Research Article

The Relationship between Changes in Weight Status and Insulin Resistance in Youth

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This study examined changes in insulin resistance (IR) in 120 youth over two years. IR was quantified via homeostatic model (HOMA-IR), and weight status changes were quantified via body mass index (BMI). When all participants were considered, the mean HOMA-IR and BMI increased 13.4% and 1.65 units, respectively. Change in BMI z-score and percent change in HOMA-IR were moderately associated ($r = 0.39$). Follow-up analyses were performed for the following weight groups: NN (normal at baseline and two years later), NO (normal to overweight), ON (overweight to normal), and OO (overweight at both points). The NO group had a greater change in HOMA-IR ($+50\%$) compared to other groups: ON (-8%), NN ($+2\%$), and OO (-0.1%) ($P < .05$). The association between changes in BMI z-score and HOMA-IR was $r = 0.49$ when only the NO and ON groups were included. These results reinforce the importance of preventing youth from becoming overweight to control IR.

1. Introduction

Insulin resistance (IR) is a precursor to type II diabetes, and recent reports show that 52% to 72% of overweight and obese youth have IR [1, 2]. While numerous cross-sectional studies have noted positive associations ($r = 0.31$ to 0.85) between insulin and measures of adiposity in youth, the relationships between change in weight status and change in IR have not been examined thoroughly [2–8]. The few longitudinal studies of youth have consistently reported that change in weight is positively associated with change in insulin or IR and negatively associated with insulin sensitivity [9–11]. However, these studies have induced weight loss by an intervention and have not examined what occurs in response to natural changes in weight status.

The current investigation will add to our understanding of the relationship between changes in weight status and IR by directly comparing changes in IR in youth who increased, decreased, or maintained their weight status over a two-year period. Analyses were first conducted with all participants in one group. Secondary analyses were conducted to compare IR among four weight groups, as described in the Methods section. We hypothesized that a larger increase in IR would occur in the participants who were normal weight and became overweight compared to those who remained normal weight. Also, we expected that a larger decline in IR would occur in participants who were overweight and became normal weight compared to those who remained overweight two years later.

2. Methods

2.1. Participants. The participants were enrolled in the Cardiovascular Health in Children III (CHIC) study, Cohort 5 (J.S. Harrell, P.I.). The CHIC III study was a longitudinal investigation assessing risk factors for cardiovascular disease in youth from rural North Carolina, taking place from 2000 to 2003. Of the 1566 participants in Cohort 5, the mean ages

at baseline and followup were 9.6 ± 1.1 years and 11.5 ± 1.0 years, respectively. The sex and racial composition of this cohort was 50% female, 50% male, 53% Black, 36% White, and 11% Other races. A total of 120 children and adolescents were selected from the 1566 participants to participate in this study, based on their weight status as described in the Group Analyses section. The age of participants in this investigation was similar to the original cohort (mean ages 9.8 ± 1.0 years at baseline and 11.6 ± 1.0 years at followup). There were slightly more males (62%), and White participants (56%), compared to the original cohort.

2.2. Procedures. All data were collected at baseline and two years later, termed baseline and followup in this study. Prior to data collection, the participants and their parents signed assent and consent forms, respectively, and all procedures were reviewed and approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Data were collected at the participants' schools by trained research assistants. Height was measured using a stadiometer (Perspective Enterprises, Portage, MI), and body mass was assessed via electronic scale (Model 2101KL, Healthometer Medical, Bridgewater, IL). BMI was calculated from these measurements (kg/m^2). Fat mass and fat free mass were estimated from measures of percent body fat, obtained from sum of skinfolds taken at the subscapular and triceps sites. These measures were taken in triplicate using Lange calipers (Cambridge Scientific, Cambridge, MD), according to the guidelines set forth by NHANES III [12]. Equations specific to each sex, race, and pubertal status were then applied to estimate percent body fat [13]. In order to ensure strong intra- and interrater reliability, respectively, all research assistants were trained by the same investigator, and height, body mass, and skinfolds were measured by more than one research assistant for every tenth participant. If the measurement for any variable was greater than pre-established quality control criteria, the research assistant was not permitted to participate in future measurements for that variable.

