Temporal Relationship Between Childhood Body Mass Index and Insulin and Its Impact on Adult Hypertension

The Bogalusa Heart Study

Tao Zhang, Huijie Zhang, Ying Li, Dianjianyi Sun, Shengxu Li, Camilo Fernandez, Lu Qi, Emily Harville, Lydia Bazzano, Jiang He, Fuzhong Xue, Wei Chen

Abstract—Although obesity and insulin resistance are closely correlated, their temporal sequences in early life and influence on adult hypertension are largely unknown. This study aims to delineate the temporal relationship patterns between body mass index (BMI) and insulin in childhood and their impact on adult hypertension. The longitudinal cohort consisted of 990 adults (630 whites and 360 blacks) who had BMI and fasting insulin measured twice 5.4 years apart in childhood (mean age, 10.5 years at baseline and 15.9 years at follow-up) and blood pressure measured 14.7 years later in adulthood (mean age, 30.5 years). Cross-lagged panel and mediation analysis models were used to examine the temporal relationship between childhood BMI and insulin and its impact on adult hypertension. After adjusting for age, race, sex, and follow-up years, the cross-lagged path coefficient (β=0.33; P<0.001) from baseline BMI to follow-up insulin was significantly greater than the path coefficient (β=-0.02; P>0.05) from baseline insulin to follow-up BMI in childhood with P<0.001 for the difference in βs. Blacks and whites showed similar patterns of the temporal relationship. The path coefficient (β=0.59; P<0.001) from BMI to insulin in the hypertensive group was significantly greater than that (β=0.24; P<0.001) in normotensive group, with P<0.001 for the difference in βs between these 2 groups. The mediation effect of childhood insulin on the childhood BMI–adult hypertension association was estimated at 21.1% (P<0.001). These findings provide evidence that higher BMI levels precede hyperinsulinemia during childhood, and this 1-directional relation plays a role in the development of hypertension. (Hypertension. 2016;68:818-823, DOI: 10.1161/HYPERTENSIONAHA.116.07991.) • Online Data Supplement

Key Words: blood pressure ▪ body mass index ▪ hyperinsulinism ▪ hypertension ▪ obesity

Obesity and insulin resistance are well-known important risk factors for cardiovascular disease, diabetes mellitus, and essential hypertension.1–4 There is a huge body of evidence showing that the strong intercorrelation between obesity and insulin resistance plays a crucial role in the development of hypertension.5–7 It is generally considered that obesity measures and insulin levels can influence each other based on pathophysiological and metabolic mechanisms.8 Studies have shown that obesity causes hyperinsulinemia,9 and on the contrary, insulin treatment results in weight gain in diabetes patients.10–12 Despite the general concept that insulin resistance is a key link between obesity and hypertension, convincing evidence is lacking from population studies on the causal sequence (temporal relationship) between obesity and insulin resistance with compensatory hyperinsulinemia. Available data are inconsistent about the temporal relationship in longitudinal cohorts of children from the Bogalusa Heart Study9 and adults from the Normative Aging Study.13

Hypertension is a complex chronic disease, and its roots extend back into early life. The notion of childhood origins of hypertension is supported by numerous publications from population-based cohorts followed since childhood, including the Bogalusa Heart Study.14,15 Although childhood body mass index (BMI) and insulin levels are extensively reported to be associated with hypertension in later life,16,17 how their causal relation patterns in childhood influence adult hypertension and to what extent obesity is associated with hypertension through insulin resistance are largely unknown.

Utilizing a longitudinal cohort from the Bogalusa Heart Study, the present study aims to delineate the temporal sequences between childhood BMI and insulin using cross-lagged panel analysis and explore the impact of their temporal relationship patterns on adult hypertension using mediation analysis.
Materials and Methods

Study Cohort

The Bogalusa Heart Study is a series of long-term studies in a semirural biracial (65% white and 35% black) community in Bogalusa, Louisiana, begun in 1973 by Dr Gerald Berenson, focusing on the early natural history of cardiovascular disease since childhood. Between 1973 and 2010, 9 cross-sectional surveys of children aged 4 to 18 years and 10 cross-sectional surveys of adults aged 19 to 52 years, who had been previously examined as children, were conducted in Bogalusa, Louisiana. This panel design of repeated cross-sectional examinations has resulted in serial observations every 2 to 3 years from childhood to adulthood. The longitudinal cohort of this study consisted of 990 adult subjects (630 whites and 360 blacks; 38.6% men; mean age, 30.5 years with a range of 20.1–49.2 years in adulthood). These adults were examined twice for BMI and insulin levels 5.4 years apart in childhood (mean age, 10.5 years at baseline and 15.9 years at follow-up) and blood pressure (BP) in adulthood were identified for the present study, with a follow-up period of 14.7 years on average (range, 5.2–33.6 years) from the last childhood survey to adulthood.

