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

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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

D yslipidemia, 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

Age-group	White		Black		P	
	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

Age-group (years)	White			Black		
	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.

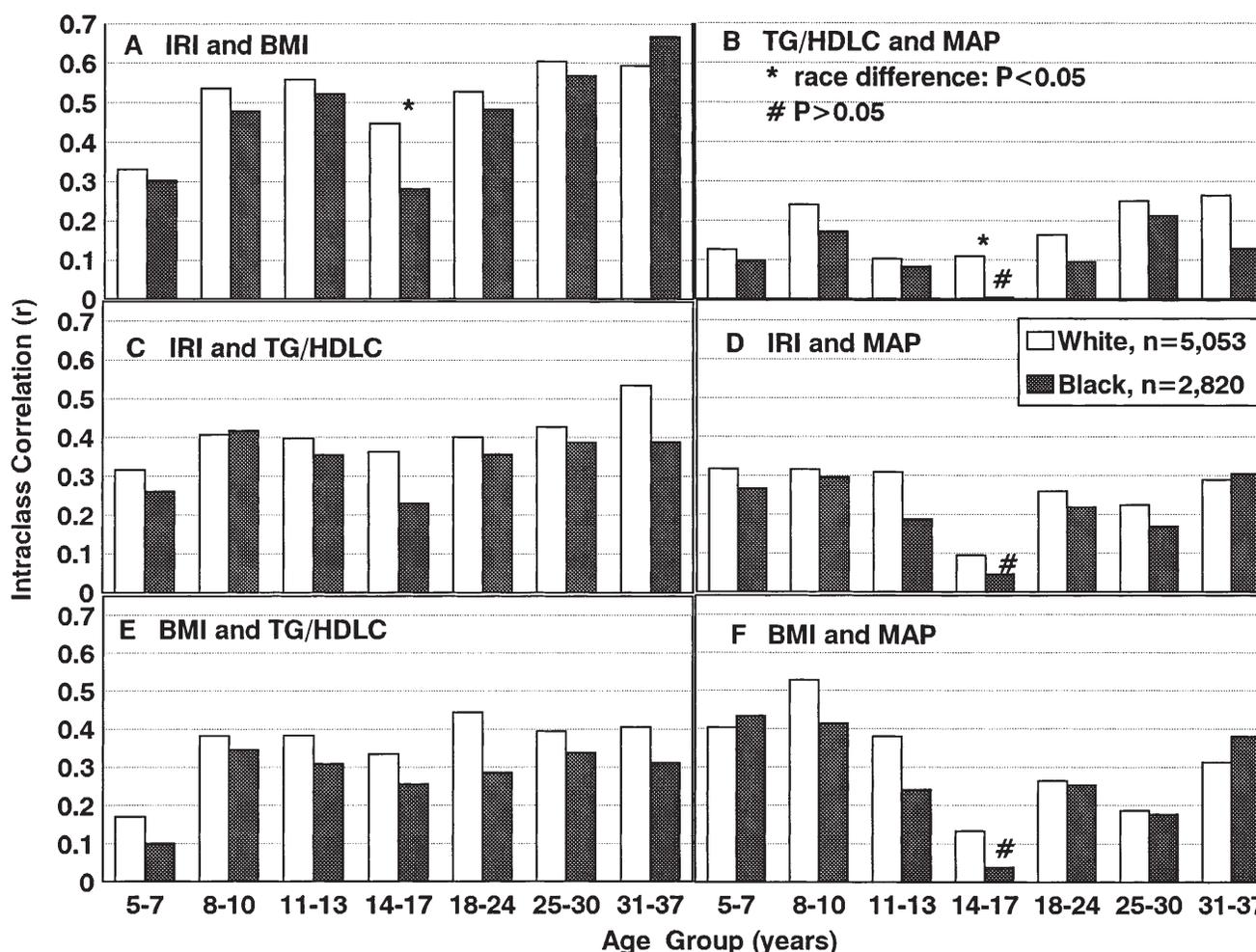**FIG. 1. Intraclass correlations between 2 risk variables by race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.001$), except for those marked with #. MAP, mean arterial pressure; TG/HDLC, ratio of TG to HDL cholesterol.**

