continuous risk variables. Intraclass correlation requires homogeneous measurements on study subjects. Although measurements on each individual were already transformed into adjusted *Z*-scores for the study year, effects of race, sex, and age on the *Z*-scores still existed. For that reason, race-, sex-, and age-specific ranking was performed on each of the risk variable *Z*-scores to obtain the relative ranking of each variable. The SAS RANK procedure choosing the option NORMAL was used to rank the continuous risk variable *Z*-scores to obtain normal scores (similar to *Z*-scores). The resulting normally distributed variables were used in 1-way analysis of variance, and then the ICC was calculated by the expression below (29,30).

$$ICC = (BMS - WMS)/[BMS + (k - 1)WMS]$$

where k is the number of risk variables measured by ranks in study subjects, BMS is between-subject mean square, and WMS is within-subject mean square. The test that ICC is different from 0 is provided by calculating F = BMS/WMS on $(n - 1)$ and $n(k - 1)$ df, where n is total sample size. Black–white difference in ICC was tested for significance by comparing the 95% CIs of ICC calculated using the formulas previously reported (29). The difference was considered significant at the significance level of 5% if the 2 CIs were not overlapped. Analysis of covariance was conducted by race and age-group to adjust for the effect of BMI on ICC.

RESULTS

Levels of risk variables of Syndrome X. Table 1 shows the levels of risk variables of Syndrome X by race, sex, and age-group. IRI was significantly higher in females than in males

TABLE 1
Levels of risk variables related to Syndrome X by race, sex, and age-group

	White		Black		*P*	
Age-group	Males	Females	Males	Females	Race	Sex
Children						
n	767	741	430	449	—	—
IRI	1.5 ± 0.9	1.9 ± 1.3	1.7 ± 1.3	2.0 ± 1.3	<0.05*	<0.01
BMI	17.5 ± 3.4	17.7 ± 3.6	17.7 ± 3.7	17.6 ± 3.6	NS	NS
TG/HDL cholesterol	1.4 ± 1.0	1.6 ± 1.1	1.0 ± 0.5	1.2 ± 0.7	<0.01	<0.01
Mean arterial pressure	70.6 ± 7.7	71.2 ± 8.0	70.5 ± 7.7	70.1 ± 8.5	NS	NS
Adolescents						
n	1,124	999	620	628		
IRI	2.3 ± 1.7	2.7 ± 1.8	2.3 ± 1.8	3.0 ± 2.6	<0.01†	<0.01
BMI	21.2 ± 4.4	21.6 ± 4.8	21.5 ± 4.5	22.2 ± 5.1	NS	<0.01‡
TG/HDL cholesterol	1.7 ± 1.2	1.8 ± 1.4	1.2 ± 1.0	1.3 ± 0.7	<0.01	NS
Mean arterial pressure	78.8 ± 7.5	79.5 ± 7.1	79.4 ± 7.6	80.3 ± 7.4	NS	<0.01
Adults						
n	601	821	300	393		
IRI	2.4 ± 2.1	2.1 ± 1.6	2.4 ± 2.1	2.8 ± 2.4	<0.01†	<0.05
BMI	26.6 ± 5.2	25.0 ± 6.1	25.7 ± 6.0	28.1 ± 7.7	<0.01†	<0.01
TG/HDL cholesterol	3.1 ± 2.8	2.2 ± 1.8	1.9 ± 2.5	1.4 ± 0.8	<0.01	<0.01
Mean arterial pressure	87.4 ± 7.7	82.5 ± 7.4	87.2 ± 8.6	84.3 ± 8.2	<0.01	<0.01

Data are *n* or means ± SD. *P* values are for race–sex differences (adjusted for age). *Males only; †females only; ‡blacks only.

for all races and age-groups, except for white adults, in whom the values were significantly higher in males than in females. Significant race difference (blacks > whites) in IRI was noted only in male children, female adolescents, and female adults. BMI was higher in female adolescents of both races and black female adults and lower in white female adults. Mean arterial pressure was higher in female adolescents and lower in female adults, irrespective of race. BMI and mean arterial pressure showed significant race differences (blacks > whites) only in female adults. The ratio of TG/HDL cholesterol was consistently higher in whites than in blacks, irrespective of age-group or sex, and it was higher in female children and male adults, irrespective of race.