All subjects in this study gave informed consent for each survey, and for those <18 years of age, consent of a parent/guardian was obtained. Study protocols were approved by the Institutional Review Board of the Tulane University Health Sciences Center.

Measurements

Standardized protocols were used by trained examiners across all surveys since 1973. Subjects were instructed to fast for 12 hours before screening. Replicate measurements of height and weight were made, and the mean values were used for analysis. Body mass index (BMI, weight in kilograms divided by the square of the height in meters) was used as a measure of overall adiposity.

BP levels were measured between 8:00 AM and 10:00 AM on the right arm of subjects in a relaxed, sitting position by 2 trained observers (3 replicates each). Systolic BP (SBP) and diastolic BP (DBP) were recorded using a mercury sphygmomanometer. The fifth Korotkoff phase was used for DBP. The mean values of the 6 readings were used for analysis. Hypertension was defined as SBP≥140 mm Hg or DBP≥90 mm Hg or taking antihypertensive medications at the time of survey. A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Phadebas; Pharmacia Diagnostics, Piscataway, NJ).

Statistical Methods

ANCOVAs were performed using generalized linear models to test differences in study variables between race and sex groups. The study of longitudinal changes of BMI and insulin measured at 2 time points in childhood is typically a cross-lagged panel design. The cross-lagged panel analysis is a form of path analysis that simultaneously examines reciprocal, longitudinal relationships among a set of intercorrelated variables. A simplified, conceptual version of the model used in the current analysis is presented in Figure 1. The path with $\beta_1$ describes the effect of baseline insulin on subsequent BMI, and the path with $\beta_2$ describes the effect of baseline BMI on subsequent insulin. Before cross-lagged path analysis, the baseline and follow-up values of BMI and insulin were adjusted for age and sex by regression residual analyses. The cross-lagged analysis models of childhood BMI and insulin were constructed, with adjustment for age, race, sex, and follow-up years in normotensive and hypertensive groups, separately.

Once the temporal relationship between childhood BMI and insulin had been established, a causal mediation model was constructed to examine whether the association of childhood BMI with adult hypertension and BP levels was mediated by childhood insulin. Childhood baseline BMI was predictor variable (X); childhood follow-up insulin was mediator (M); hypertension or BP levels were outcome variables (Y). In general, there are 4 steps for mediation analyses: (1) showing that the predictor variable affects the mediator (Model $M=X\beta_1$); (2) showing that the predictor variable affects the outcome (Model $Y=\beta_2X$); (3) showing that the mediator determines the outcome controlling for the predictor (Model $Y=\beta_3+\beta_4M$); (4) calculating the proportion of mediation: mediation effect ($\% = (\beta_3/\beta_2)\times 100\%$). Mediation analysis was performed using R package mediation, adjusted for age, race, sex, and follow-up years. The probit and linear regression models were performed for hypertension and BP levels, respectively.

Results

Table 1 summarizes mean levels of study variables in childhood at baseline and follow-up, and in the last adulthood survey by race and sex. The mean levels of continuous variables were compared between race and sex groups, adjusting for age (except age itself). Baseline BMI in childhood did not differ significantly between race and sex groups; baseline insulin in childhood had significant race difference in women (blacks>whites) and significant sex difference in blacks (women>men). Follow-up BMI and insulin in childhood showed significant race difference in women (blacks>whites) and significant sex difference in blacks (women>men). Follow-up BMI and insulin in adulthood showed significant race difference in women (blacks>whites); follow-up insulin in childhood showed significant sex difference in blacks (women>men). Both adulthood BMI and insulin showed significant race differences in women (blacks>whites) and significant sex difference (women>men) in blacks. Blacks and men had significantly higher adulthood SBP levels than whites and women, respectively; adulthood DBP differed significantly between men and women, but did not differ significantly between races. The prevalence of hypertension showed significant sex difference (men>women) in whites and significant race difference in both sexes.