Researchers have noted that pubertal status [5, 7, 14, 15] and aerobic fitness [16] influence HOMA-IR; thus, both measures were included in this investigation. Pubertal development was quantified using self-report questionnaires [17]. Aerobic fitness was assessed using a multistage sub-maximal cycle ergometer test, the Physical Work Capacity 195 or PWC_{195} [18]. The workload corresponding to a heart rate of 150–170 bpm was used to predict the maximal volume of oxygen uptake (pVO_2max), and strong correlations ($r = 0.81$) have been shown between this test and measured VO_2max in children [18]. The results of the test were expressed in mL of oxygen per kg fat-free mass per minute (VO_2/kg_{FFM}), to eliminate the effect of fat mass.

Blood was drawn using standard venipuncture methods, between 7 and 9 am, following an 8-hour fast. The samples were centrifuged, and the plasma was stored in vials and frozen in a −80°C freezer for later analysis. Insulin was measured from the stored plasma using radioimmunoassay procedures (Linco, St. Charles, MO), while glucose was analyzed via automated hexokinase oxidase procedures. These values were used to calculate IR using the homeostatic model assessment equation (HOMA-IR); (fasting insulin (μU/mL) multiplied by fasting glucose concentration (mmol/L))/22.5 [19]. Several recent investigations have shown that HOMA is both reliable and valid for use in pediatric populations [20–22].

2.3. Statistical Analysis. Initially, the statistical analyses were performed with all participants combined into one group ($n = 120$). The percent change in HOMA-IR ((follow-up − baseline)/baseline) was calculated for each participant. Likewise, change in weight status was analyzed by calculating the z-score of BMI change (follow-up BMI z-score minus baseline BMI z-score). The relationship between percent change in IR and change in BMI z-score was examined using Pearson correlations. This association was then examined after controlling for change in pubertal status and aerobic fitness, expressed in mL/kg_{FFM}/min (VO_2/kg_{FFM}).

To establish which variable had the greatest influence on HOMA-IR, we repeated these correlation analyses using percent changes in insulin and glucose as the dependent variables. The alpha level was set at $P < .05$, and 95% confidence intervals were computed for the correlations. All statistical analyses were conducted using SAS Statistical Software, Version 9.1 (Cary, NC).

2.4. Group Analyses of Weight Status Change. For the group analyses of weight status change, participants were divided into four groups (NO, NN, ON, OO) based upon their BMI percentile at baseline and followup. BMI percentile was derived from the Centers for Disease Control and Prevention (CDC) growth charts from the year 2000 [23]. Normal weight was defined as >5th and <85th BMI percentile for age and sex, while overweight was defined as ≥85th BMI percentile for age and sex. The NO group was comprised of participants ($n = 35$) who were normal weight at baseline and overweight at followup. These individuals were selected from participants in the original cohort who met these criteria ($n = 60$) and had complete data (35 out of 60). A comparison group, NN, was comprised of 35 participants who were normal weight at both time points. This group was randomly selected from participants from the original cohort who matched those in the NO group by sex, race (Black, White, or Other), and pubertal status at baseline. Conversely, the ON group was comprised of 25 participants who were overweight at baseline and normal weight at followup and had complete data available (25 out of 35 total). Participants for the corresponding comparison group, OO, ($n = 25$) were randomly selected from eligible participants who matched those in the ON groups by sex, race, and pubertal status at baseline.

