Original Contribution

Clustering of Long-term Trends in Metabolic Syndrome Variables from Childhood to Adulthood in Blacks and Whites

The Bogalusa Heart Study

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Clustering of long-term rates of change in metabolic syndrome variables (body mass index, homeostasis model assessment of insulin resistance, ratio of triglycerides to high-density lipoprotein cholesterol, and mean arterial pressure) from childhood to adulthood was evaluated longitudinally (1982–2003) in a cohort of 389 Blacks and 631 Whites who were examined 3–6 times both as children (ages 4–17 years) and as adults (ages 18–38 years) over an average of 16 years (3,874 observations). The incremental area under the growth curve was used as a measure of long-term rates of change in risk variables since childhood. Intraclass correlations, a measure of the degree of clustering, among the four variables were significant ($p < 0.001$) for childhood, adulthood, and incremental area values and were higher in adulthood than in childhood. Blacks showed a higher degree of clustering of long-term rates of change in risk variables than did Whites. Adjustment for body mass index reduced the degree of clustering by approximately 50%. These results show that metabolic syndrome variables coexist in terms not only of their levels in childhood and adulthood but also of long-term rates of change. Obesity is of critical importance in the development of metabolic syndrome, and its prevention beginning in childhood needs to be addressed.

insulin resistance; longitudinal studies; metabolic syndrome X; obesity

Abbreviations: HDLC, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; ICC, intraclass correlation coefficient.
The Bogalusa Heart Study is a long-term, community-based study of the early natural history of cardiovascular disease in Black and White children followed into adulthood. Longitudinal data from this study provide an opportunity to examine clustering of metabolic syndrome variables in childhood versus adulthood and how long-term rates of change cluster from childhood to adulthood.

MATERIALS AND METHODS

Study cohort

Between 1982 and 2003, in Bogalusa, Louisiana, five cross-sectional surveys of children aged 4–17 years and six cross-sectional surveys of young adults aged 18–43 years who had been previously examined as children were conducted for an analysis of cardiovascular disease risk factors. This panel design of repeated cross-sectional examinations conducted approximately every 3–4 years has produced data from serial observations ranging from childhood to adulthood. A total of 1,020 subjects who had been examined 3–6 times (at least once in childhood and at least once in adulthood) formed the study cohort for this report. Data from 3,874 observations made during an average period of 16.1 years (range, 8–21 years) were available. The average number of measurements was 3.8. The cohort comprised 61.9 percent Whites and 40.9 percent males. For subjects who were using antihypertensive, cholesterol-lowering, or insulin medication at any examination (n = 78), the corresponding values were set to missing and the remaining measurements were used for analyses.

All subjects in the study gave informed consent at each examination. For subjects under 18 years of age, the consent of a parent was obtained. Study protocols were approved by the institutional review board of the Tulane University Health Sciences Center.

General examinations

All examinations followed the same protocols, and procedures used for the general examinations have been described elsewhere (12). Height and weight were measured twice to ±0.1 cm and ±0.1 kg, respectively. Body mass index (weight in kilograms divided by the square of height in meters) was used as a measure of obesity. Blood pressure was measured on the right arm by two different nurses (randomly assigned) while the subject sat in a relaxed position. The fourth Korotkoff phase was used as a measure of diastolic blood pressure for children and adults, because an earlier study (13) showed the fourth phase to be more reliably measured in children and more predictive of adult hypertension. Means of replicate readings were used in all analyses. Mean arterial pressure (diastolic blood pressure + 1/3 pulse pressure) was used as a measure of hemodynamic status.

Serum lipid, insulin, and glucose levels

From 1982 to 1986, cholesterol and triglyceride levels were measured using chemical procedures with a Technicon Auto Analyzer II (Technicon Instrument Corporation, Tarrytown, New York) according to the laboratory manual of the Lipid Research Clinics Program (14). Subsequently, these variables were assayed using enzymatic procedures (15, 16) on an Abbott VP instrument (Abbott Laboratories, North Chicago, Illinois) between 1986 and 1996 and on a Hitachi 902 Automatic Analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana) afterward. Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis (17). Both chemical and enzymatic procedures met the performance requirements of the Centers for Disease Control and Prevention’s lipid standardization program (http://www.cdc.gov/labstandards/crmhn.htm). Measurements made in quality control samples assigned by the Centers for Disease Control and Prevention showed no consistent bias over time within or between surveys or instruments. The ratio of fasting triglyceride level to high-density lipoprotein cholesterol (HDLC) level was used as a measure of dyslipidemia, since the combination of high triglyceride levels and low HDLC levels characterizes the dyslipidemia in metabolic syndrome (18).