Age-related patterns of clustering of risk variables

Risk ratio. The ratios of observed frequency to expected frequency (risk ratios) were used to assess the degree of clustering of adverse levels of 4 risk variables by race and age-group (Table 2). Risk ratios were significantly different from 1 for all races and age-groups ($P < 0.01$), with whites showing higher values than blacks in 5 of 7 age-groups. Risk ratios were higher in prepubertal ages spanning 5–10 years and in certain young adult age-groups than in pubertal years (ages 11–17 years), regardless of race. The overall risk ratio for whites was significantly higher than that for blacks (9.8 vs. 7.4, $P < 0.05$) in the total sample.

Intraclass correlation. Figure 1 shows ICCs of 2 risk variables by race and age-group. Most of the ICCs were significantly different from 0 ($P < 0.05$–0.001). Among these combinations, the correlations between IRI and BMI (Fig. 1*A*) were the strongest and ranged from 0.28 to 0.67. In contrast, the correlations between TG/HDL cholesterol ratio and mean arterial pressure were the lowest (Fig. 1*B*). Further, the correlations of either IRI or BMI with TG/HDL cholesterol ratio (Fig. 1*C* and *E*) were generally higher than those with mean arterial pressure (Fig. 1*D* and *F*). Although the correlations were generally higher in whites than in blacks, their 95% CIs overlapped in most cases (Fig. 1*A* and 1*B*).

Four sets of combinations were generated for 3-variable clustering (Fig. 2). The intraclass correlations were all significantly greater than 0 ($P < 0.001$). Similar to the risk ratios, the intraclass correlations were higher during preadolescence and adulthood than during adolescence. The age-related patterns were very similar in all cases and closely resembled the pattern noted for IRI–BMI correlations shown in Fig. 1*A*. The magnitudes of correlations that included both IRI and BMI (Fig. 2*A* and *B*) were relatively higher than those that included only IRI or BMI (Fig. 2*C* and *D*).

The ICCs for the 4-variable combination, shown in Fig. 3, were all significantly greater than 0 ($P < 0.001$), with whites showing consistently higher values than blacks in all age-groups. However, only in the 14- to 17-year-old age-group was there no overlap in the 95% CIs. When all the age-groups were combined, whites showed higher ICCs (0.33 vs. 0.26) than blacks with no overlap in the 95% CIs. The age-related patterns of intraclass correlations for the 4-variable combination were very similar to those of the 3-variable combinations shown in Fig. 2 and the IRI–BMI correlations shown in Fig. 1*A*, regardless of race.

The intraclass correlations of IRI, TG/HDL cholesterol ratio, and mean arterial pressure adjusted for BMI are shown in Fig. 4. The intraclass correlations of these 3 variables shown in Fig. 2*C* were not adjusted for BMI. As can be seen, the adjustment for BMI resulted in ~50% reduction in the intraclass correlations, and the age-related pattern was no longer evident.

DISCUSSION

In the present study, both risk ratios and intraclass correlations were used to assess the age-related patterns of the clustering of cardiovascular risk variables of Syndrome X. The risk ratio is easy to calculate and commonly used to estimate the clustering of risk factors. However, the risk ratio has limitations and is influenced by the diagnostic or percentile cutoff values chosen to define the risk variables. Furthermore, there is uncertainty whether the expected prevalence of paired associations should allow for the expected absence of other disorders to avoid overestimation (31,32). In the current study, using this classic approach, a significant clustering of insulin resistance, obesity, dyslipidemia, and high blood pressure defined by race-, sex- and age-specific 75th percentiles of IRI, BMI, TG/HDL cholesterol ratio, and mean arterial pressure, respectively, was noted (Table 2). In the total study sample, the observed number of subjects with 4 disorders was 9.8 and 7.4 times the expected number under a null hypothesis of no association for whites and blacks, respectively, which is consistent with the previous findings in other studies (7,33,34).

The ICC measures how closely subjects maintain their ranks of multiple risk variables by comparing intraindividual

TABLE 2
Clustering of adverse levels of IRI, BMI, TG/HDL cholesterol ratio, and mean arterial pressure by race and age-group

	White			Black		
Age-group (years)	*n*	O	O/E	*n*	O	O/E
5–7	551	19	8.8	348	14	10.3
8–10	957	45	12.0	531	21	10.1
11–13	1,099	42	9.8	548	12	5.6
14–17	1,024	35	8.8	700	12	4.4
18–24	473	19	10.3	340	12	9.0
25–30	527	21	10.2	211	6	7.2
31–37	422	13	7.9	142	5	8.9
Total	5,053	194	9.8	2,820	82	7.4

Adverse levels were defined as values above the race-, sex-, and age-specific 75th percentiles. O, actual number of individuals with adverse levels of 4 variables observed in the sample; E, expected number calculated by multiplying the sample size by 0.25^4. All the O/E ratios are significant at the level of 0.01.