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 fac-

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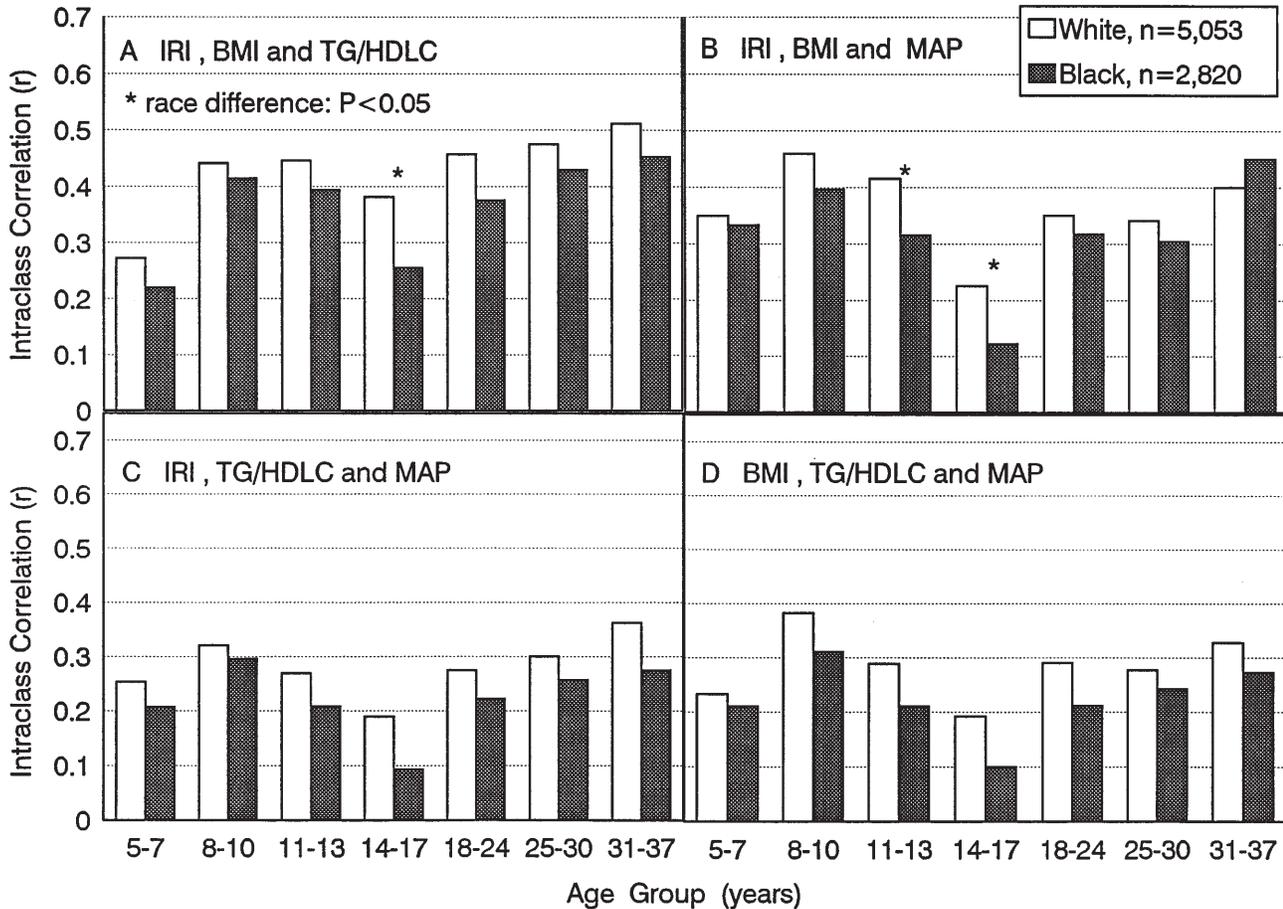
FIG. 2. Intraclass correlations between 3 risk variables by race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.001$). MAP, mean arterial pressure; TG/HDLC, ratio of TG to HDL cholesterol.
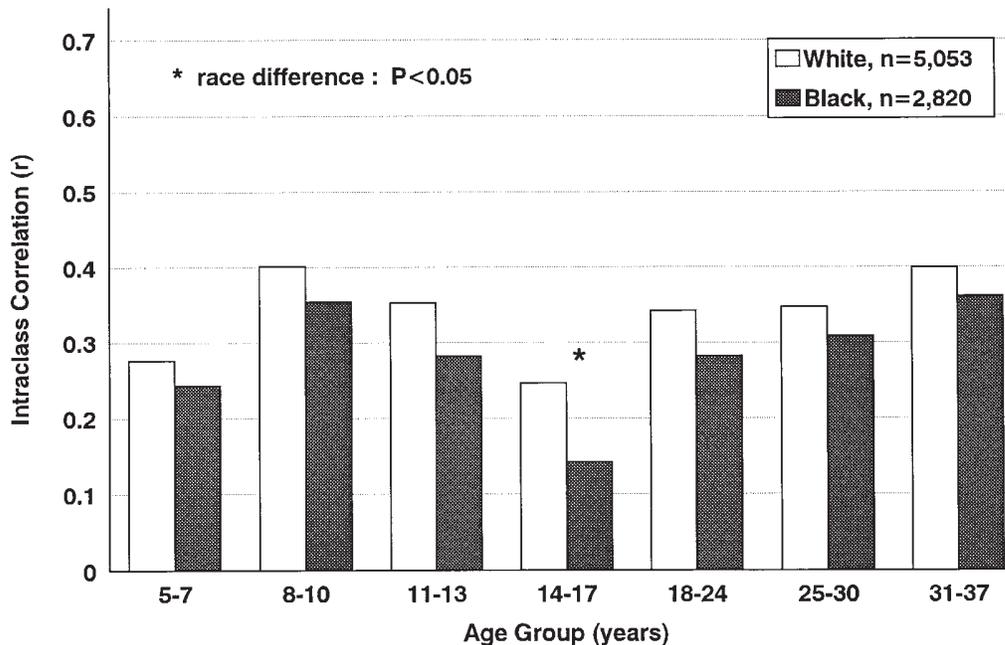