Plasma immunoreactive insulin was measured by means of a commercial radioimmunoassay kit (Padebas Pharmacia, Piscataway, New Jersey) and plasma glucose by an enzymatic method using a Beckman Instant Glucose Analyzer (Beckman Instruments, Palo Alto, California). Homeostasis model assessment (HOMA) of insulin resistance was conducted through the calculation fasting insulin (μU/ml) × fasting glucose (mmol/liter)/22.5. This model is considered useful for assessing insulin resistance in epidemiologic studies (19).

Intraclass correlation coefficients (ICCs) were used as a measure of reproducibility of the entire process from blood collection to data processing. ICCs for the correlation between blind duplicate values (n = 86) ranged from 0.97 to 0.99 for triglycerides, from 0.92 to 0.98 for HDLC, from 0.94 to 0.98 for insulin, and from 0.86 to 0.98 for glucose.

Statistical methods

The metabolic syndrome variables considered for this analysis were body mass index, HOMA, mean arterial pressure, and triglyceride:HDLC ratio. Data for HOMA and triglyceride:HDLC ratio were log-transformed to improve normality before the subsequent analyses. Growth curves for these variables versus age (linear and nonlinear terms) were determined for each subject in a random-effects model with SAS PROC MIXED (20), using multiple measurements. The MIXED model generalizes the standard linear model as $Y = X\beta + Zu + e$, where $Y$ is the vector of multiple observations, $X\beta$ is the fixed effect, $Zu$ is the random effect, and $e$ is an unknown error term. To avoid col-linearity of age with its higher-order terms, the participant’s age was centered by subtracting the sample mean age (21 years). A quadratic curve was fitted for body mass index, HOMA, and triglyceride:HDLC ratio, and a cubic curve was fitted for mean arterial pressure in race-sex groups. As figure 1 shows, using mean arterial pressure as an example, the area under the curve was calculated as the integral of...
the growth curve during the follow-up period for each participant (21, 22). Use of the incremental area (total area minus baseline area) enabled us to measure combined linear and nonlinear long-term rates of change in the metabolic syndrome variables over time. Since individual participants had different follow-up periods, the incremental area was divided by the number of years of follow-up. In addition to the longitudinal analyses, cross-sectional analyses were performed on clustering of the metabolic syndrome variables in childhood (first measurement) and adulthood (last measurement).

The four metabolic syndrome components are age-related, and data collection spanned a period of 21 years. Thus, childhood and adulthood values for the four variables were separately adjusted for age in cross-sectional analyses using regression models in race-sex groups by survey year. The observed individual variable values \( Y_i \) can be expressed as \( Y_i = \beta_0 + \beta \text{age}_i + e_i \), and their predicted values \( \hat{Y}_i \) can be expressed as \( \hat{Y}_i = \beta_0 + \hat{\beta} \text{age}_i \). The residual value \( R_i \) is calculated as \( R_i = Y_i - \hat{Y}_i \). Regression residuals were then standardized with \( z \) transformation by race, sex, and survey year. The incremental area values were treated in the same manner, and the corresponding baseline values were also included in the regression models to control for regression-to-the-mean bias. The standardized regression residuals were used for the subsequent correlation analyses.

Pairwise correlations of any two variables were examined using Pearson correlations. The differences in the Pearson correlation coefficients between race groups and between childhood and adulthood were tested by Fisher’s \( z \) transformation. The ICC was introduced in the present study as a measure of the degree of clustering of the four continuous risk variables. \( Z \) scores for the regression residuals of the four variables had a homogeneous unit (standard deviation) and can be considered four repeated measurements on the same individual. Using one-way analysis of variance, ICCs were calculated by means of the formula (9, 23)

\[
\text{ICC} = \frac{(\text{MS}_B - \text{MS}_W)}{[\text{MS}_B + (k - 1)\text{MS}_W]},
\]

where \( \text{MS}_B \) is the between-individual mean square, \( \text{MS}_W \) is the within-individual mean square, and \( k \) is the number of variables (\( k = 4 \) in this case). The test that an ICC is higher than zero is performed by calculating \( F = \text{MS}_B/\text{MS}_W \) on \( (n - 1) \) and \( n(k - 1) \) degrees of freedom, where \( n \) is the total sample size. Differences in ICCs between Blacks and Whites and among various measures were tested for significance by comparing their 95 percent confidence intervals using previously described formulas (23).

**RESULTS**

Table 1 shows mean levels of the metabolic syndrome variables in childhood and adulthood and for incremental area values, by race and sex. In general, the four components showed fewer differences in childhood and more differences in adulthood between race and sex groups. There was a significant racial difference (Black < White) for the triglyceride: HDL-C ratio, starting in childhood. Significant race and sex differences were noted for incremental areas, except for body mass index and mean arterial pressure in males.
Table 2 shows sex- and age-adjusted Pearson coefficients for the correlation between any two risk variables in childhood and adulthood and for incremental area values by race. Except for the body mass index-blood pressure correlation in Blacks, the correlations between all pairs of variables in childhood were lower than those in adulthood, with seven pairs showing significant differences. White adults had consistently higher correlations for all pairs of variables than Black adults, though not significantly for some pairs, whereas Blacks had significantly higher correlations of incremental area values than Whites, except for the correlations of body mass index-blood pressure and HOMA-blood pressure.