Table 2 presents pair-wise Pearson correlations between childhood baseline and follow-up values of BMI and insulin in the total sample and by race and hypertension groups, adjusted for covariates where appropriate. All correlation coefficients of the Z-transformed variables of BMI and insulin at baseline and follow-up were calculated, with adjustment for follow-up years. The cross-lagged correlations. Pearson correlation coefficients of the Z-transformed variables (Z scores) were derived from the standardized variables (Z scores) by race and sex. The cross-lagged correlations were adjusted for age and sex by regression residual analyses.
coefficients were significantly different from zero ($P<0.05$), but did not differ significantly between races and between normotensives and hypertensives except for the correlations between baseline BMI and follow-up insulin.

Figure 1 presents cross-lagged path analysis of childhood BMI and insulin. After adjusting for age, race, sex, and follow-up years, the path coefficient from baseline BMI to follow-up insulin ($\beta_2=0.33$) was significantly greater than the path coefficient from baseline insulin to follow-up BMI ($\beta_1=-0.02$), with $P<0.001$ for difference between $\beta_1$ and $\beta_2$. Autocorrelation also known as tracking correlation of BMI ($r_2$) were significantly greater than that of insulin ($r_3$). The variance ($R^2$) of

### Table 1. Descriptive Data of Study Variables in Baseline and Follow-Up Childhood, Adulthood by Race and Sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whites (n=630)</th>
<th>Blacks (n=360)</th>
<th>$P$ Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>n</td>
<td>252</td>
<td>378</td>
<td>130</td>
</tr>
<tr>
<td>Childhood baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>10.6 (3.1)</td>
<td>10.5 (3.1)</td>
<td>10.5 (3.4)</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>18.5 (3.9)</td>
<td>18.5 (4.1)</td>
<td>18.2 (3.9)</td>
</tr>
<tr>
<td>Insulin, $\mu$U/mL</td>
<td>10.0 (9.9)</td>
<td>11.2 (8.5)</td>
<td>10.5 (9.9)</td>
</tr>
<tr>
<td>Childhood follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>15.8 (2.4)</td>
<td>15.8 (2.5)</td>
<td>16.1 (2.3)</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>22.4 (4.6)</td>
<td>22.1 (4.9)</td>
<td>23.0 (5.3)</td>
</tr>
<tr>
<td>Insulin, $\mu$U/mL</td>
<td>11.0 (6.3)</td>
<td>11.7 (7.4)</td>
<td>11.3 (7.5)</td>
</tr>
<tr>
<td>Adulthood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>31.9 (7.5)†</td>
<td>30.4 (7.7)</td>
<td>29.7 (8.1)</td>
</tr>
<tr>
<td>Follow-up years§</td>
<td>16.2 (6.8)‡</td>
<td>14.6 (7.1)</td>
<td>13.5 (7.5)</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>29.2 (6.5)</td>
<td>27.8 (8.0)</td>
<td>28.5 (7.0)‡</td>
</tr>
<tr>
<td>Insulin, $\mu$U/mL</td>
<td>12.7 (10.0)</td>
<td>11.5 (7.4)</td>
<td>12.1 (9.6)†</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td></td>
<td></td>
<td>116.1 (10.5)‡</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td></td>
<td></td>
<td>72.1 (9.1)‡</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td></td>
<td></td>
<td>35 (13.9)†</td>
</tr>
</tbody>
</table>

Continuous variables are presented as means (SD). BMI indicates body mass index; and BP, blood pressure.

*P values for race difference in continuous metabolic variables were adjusted for age.

Sex difference within race groups: †$P<0.05$; ‡$P<0.01$.

§Follow-up period from the time point of last childhood survey.

||Individuals who took medications were excluded.