FIG. 3. Intraclass correlations between IRI, BMI, TG/HDL cholesterol ratio, and mean arterial pressure by race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.001$).
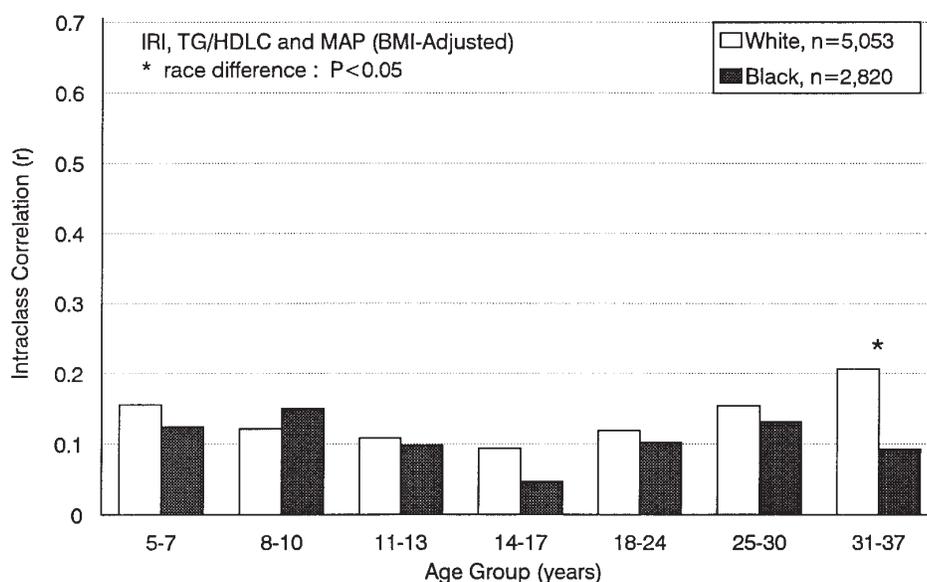
FIG. 4. Intraclass correlations between IRI, TG/HDL cholesterol ratio, and mean arterial pressure adjusted for BMI according to race and age: the Bogalusa Heart Study. All of the ICCs are significantly greater than 0 ($P < 0.05$)