Figure 2 shows age- and sex-adjusted ICCs (degree of clustering) for metabolic syndrome variables by race for childhood, adulthood, and incremental area values. All ICCs for the four variables were significantly greater than zero \((p < 0.001)\) and were higher in adulthood than in childhood for both Blacks and Whites (figure 2, part A). The ICC for the four incremental area values in Blacks was significantly greater than that in Whites \((p < 0.05)\). With respect to the intraclass correlations of three risk variables adjusted for HOMA (part B) or body mass index (part C), unlike HOMA, the adjustment for body mass index resulted in an approximately 50 percent reduction in the ICCs for the other three variables in Blacks and Whites.

**DISCUSSION**

It has been well documented in previous population studies that adverse levels of adiposity, insulin, glucose, blood pressure, triglycerides, and HDLC co-occur as part of the “metabolic syndrome” to a greater degree than would be expected by chance \((9, 24)\). Since levels of these variables change with age from childhood to adulthood, adulthood levels are largely determined by the rates of change from childhood. Based on observations regarding the prevalence of the metabolic syndrome in both childhood and adulthood \((5–9)\), long-term trends in metabolic syndrome variables over time are hypothesized to be correlated. In a 4.5-year study, Maison et al. \((10)\) found that different features of the metabolic syndrome changed together over time in adults, whereas Blacks had significantly higher correlations of adverse levels of adiposity, insulin, glucose, blood pressure, triglycerides, and HDLC co-occur as part of the “metabolic syndrome” to a greater degree than would be expected by chance. Since levels of these variables change with age from childhood to adulthood, adulthood levels are largely determined by the rates of change from childhood. Based on observations regarding the prevalence of the metabolic syndrome in both childhood and adulthood, long-term trends in metabolic syndrome variables over time are hypothesized to be correlated. In a 4.5-year study, Maison et al. \((10)\) found that different features of the metabolic syndrome changed together over time in adults, whereas Blacks had significantly higher correlations of adverse levels of adiposity, insulin, glucose, blood pressure, triglycerides, and HDLC co-occur as part of the “metabolic syndrome” to a greater degree than would be expected by chance.
are not applicable to children, we used body mass index, HOMA, mean arterial pressure, and triglyceride:HDLC ratio as continuous variables to define the metabolic syndrome in children. In addition, these four components are consistent with those used in our previous studies (8, 9). In this study, we found that not only did the adverse levels of multiple variables tend to coexist in the same individual in both childhood and adulthood, but their rates of change also clustered over time. These observations are unique in their use of the incremental area under the growth curve as a measure of long-term rate of change in risk variables and their clustering from childhood to adulthood.

It is of interest that adjusting for body mass index resulted in a dramatic reduction in the degree of clustering of the remaining components in terms of childhood and adulthood values and rates of change in the present longitudinal cohort, whereas HOMA did not exert such an impact on the clustering. This is consistent with our earlier longitudinal study showing that childhood adiposity is a more powerful predictor than childhood insulin levels for the development of metabolic syndrome in adulthood (25). A similar influence of adiposity on the age-related trends in correlation of the metabolic syndrome variables was also observed in our previous cross-sectional study in the Bogalusa population (9).

A longitudinal study of adults suggested that obesity played a role in the development of the metabolic syndrome in adults (10). Taken together, findings from this and other studies support the prevailing notion that obesity plays a central role in the development of metabolic syndrome (5, 6, 9, 10, 25, 26).

The metabolic syndrome is highly prevalent, and incidence increases with age in the general population. Prevalence among US adults increases from 6.7 percent in the second decade of life to 43.5 percent in the sixth decade (7). Approximately 50 percent of severely obese children have the metabolic syndrome (6). In this longitudinal study cohort, significant ICCs for correlations among the four variables were noted in both childhood and adulthood. The degree of clustering in adulthood was consistently greater than that in childhood in both Blacks and Whites. A similar age-related trend in the clustering patterns was observed in our previous cross-sectional study (9), with children having lower ICCs than adults in both Blacks and Whites. Further, the metabolic syndrome tended to persist from childhood to adulthood in an 8-year follow-up of the Bogalusa population (8). These observations provide cumulative evidence for origination of the metabolic syndrome in childhood.