### Table 2. Pearson Correlation Coefficients Between BMI and Insulin in Childhood

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>Baseline BMI</th>
<th>Baseline Insulin</th>
<th>Follow-Up BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total*</td>
<td>Baseline insulin</td>
<td>0.32</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Follow-up BMI</td>
<td>0.83</td>
<td>0.25</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Follow-up insulin</td>
<td>0.35</td>
<td>0.16</td>
<td>0.49</td>
</tr>
<tr>
<td>Whites/blacks†</td>
<td>Baseline insulin</td>
<td>0.31/0.33</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Follow-up BMI</td>
<td>0.83/0.83</td>
<td>0.23/0.26</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Follow-up insulin</td>
<td>0.31/0.44‡</td>
<td>0.11/0.25</td>
<td>0.46/0.54</td>
</tr>
<tr>
<td>Normotensives/ hypertensives§</td>
<td>Baseline insulin</td>
<td>0.26/0.46</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Follow-up BMI</td>
<td>0.81/0.86</td>
<td>0.19/0.37</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Follow-up insulin</td>
<td>0.25/0.62‖</td>
<td>0.09/0.33</td>
<td>0.42/0.68</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

*Adjusted for age, sex, race, and follow-up years. Correlation coefficients $>0.09$ are significant ($P<0.05$).

†Adjusted for age, sex, and follow-up years. Correlation coefficients $>0.11$ for whites and $0.14$ for blacks are significant ($P<0.05$).

‡$P=0.022$ for race difference between normotensives and hypertensives.

§Adjusted for age, gender, race and follow-up years. Correlation coefficients $>0.10$ for normotensives and $0.25$ for hypertensives are significant ($P<0.05$).

‖$P<0.001$ for difference between normotensives and hypertensives.
follow-up BMI explained by baseline predictors was greater than that of follow-up insulin. RMR and CFI were 0.063 and 0.93, respectively, indicating a relatively good fit to the observed data according to the criteria of RMR<0.05 and CFI>0.90.

Figure 2 presents cross-lagged analysis models of childhood BMI and insulin in normotensive and hypertensive groups, adjusted for age, race, sex, and follow-up years. The path coefficient (β) from baseline insulin to follow-up BMI did not differ significantly between normotensive and hypertensive groups (P=0.919). The path coefficient (β) from baseline BMI to follow-up insulin was significantly greater in the hypertensive group than in the normotensive group (0.59 versus 0.24; P<0.001). Model fitting parameters were RMR=0.069 and CFI=0.93 in the normotensive group and RMR=0.047 and CFI=0.94 in the hypertensive group.

Figure 3 shows the mediation effect of childhood follow-up insulin on the childhood baseline BMI–adult hypertension association, adjusting for age, race, sex, and follow-up years. The total effect of BMI on hypertension measured as standardized regression coefficient (βTot=0.143; P<0.001) was estimated without insulin in the model. Indirect effect 1 (β1=0.774) was significantly greater than indirect effect 2 (β2=0.038), with the overall indirect effect being 0.029 (0.774x0.038). The percentage of the total effect mediated by childhood insulin was estimated at 21.1% (P<0.001).

Because there were wide ranges of follow-up years during childhood and from childhood to adulthood, the path coefficients (β1 and β2) were estimated in tertile subgroups of follow-up years. β1 and β2 did not differ significantly between tertile subgroups of follow-up years during childhood (Table S1 in the online-only Data Supplement) and between tertile subgroups of follow-up years from last childhood survey to adulthood (Table S2).

Figure 1 presents the cross-lagged path analysis models of childhood BMI and insulin by race groups. Although the difference between β1 and β2 was significant (P<0.001) within each race group, the path coefficients (β1 and β2) did not show significant different between blacks and whites (P=0.880 for β1, and P=0.120 for β2). Autocorrelation also known as tracking correlation of BMI (r1) was significantly greater than that of insulin (r2). The variance (R2) of follow-up BMI explained by baseline predictors was greater than that of follow-up insulin. The difference in the tracking correlations (r1 and r2) and path coefficients (β1 and β2) did not differ significantly between blacks and whites. Model fitting parameters were RMR=0.064 and CFI=0.93 in whites and RMR=0.056 and CFI=0.94 in blacks.

Figure S2 illustrates age-adjusted, race-adjusted, sex-adjusted, and baseline value–adjusted yearly rates of change in insulin and BMI by quartiles of their baseline values in the total sample. The covariate-adjusted rate of change in insulin during the follow-up period significantly increased across increasing quartiles of baseline BMI (P<0.001). However, the rate of change in BMI did not show a significantly increasing trend across quartiles of baseline insulin (P=0.762). The results of the rates of change shown in Figure S2 were consistent with the BMI-to-insulin relationship using the cross-lagged path analyses shown in Figure 1.