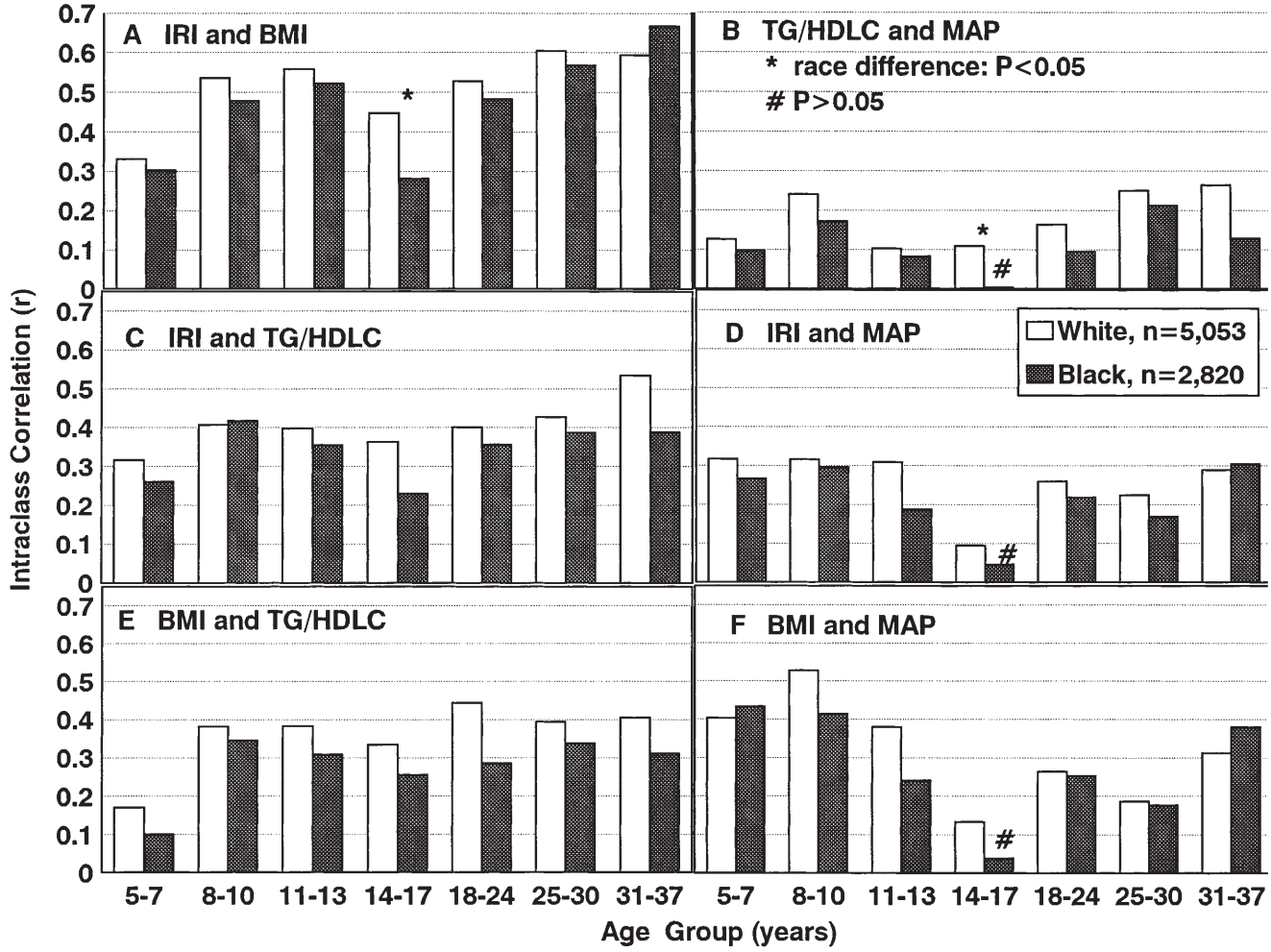

FIG. 1. Intraclass correlations between 2 risk variables by race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.001$), except for those marked with #. MAP, mean arterial pressure; TG/HDLC, ratio of TG to HDL cholesterol.

and interindividual variations. With higher intraclass correlation, the intraindividual variability in ranking of risk variables is smaller compared with the interindividual variability. Therefore, the higher the intraclass correlation, the stronger the clustering of risk variables. Unlike risk ratios, intraclass correlations involve continuous variables that obviate problems associated with the definition of cutoff points and not allowing for the expected absence of other disorders. Therefore, we used this additional approach to examine the age-related patterns of the clustering of risk variables.