For analysis of the clustering of risk factors, dichotomous variables defined by diagnostic or percentile cutoff values are commonly used (9, 24). In the present study, we applied the ICC to assess the degree of clustering of the metabolic syndrome components as continuous variables. The ICC measures how closely multiple (>2) risk factors are intercorrelated by comparing between-individual and within-individual variations. With higher ICCs, the within-individual variability in the ranking of risk variables is smaller than the

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**TABLE 2. Pearson coefficients for correlations among metabolic syndrome risk variables in childhood and adulthood and for the incremental area† in Whites (n = 631) and Blacks (n = 389), Bogalusa Heart Study, 1982–2003§**

<table>
<thead>
<tr>
<th></th>
<th>HOMA‡ (insulin resistance)</th>
<th>Mean arterial pressure</th>
<th>Triglyceride:HDLC‡ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whites</td>
<td>Blacks</td>
<td>Whites</td>
</tr>
<tr>
<td>Body mass index#</td>
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<td></td>
<td></td>
</tr>
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<td>0.331</td>
<td>0.364</td>
<td>0.275</td>
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<tr>
<td>Adulthood</td>
<td>0.613*</td>
<td>0.505*†</td>
<td>0.428*</td>
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<td>HOMA (insulin resistance)</td>
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<td></td>
<td>0.318*</td>
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</tr>
<tr>
<td>Childhood</td>
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* p < 0.05 for childhood-adulthood comparisons.
† p < 0.05 for race comparisons.
‡ Area under the curve of mean arterial pressure.
§ Correlation coefficients were adjusted for sex and age; for incremental area, they were also adjusted for the corresponding baseline values. Coefficients above 0.078 for Whites and above 0.100 for Blacks were significantly greater than zero at p < 0.05.
¶ HOMA, homeostasis model assessment; HDLC, high-density lipoprotein cholesterol.
# Weight (kg)/height (m)².
between-individual variability. Therefore, the higher the ICC, the stronger the clustering of risk variables. Unlike the categorical approach, the use of ICCs involves continuous variables and obviates problems associated with the definition of cutoff points. However, a limitation of this approach is that a standard significance test for differences between ICCs is not available. We had to rely on a conservative method, the use of 95 percent confidence intervals, for this purpose.

It is well known that Whites have a higher prevalence of metabolic syndrome than Blacks in childhood and adulthood (5, 7, 26). In our previous cross-sectional study, we found a consistent racial difference in ICCs (White > Black) for multiple metabolic syndrome variables in children, adolescents, and young adults (9). In this longitudinal study, Whites had a greater degree of clustering of four variables in adulthood but not in childhood. In contrast, we found consistently higher correlations of rates of change in these variables from childhood to adulthood in Blacks than in Whites. Although Maison et al. (10) recently reported that the metabolic syndrome components change together over 4.5 years during adulthood, longitudinal observations from childhood to adulthood can describe in more detail within-individual variations over time, such as linear and nonlinear trends. Longitudinal trends in the metabolic syndrome components, measured as incremental area in this study, reflect interactions between environmental and genetic factors. Berg (27) proposed the concept of a “variability gene” effect to explain within-individual variations in cardiovascular disease risk factors over time. The genes, whose expression depends on environmental exposure, are referred to as “variability genes.” The observation in this study that there is a greater degree of clustering of rates of change in metabolic syndrome components in Blacks than in Whites suggests that there is a racial difference in the genetic basis and long-term burden of lifestyles. Further studies are needed in this regard.

In summary, in this analysis, metabolic syndrome variables (including obesity, insulin resistance, hypertension, and dyslipidemia) clustered in Blacks and Whites in childhood and adulthood, as well as long-term (measured as incremental area). Adjustment for body mass index substantially reduced the degree of clustering. These results suggest that the metabolic syndrome variables coexist in terms not only of absolute levels in childhood and adulthood but also of rates of change from childhood to adulthood. Such observations underscore the importance of obesity in the development of metabolic syndrome. From a practical standpoint of weight control, dietary moderation and physical activity early in life are primary targets for prevention.

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**FIGURE 2.** Intraclass correlations of metabolic syndrome variables for childhood (white bars), adulthood (black bars), and the incremental area (area under the curve of mean arterial pressure) (hatched bars), by race, Bogalusa Heart Study, 1982–2003. A, all four variables (body mass index (weight (kg)/height (m)^2), homeostasis model assessment (HOMA) of insulin resistance, ratio of triglyceride level to high-density lipoprotein cholesterol (HDLc) level, and mean arterial pressure); B, body mass index, mean arterial pressure, and triglyceride:HDLc ratio; C, HOMA, mean arterial pressure, and triglyceride:HDLc ratio. All intraclass correlation coefficients were significantly greater than zero (p < 0.05), except for that marked not significant (NS), after adjustment for age, sex, and/or HOMA or body mass index.
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Conflict of interest: none declared.

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