Figure S3 illustrates age-adjusted, race-adjusted, sex-adjusted, and baseline value–adjusted yearly rates of change in insulin by quartiles of baseline BMI in hypertensive and normotensive groups. The covariate-adjusted rate of change in insulin during the follow-up period significantly increased across increasing quartiles of baseline BMI in both groups (P<0.001). Furthermore, the magnitude of the rate of change in insulin was greater in hypertensives than in normotensives. The results of the rate of change in insulin shown in Figure S3 were consistent with the BMI-to-insulin 1-directional relationship using the cross-lagged path analysis models shown in Figure 2.

Figures S4 and S5 show the mediated effect of childhood insulin on the childhood BMI–adult BP association, adjusting for age, race, sex, and follow-up years. For hypertensives who were under treatment, forced values of 140 and 90 mm Hg were given for SBP and DBP, respectively. The percentages of total effect on the childhood BMI–adult BP association mediated by childhood insulin were estimated at 21.5% (P<0.001) and 24.8% (P<0.001) for adulthood SBP and DBP, respectively.

Discussion
Although the strong intercorrelation between obesity and insulin resistance has been well documented in pediatric and adult populations,24–26 the temporal relationship between obesity and insulin resistance during different age period is incompletely elucidated. Despite the extensive studies showing...
that insulin treatment results in weight gain in diabetes mellitus patients, existing data in the general population are limited and inconsistent about whether an increase in obesity measures antedates increases in insulin levels or vice versa, or whether the relationship is bidirectional. The Bogalusa Heart Study has attempted to demonstrate the temporal relationship between BMI and insulin over a 3-year follow-up in children, adolescents, and young adults; but the results were not conclusive, especially in adolescents. The Normative Aging Study reported that the chicken-egg question of the dynamics of the relationship between insulin levels and obesity is far from straightforward because changes in either one may precede changes in the other using the 4 successive examinations with mean intervals of 3.7, 3.3, and 3.0 years in adults. Previous studies have used traditional longitudinal analysis models that cannot specifically address the causal relation. The present study examined the temporal relationship between BMI and insulin levels in a longitudinal cohort of black and white children using a cross-lagged path analysis model, a powerful statistical approach to dissecting a causal relationship between intercorrelated variables. The results indicated that increased BMI at baseline preceded increased insulin levels at follow-up during childhood, with blacks and whites showing similar patterns of this 1-directional relationship. The findings from this and our previous study in children support the notion that the temporal nature of the dynamics of the relationship between obesity and hyperinsulinemia begins in early life.

It is generally considered that obesity measures and insulin levels can influence each other based on pathophysiological and metabolic mechanisms. The adipose tissue is crucial in regulating insulin sensitivity through increased adipocyte size, decreased numbers of insulin receptors, increased levels of circulating free fatty acids, and the accumulation of lipids in target tissues (lipotoxicity). On the contrary, there are mechanisms by which hyperinsulinemia could lead to obesity through affecting dietary intake (carbohydrate craving) or other mechanisms. Furthermore, there is overwhelming evidence for the effect of insulin therapy on body weight increase in diabetic patients. Several explanations for the mechanisms by which intense insulin treatment causes weight gain have been suggested, including hyperphagia after hypoglycemic stimuli, alteration of physical activity level, the anabolic or lipogenic actions of insulin, and decreased glycoursia. The current study found that baseline hyperinsulinemia did not lead to follow-up obesity. These observations suggest that the mechanisms for the insulin therapy–induced obesity in diabetic patients might be different from those for the association between obesity and hyperinsulinemia as a compensatory indicator of insulin resistance in the general population.

Obesity, especially increased central adiposity, and obesity-induced insulin resistance are major risk factors for essential hypertension. Obesity and hyperinsulinemia may increase BP through multiple mechanisms, including (1) physical compression of the kidneys by fat in and around the kidneys, (2) activation of the renin–angiotensin–aldosterone system, (3) direct effects of insulin to stimulate renal sodium reabsorption, and (4) sympathetic stimulation of the heart, blood vessels, and kidney. In addition, the association of obesity and insulin resistance with hypertension has been reported to originate in early life. The current study provided evidence for the early origin hypothesis of hypertension by demonstrating that the 1-directional relationship from obesity to hyperinsulinemia in childhood was significantly stronger in the adult hypertensive group than in the normotensive group.