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

REFERENCES

1. Castelli WP: Epidemiology of coronary heart disease: the Framingham Study. *Am J Med* 76:4–12, 1984
2. Ducimetiere P, Eschwege E, Papoz L, Richard JL, Claud JR, Rosselin G: Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. *Diabetologia* 19:205–210, 1980
3. Hubert HB, Feinleib M, McNamara PM, Castelli WP: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 65:968–977, 1983
4. Newman WP III, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL, Williamson GS, Webber LS, Berenson GS: Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: the Bogalusa Heart Study. *N Engl J Med* 314:138–144, 1986
5. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. *JAMA* 264:3018–3024, 1990
6. Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA: Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N Engl J Med* 338:1650–1656, 1998
7. Smoak CG, Burke GL, Webber LS, Harsha DW, Srinivasan SR, Berenson GS: Relation of obesity to clustering of cardiovascular disease risk factors in children and young adults: the Bogalusa Heart Study. *Am J Epidemiol* 125:364–372, 1987
8. Bao W, Srinivasan SR, Wattigney WA, Berenson GS: Persistence of multiple cardiovascular risk clustering related to Syndrome X from childhood to young

adulthood: the Bogalusa Heart Study. *Arch Intern Med* 154:1842–1847, 1994

9. Raitakari OT, Porkka KVK, Rönnemaa T, Knip M, Uhari M, Åkerblom HK, Viikari JSA: The role of insulin in clustering of serum lipids and blood pressure in children and adolescents. *Diabetologia* 38:1042–1050, 1995

10. Arslanian S, Suprasongsin C: Insulin sensitivity, lipids, and body composition in childhood: is "Syndrome X" present? *J Clin Endocrinol Metab* 77:725–730, 1996

11. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin-resistance syndrome (Syndrome X). *Diabetes* 41:715–722, 1992

12. Schmidt MI, Watson RL, Duncan BB, Metcalf P, Brancati FL, Sharrett AR, Davis CE, Heiss G: Clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension and its association with fasting insulin and central and overall obesity in a general population. *Metabolism* 45:699–706, 1996

13. Meigs JB, D'Agostino RB Sr, Wilson PWF, Cupples LA, Nathan DM, Singer DE: Risk variables clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes* 46:1594–1600, 1997

14. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988

15. Kaplan NM: The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 149:1514–1520, 1989

16. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991

17. Liese AD, Mayer-Davis EJ, Haffner SM: Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* 20:157–172, 1998

18. Berenson GS, McMahan CA, Voors AW, Webber LS, Srinivasan SR, Frank GC, Foster TA, Blonde CV: *Cardiovascular Risk Factors in Children: The Early Natural History of Atherosclerosis and Essential Hypertension.* Oxford, U.K., Oxford University Press, 1980

19. Berenson GS: *Causation of Cardiovascular Risk Factors in Children: Perspectives of Cardiovascular Risk in Early Life.* New York, Raven Press, 1986

20. The Bogalusa Heart Study 20th Anniversary Symposium. *Am J Med Sci* 310:S1– S138, 1995

21. Lipid Research Clinics Program: *Manual of Laboratory Operations. Vol. 1: Lipid and Lipoprotein Analysis.* Washington, DC, National Institutes of Health, 1974 (DHEW publ. no. [NIH] 75-628)

22. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC: Enzymatic determination of total serum cholesterol. *Clin Chem* 20:470–475, 1974

23. Bucolo G, David H: Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 19:476–482, 1973

24. Srinivasan SR, Berenson GS: Serum lipoproteins in children and methods for study. In *CRC Handbook of Electrophoresis. Vol. III: Lipoprotein Methodology and Human Studies.* Lewis LA, Ed. Boca Raton, FL, CRC Press, 1983, p. 185–203

25. Austin MA: Epidemiologic association between hypertriglyceridemia and coronary heart disease. *Semin Thromb Hemost* 14:137–142, 1988

26. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985

27. SAS Institute: *SAS/STAT User's Guide.* Version 6. 4th ed. Cary, NC, SAS Institute, 1994

28. Rosner B: Hypothesis testing: one-sample inference. In *Fundamentals of Biostatistics.* 2nd ed. Boston, MA, Duxbury Press, 1986, p. 227–230

29. Shrout PE, Fleiss JL: Intra-class correlation: uses in assessing rater reliability. *Psychol Bull* 86:420–428, 1979

30. Chen W, Srinivasan SR, Bao W, Wattigney WA, Berenson GS: Sibling aggregation of low- and high-density lipoprotein cholesterol and apolipoproteins B and A-I levels in black and white children: the Bogalusa Heart Study. *Ethn Dis* 7:241–249, 1997