A one-way ANOVA was computed to compare the following variables between the four weight groups at baseline: age, pubertal stage, body mass, height, BMI, BMI percentile, VO_2/kg_{FFM}, glucose, insulin, and HOMA-IR. A Mantel-Haenszel chi-square was calculated to assess group

differences at baseline for the categorical variables race and sex. To assess group differences in percent change in HOMA-IR and BMI change z-score, one-way ANOVAs were computed. Finally, the association between percent change in IR and change in BMI z-score was examined for the two groups that altered their weight status (NO and ON), using Pearson correlations. Partial correlations between these variables were calculated after controlling for changes in pubertal status and VO_2/kg_{FFM}. These correlations were repeated using percent change in insulin and glucose, respectively, in place of percent change in HOMA-IR to determine which variable was driving the change in HOMA-IR.

3. Results

3.1. All Participants. Descriptive characteristics of all participants are presented in Table 1. With the exception of a fairly high BMI, none of the other characteristics were remarkable. The Pearson correlation between BMI change z-score and percent change in HOMA-IR was 0.39, $P < .05$. After controlling for changes in pubertal status and aerobic fitness (VO_2/kg_{FFM}), the partial correlation increased slightly to 0.40; $P < .05$ (Table 2).

The correlations between percent change in glucose and BMI change z-score were not significant when all participants were included ($P = .14$); therefore no further analyses were conducted using glucose. However, the Pearson correlations and partial correlations for BMI change z-score and percent change in insulin were significant and nearly identical to those for percent change in HOMA-IR (Table 2).

3.2. Weight Group Analysis. Descriptive characteristics of the four weight groups are presented in Table 3. When comparing the four groups, there were no differences for sex but there were significant differences for race, such that the OO and ON groups had fewer Black participants than the NN and NO groups (χ^2: $P < .05$). Despite similar medians and ranges of pubertal stages in all four groups ($P > .05$), participants in the NO were approximately one year younger than participants in the other groups ($P < .05$). There were no group differences in glucose at baseline but the OO group had larger mean values for insulin and HOMA-IR, compared to all other groups ($P < .05$).

Over the two-year study period, the NO group had a greater percent change in HOMA-IR (+50%) than all other groups, as shown in Table 3 ($P < .05$). The NN group had a small increase in HOMA, and the ON group had a slight decrease, while the OO group changed very little over the two-year study period. Group differences for percent change in insulin were identical to those for percent change in HOMA-IR (Table 3). When analyzing percent change in glucose, there were significant differences ($P < .05$) between the NN versus ON and OO groups (Table 3). The ON group was the only one to show a reduction in glucose.

The correlation between BMI change z-score and percent change in HOMA-IR was 0.49 ($P < .05$) when only the NO and ON groups were analyzed (Table 2). This relationship
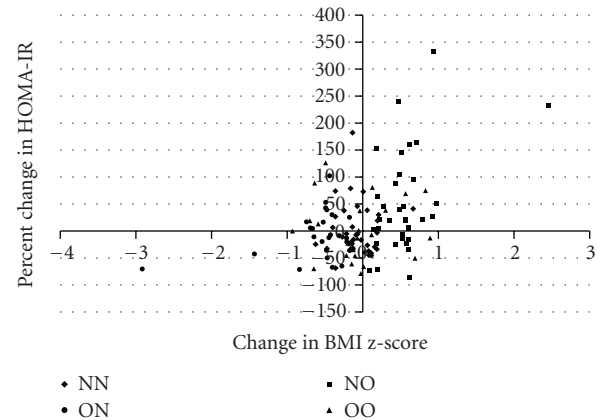

Figure 1: Scatterplot of the relationship between percent change in HOMA-IR and BMI change z-score, depicted by weight group.

can be seen by comparing these groups in the scatterplot in Figure 1. Controlling for changes in VO_2/kg_{FFM} and pubertal status did not alter the relationship significantly, as the correlation was 0.50 (Table 2). Repeating the correlations for the NO and ON groups with insulin and glucose in place of HOMA-IR revealed associations of 0.31 and 0.49, respectively.