The present study shows marked age-related differences in the degree of clustering of risk variables of Syndrome X during periods of childhood and young adulthood spanning 4 decades of life. In both races, the intraclass correlations of 4 risk variables were significant in all age-groups and were higher in preadolescents and young adults than in adolescents. Although both risk ratios and intraclass correlations showed similar age-related patterns during preadolescent and adolescent periods, the intraclass correlations, unlike risk ratios, increased continuously across age-groups during young adulthood (Table 2 and Fig. 3). To the best of our knowledge, standard significance tests for consistency in patterns of intraclass correlations are not available. Thus, our conclusion on age-specific patterns of the clustering of risk factors was based on the fact that similar age-related patterns were consistently observed for both risk ratios and intraclass correlations, regardless of race and combinations of risk variables. Although the race difference was not significant in most cases, the degree of clustering by both measures tended to be consistently higher in whites than in blacks in all age-groups. Moreover, it should be noted that in the total sample, both the intraclass correlation and the risk ratio were higher in whites than in blacks. This observation has not been made previously.

Age-related increases in insulin resistance have been shown in young, middle-aged, and elderly healthy normal-weight adults (16). Aging per se is characterized by a postreceptor defect in insulin action (35) and peripheral hyperinsulinemia (36). Furthermore, body fat increases with age (37). Body fat mass and fat pattern and related insulin sensitivity, which play a central role in Syndrome X (11,14–16), begin to change adversely during growth and sexual maturation (38–42). In view of these observations, one would expect a linear increase in the degree of clustering with age in all age-groups, including adolescents. However, paradoxically, the degree of clustering was lower during puberty in both races. In this regard, additional metabolic variables that were not studied in the present study may be involved during puberty.