Insulin resistance is considered a key link between obesity and hypertension based on the above-described mechanisms. The joint or synergistic effect of obesity and insulin resistance on the development of hypertension has been documented in previous studies; however, data are lacking about the mediation effect of insulin resistance on the obesity–hypertension association. In the present study, the BMI–insulin directionality in childhood was first established in the cross-lagged analysis models, and then the temporal patterns were linked to adult hypertension developed 14.7 years later since the last survey in childhood. The results of the present causal mediation analysis showed that although the childhood BMI–adult hypertension association was partially mediated by hyperinsulinemia (21.1%), it was much smaller than the direct effect of childhood BMI on adult hypertension (78.9%). The findings of this study suggest that the underlying pathophysiological and metabolic mechanisms for the obesity–hypertension relationship might be more important than mechanisms for the effect of insulin resistance on hypertension. No data in this regard are available for comparison; further studies are needed to validate the findings from the current study.

**Perspectives**

The current study demonstrates that increased BMI levels preceded hyperinsulinemia in childhood in a longitudinal assessment of the directionality analysis between BMI and insulin in childhood using a cross-lagged path analysis model. Importantly, this 1-directional relationship was much stronger in hypertensives than in normotensives. A significant mediation effect of childhood insulin on the childhood BMI–adult hypertension association was demonstrated. These findings of the causal inference analysis of childhood BMI and insulin in relation to adult hypertension would improve our understanding of the pathobiology, mechanisms, and natural history of human essential hypertension and facilitate selection of novel therapeutic and intervention strategies by targeting at the causal factors, especially early in life, to prevent subsequent hypertension.

**Acknowledgments**

The Bogalusa Heart Study is a joint effort of many investigators and staff members whose contribution is gratefully acknowledged. We especially thank the Bogalusa, LA, school system, and most importantly the children and adults who have participated in this study over many years. We wish to thank the reviewers for their insightful comments.

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**Disclosures**

None.
References


Novelty and Significance

What Is New?

- The current study demonstrates that increased BMI levels predicted hyperinsulinemia in childhood using a cross-lagged path analysis model.
- This 1-directional relation was much stronger in hypertensives than in normotensives.
- A significant mediation effect of childhood insulin on the childhood BMI–adult hypertension association was demonstrated.

What Is Relevant?

- These findings of the causal inference analysis of childhood BMI and insulin in relation to adult hypertension would improve our understanding of the pathobiology, mechanisms, and natural history of human essential hypertension and facilitate selection of novel therapeutic and intervention strategies by targeting at the causal factors, especially early in life, to prevent subsequent hypertension.

Summary

Elevated BMI preceded increased insulin during childhood, with blacks and whites showing similar patterns of the 1-directional relationship. The temporal sequence from baseline BMI to follow-up insulin in childhood was significantly stronger in hypertensives than in normotensives in adulthood. The effect of childhood BMI on adult hypertension was partially mediated by childhood insulin.
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Authors have no conflict of interest.
**Supplement Table S1.** Cross-lagged path coefficients (95% confidence intervals) of BMI and insulin by tertile groups of follow-up years in childhood, with adjustment for covariates*

<table>
<thead>
<tr>
<th>Follow-up years in childhood</th>
<th>Insulin→BMI</th>
<th>BMI→Insulin</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β₁  95%CI</td>
<td>β₂  95%CI</td>
<td></td>
</tr>
<tr>
<td>2.0~3.5 years (n=330)</td>
<td>-0.020 -0.065~0.026</td>
<td>0.304 0.207~0.401</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3.6~5.9 years (n=330)</td>
<td>0.031 -0.026~0.087</td>
<td>0.294 0.188~0.400</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6.0~14.7 years (n=330)</td>
<td>-0.001 -0.083~0.082</td>
<td>0.369 0.247~0.49</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Covariates included age, gender, race and follow-up years.

† p-values for difference between β₁ and β₂ were adjusted for age, gender, race and follow-up years.
**Supplement Table S2.** Cross-lagged path coefficients (95% confidence intervals) of BMI and insulin in hypertension and normal groups, with adjustment for covariates*, by tertile groups of follow-up years from the second measurement in childhood to adulthood