31. Turner RC, Stratton IM, Matthews DR: Of insulin resistance and normalcy. *Diabetologia* 35:696–698, 1992

32. Ferrannini E, Haffner SM, Michell BD, Stern MP: Response from the authors. *Diabetologia* 35:697–698, 1992

33. Schmidt MI, Duncan BB, Watson RL, Sharrett AR, Brancati FL, Heiss G: A metabolic syndrome in whites and African Americans. *Diabetes Care* 19:414–418, 1996

34. Ferrannini E, Haffner SM, Mitchell BD, Stern MP: Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 34:416–422, 1991

35. Jackson RA: Mechanisms of age-related glucose intolerance. *Diabetes Care* 13 (Suppl. 2):9–19, 1990

36. Fink RI, Kolterman OG, Groffin J, Olefsky JM: Mechanisms of insulin resistance in aging. *J Clin Invest* 71:1523–1535, 1983

37. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC: Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol* 141:1117–1127, 1995

38. Deutsch MI, Mueller WH, Malina RM: Androgen in fat patterning is associated with obesity in adolescents and young adults. *Am Hum Biol* 12:275–286, 1985

39. Frisancho AR, Flegel PN: Advanced maturation associated with centripetal fat pattern. *Hum Biol* 54:717–727, 1982

40. Baumgartner RN, Roche AF, Guo S, Lohman T, Boileau RA, Slaughter MH: Adipose tissue distribution: the stability of principal components by sex, ethnicity and maturation stage. *Hum Biol* 58:719–735, 1986

41. Amiel SA, Sherwin RS, Simonson DC, Lanritano AA, Tamborlane WV: Impaired insulin action in puberty: a contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 315:215–219, 1986

42. Svec F, Nastasi K, Hilton C, Bao W, Srinivasan SR, Berenson GS: Black-white contrasts in insulin levels during pubertal development: the Bogalusa Heart Study. *Diabetes* 41:313–317, 1992

43. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jørgensen K, Müller J, Hall K, Skakkebæk NE: Serum insulin-like growth factor-1 in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size and body mass index. *J Clin Endocrinol Metab* 78:744–752, 1994

44. Lee PA, Xenakis T, Winer J, Matsenbaugh S: Puberty in girls: correlation of serum levels of gonadotropins, prolactin, androgens, estrogens, and progestins with physical changes. *J Clin Endocrinol Metab* 43:775–784, 1976

45. Lee PA, Migeon CJ: Puberty in boys: correlation of plasma levels of gonadotropins (LH, FSH), androgens (testosterone, androstenedione, dehydroepiandrosterone and its sulfate), estrogens (estrone and estradiol) and progestins (progesterone and 17-hydroxy-progesterone). *J Clin Endocrinol Metab* 41:556–562, 1975

46. Diez J, Ruilope LM, Rodicio JL: Insulin response to oral glucose in essential hypertensives with increased circulating levels of insulin-like growth factor-1. *J Hypertens* 9 (Suppl. 6):S174–S175, 1991

47. Smith CP, Dunger DB, Williams AJK, Taylor AM, Perry LA, Gale EAM, Preece MA, Savage MD: Relationship between insulin, insulin-like growth factor 1, and dehydroepiandrosterone sulfate concentrations during childhood, puberty, and adult life. *J Clin Endocrinol Metab* 68:932–937, 1989

48. Hindmarsh P, Di Silvio L, Pringle PJ, Kurtz AB, Brook CGD: Changes in serum insulin concentration during puberty and their relationship to growth hormone. *Clin Endocrinol* 28:381–388, 1988

49. Bloch CA, Clemons P, Sperling MA: Puberty decreases insulin sensitivity. *J Pediatr* 110:481–487, 1987

50. Srinivasan SR, Freedman DS, Sundaram GS, Webber LS, Berenson GS: Racial (black-white) comparisons of the relationship of levels of endogenous sex hormones to serum lipoproteins during male adolescence: the Bogalusa Heart Study. *Circulation* 74:1226–1234, 1986

51. Jiang X, Srinivasan SR, Dalferes ER Jr, Berenson GS: Plasma insulin-like growth factor-1 distribution and its relation to blood pressure in adolescents: the Bogalusa Heart Study. *Am J Hypertens* 10:714–719, 1997

52. Chen W, Srinivasan SR, Elkasabany A, Berenson GS: The cardiovascular risk factors clustering features of insulin resistance syndrome (Syndrome X) in a biracial (black-white) population of children, adolescents and young adults: the Bogalusa Heart Study. *Am J Epidemiol* 150:667–674, 1999