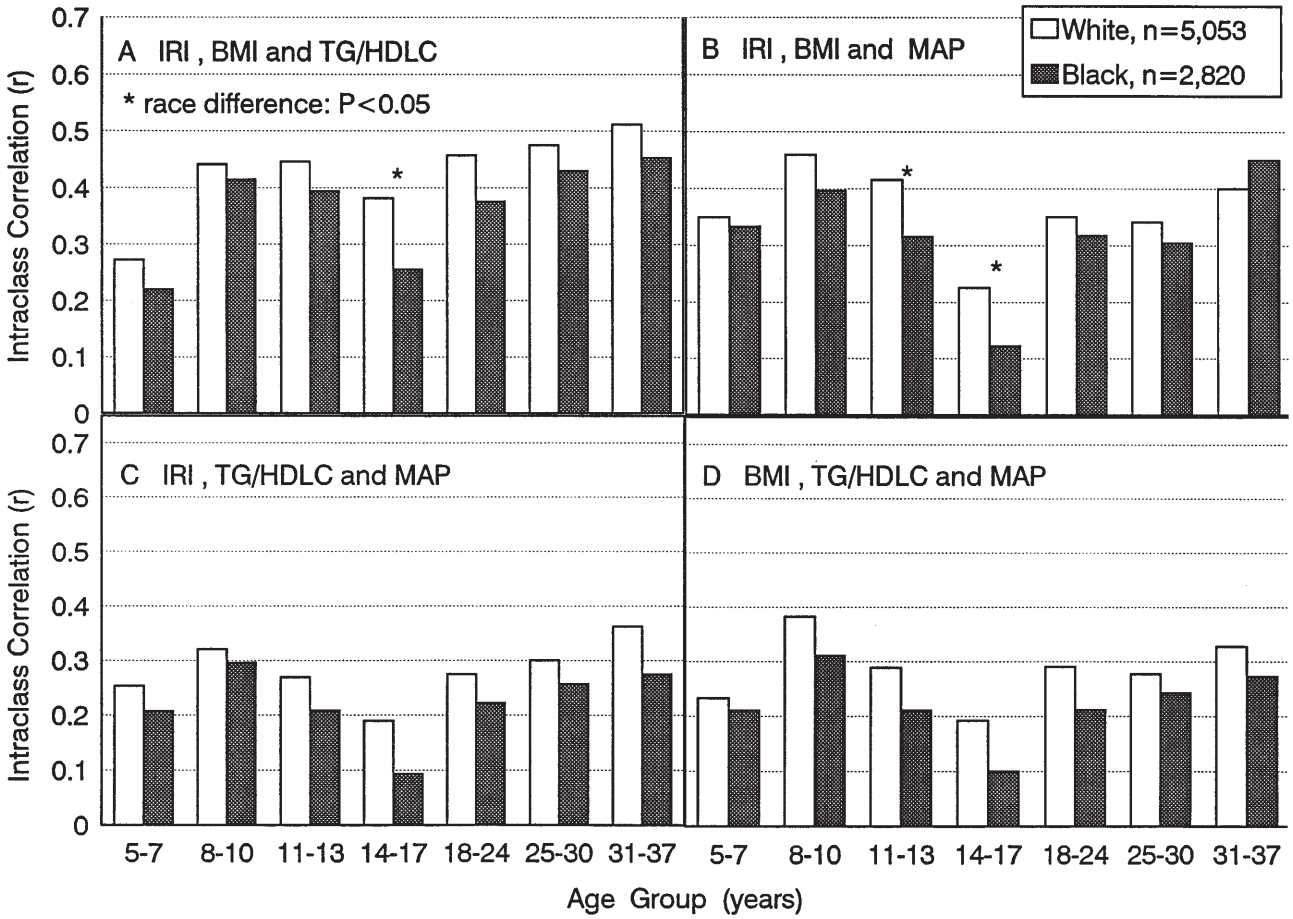

FIG. 2. Intraclass correlations between 3 risk variables by race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.001$). MAP, mean arterial pressure; TG/HDLC, ratio of TG to HDL cholesterol.

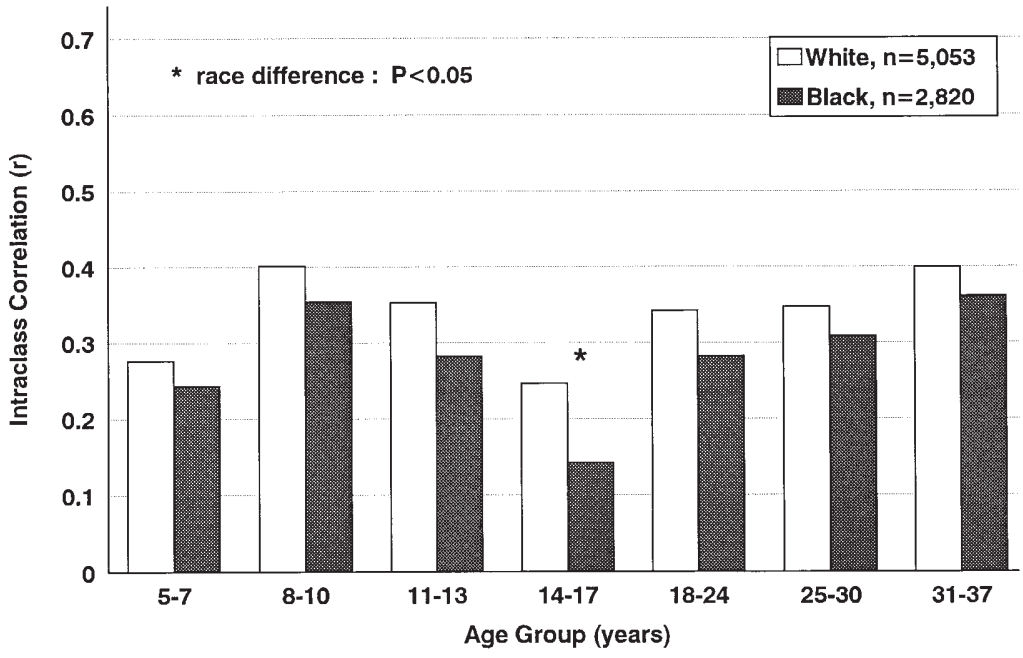

FIG. 3. Intraclass correlations between IRI, BMI, TG/HDL cholesterol ratio, and mean arterial pressure by race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.001$).