<table>
<thead>
<tr>
<th>Follow-up years</th>
<th>Insulin → BMI</th>
<th>BMI → Insulin</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β₁ 95%CI</td>
<td>β₂ 95%CI</td>
<td></td>
</tr>
<tr>
<td>Normotensive (n=870)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0-9.0 years (n=290)</td>
<td>0.040 -0.034~0.114</td>
<td>0.380 0.270~0.490</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9.1~17.2 years (n=290)</td>
<td>-0.061 -0.214~0.092</td>
<td>0.160 0.040~0.280</td>
<td>0.008</td>
</tr>
<tr>
<td>17.3-30.2 years(n=290)</td>
<td>-0.058 -0.134~0.018</td>
<td>0.250 0.136~0.364</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive (n=120)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2-17.8 years (n=40)</td>
<td>-0.073 -0.308~0.162</td>
<td>0.500 0.186~0.814</td>
<td>0.007</td>
</tr>
<tr>
<td>17.9~23.9 years (n=40)</td>
<td>0.083 -0.152~0.318</td>
<td>0.790 0.378~1.202</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24.0-29.7 years(n=40)</td>
<td>-0.061 -0.214~0.092</td>
<td>0.600 0.345~0.855</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Covariates included age, gender, race and follow-up years.
† p-values for difference between β₁ and β₂
Supplement Figure S1. Cross-lagged analysis models of childhood BMI and insulin in whites and blacks, adjusted for race, age, gender, and follow-up years

$\beta_1, \beta_2 =$ cross-lagged path coefficients; $r_1 =$ synchronous correlations; $r_2, r_3 =$ tracking correlations; $R^2 =$ variance explained;

Goodness-of-fit: RMR=0.064 and CFI=0.93 for whites; RMR=0.056 and CFI=0.94 for blacks;

Coefficients different from 0: * p<0.05, ** p<0.01

p=0.120 for difference in $\beta_2$s between whites and blacks

Baseline BMI

Baseline Insulin

Follow-up BMI

Follow-up Insulin

$\beta_1 = 0.03$ (Whites)

$\beta_1 = 0.02$ (Blacks)

$\beta_2 = 0.31**$ (Whites)

$\beta_2 = 0.40**$ (Blacks)

$\beta_2 = 0.31**$ (Blacks)

$\beta_2 = 0.40**$ (Blacks)

$r_1=0.31**$ (Whites)

$r_1=0.33**$ (Blacks)

$r_2=0.84**$ (Whites)

$r_2=0.84**$ (Blacks)

$r_3=0.02$ (Whites)

$r_3=0.12*$ (Blacks)

(R²=0.69 for Whites)

(R²=0.69 for Blacks)

(R²=0.10 for Whites)

(R²=0.21 for Blacks)
**Supplement Figure S2.** Age-, race-, gender- and baseline value-adjusted yearly rates of change (Δ) of insulin and BMI by quartiles of their baseline values in the total sample

- **Δ Insulin (μU/mL/year):**
  - I: 0
  - II: 0
  - III: 0
  - IV: 1
  - p < 0.001 for trend

- **Δ BMI (kg/m²/year):**
  - I: 0
  - II: 0.8
  - III: 0.8
  - IV: 0.8
  - p = 0.762 for trend
Supplement Figure S3. Age-, race-, gender- and baseline value-adjusted yearly rate of change (Δ) of insulin by quartiles of baseline BMI in the hypertensive and normotensive groups.

Baseline BMI Quartiles

Hypertensives

Normotensives

p<0.001 for trend

p<0.001 for trend
Supplement Figure S4. Mediation effect of childhood insulin on the childhood BMI-adult systolic BP association * p<0.001

Indirect Effect
\[ \beta_{\text{ind}} = \beta_1 \times \beta_2 = 0.053^* \]

Total Effect \( \beta_{\text{tot}} = 0.248^* \)

Mediation Effect = 21.5%*

Indirect Effect 1 \( \beta_1 = 0.384^* \)

Indirect Effect 2 \( \beta_2 = 0.136^* \)

Direct Effect \( \beta_{\text{dir}} = 0.193^* \)
Supplement Figure S5. Mediation effect of childhood insulin on the childhood BMI-adult diastolic BP association
* p<0.001

Indirect Effect
$\beta_{\text{Ind}} = \beta_1 \times \beta_2 =0.054^*$

Indirect Effect 1
$\beta_1=0.384^*$

Indirect Effect 2
$\beta_2=0.139^*$

Total Effect $\beta_{\text{Tot}}=0.214^*$
Mediation Effect=24.8%*

Childhood BMI at Baseline

Adulthood Diastolic BP

Direct Effect $\beta_{\text{Dir}}=0.158^*$