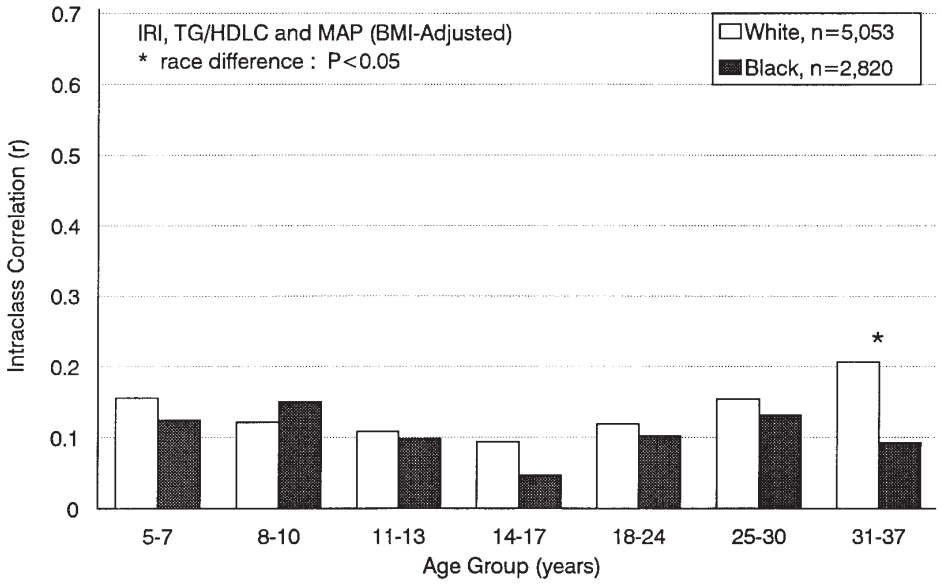

FIG. 4. Intraclass correlations between IRI, TG/HDL cholesterol ratio, and mean arterial pressure adjusted for BMI according to race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.05$)

It should be noted that the sexual maturation process is characterized by a complex interplay among various gonadal and adrenal steroid hormones, growth hormone, and growth factors that rise dramatically during this period (43–45). Higher insulin resistance during puberty has been found to be mediated by these factors, independent of body fat mass (46–49). Likewise, our observations in Bogalusa children showed that increases in sex hormones and IGF-1 during puberty adversely influence lipoprotein and blood pressure levels, independent of adiposity (50,51). Therefore, body fatness may not be the dominant determinant of insulin resistance and other cardiovascular risk variables during puberty. The current observational study cannot address the issue of a physiological basis for the decrease in clustering of risk variables during puberty. Further studies are needed in this direction.

It is of interest that adjusting for BMI resulted in ~50% reduction in the degree of clustering of the remaining components of Syndrome X, and the age-related pattern was no longer evident. In addition, among the various combinations involving 2 risk variables, IRI and BMI showed the strongest intraclass correlations (Fig. 1*A*) and closely resembled the clustering patterns of 3 and 4 variables that involved both BMI and IRI (Fig. 2*A* and *B* and Fig. 3). Furthermore, a factor analysis of Syndrome X in this population showed that this syndrome is characterized by a metabolic factor and a hemodynamic factor with hyperinsulinemia loading on both factors in the total sample (52). It is of interest that in this factor analysis, obesity showed higher loading values in children and adults than in adolescents, which is consistent with the age-related clustering patterns noted in this study. Taken together, it appears that the age-related changes in obesity may account for the degree of clustering of cardiovascular risk variables of Syndrome X, especially during periods of preadolescence and adulthood. This is in agreement with the prevailing notion that obesity and the attendant insulin resistance play a central role in Syndrome X (11,14–17).

In summary, our studies suggest that the association between age and the degree of clustering of cardiovascular risk variables of Syndrome X varies during childhood and young adulthood and may be influenced by obesity and the attendant insulin resistance. Although the current cross-sectional study cannot establish causality of relationship, the observed strong clustering of adiposity and insulin resistance with other risk variables of Syndrome X has practical implications for prevention of cardiovascular disease through weight control and physical activity early in life.

ACKNOWLEDGMENTS

This study was supported by Grant HL 38844 from the National Heart, Lung, and Blood Institute of the U.S. Public Health Service.

The Bogalusa Heart Study is a joint effort of many investigators and staff members whose cooperation is gratefully acknowledged. We especially thank the Bogalusa, LA, schools, teachers, parents, and most importantly, the children and young adults who participated in the study. We thank the Bogalusa Heart Study field staff and the Core Laboratory staff.

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