4. Discussion

This investigation is one of the first to explore the relationship between natural progressions in weight status and changes in HOMA-IR over a two-year period in youth. Changes in weight status were not artificially manipulated by an intervention; some children started normal weight and became overweight, while some who were overweight became normal weight. When analyzing all participants as one group, there was a significant correlation ($r = 0.39$) between BMI change z-score and percent change in HOMA-IR even after accounting for any change in pubertal status or aerobic fitness ($r = 0.40$). This suggests that changes in pubertal status and aerobic fitness did not influence the positive relationship between changes in BMI z-score and HOMA-IR. Similar associations were found in an investigation of 9-10-year-old girls followed up ten years later [24]. In that investigation, a correlation of 0.24 was reported between change in BMI and HOMA-IR and similar to the current study; these authors did not use a weight change intervention. Therefore, there appears to be a weak to moderate, positive relationship between naturally occurring alterations in weight status and IR in youth.

4.1. Changes in HOMA-IR among the Weight Groups. As expected, HOMA-IR increased in the NO group and decreased in the ON group. The change in BMI z-score over the two-year period was remarkably similar in these groups, as it increased by 0.55 in the NO group and decreased by 0.60 in the ON group. Despite these similarities, the 7.7% reduction in HOMA-IR in the ON group was smaller than expected; this may be attributed to the relatively low

HOMA-IR in the ON group at baseline. When comparing participants who became overweight (NO group) to those who remained normal weight (NN group), the 50% increase in HOMA-IR in the NO group was much larger than the 2% increase seen in the NN group. This suggests that becoming overweight is related to substantial increases in HOMA-IR that are not present when normal weight status is maintained. Taken together, these findings imply that changes in HOMA-IR may be most sensitive to natural increases in weight status, compared to decreases in or maintenance of weight status. To our knowledge, no previous investigation has directly compared participants using these weight status groups.

The lack of differences in the percent change in HOMA-IR between the OO and ON groups may be attributable to several factors. First, the mean HOMA-IR value for the ON group was 3.3 units at baseline, which was slightly lower than expected for overweight participants. This relatively low baseline value limits the capacity for further reduction in HOMA-IR in response to weight status change. Second, research has shown that insulin sensitivity declines as youth mature and pass through puberty [7, 14, 15]. In this investigation, most participants advanced by at least one pubertal stage over the two-year period. The ON group had the highest median pubertal stage at followup, which may have increased their resistance to insulin and decreased any weight-related reductions in IR. A third factor that may explain the similar changes in HOMA-IR between the OO and ON groups is the magnitude of weight status change [11, 25, 26]. For example, Reinehr et al. found significant improvements in insulin sensitivity only when obese children decreased their BMI standard deviation score by ≥ 0.5 (or 2.2 BMI kg/m^2) over a one-year period [11]. A similar investigation found that reductions in BMI SD score of ≥ 0.5 were also needed in order to elicit significant reductions in HOMA-IR after one year, and the reduction of BMI in that group was 3.2 kg/m^2 [26]. In the current investigation, the ON group had a mean BMI reduction of 0.9 kg/m^2, which suggests that the weight status reduction may have been too small in magnitude to influence IR. Finally, the degree of overweight may influence the amount of change in IR. For example, Savoye et al. found reductions in HOMA-IR of 1.5 units in a group of obese participants who decreased their BMI by 1.7 kg/m^2 in one year [27]. The starting BMI for their group was 35.8 kg/m^2, however, which is much higher than the baseline BMI of 21.4 kg/m^2 seen in our ON group. Taken together, these factors may explain why we saw a small percent decrease in IR in the ON group despite a 0.60-unit reduction in BMI changes z-score and subsequently, why we did not observe significant differences between the OO and ON groups.

The Pearson correlation between BMI change z-score and percent change in HOMA-IR in the NO and ON participants was moderate in strength ($r = 0.49$). The partial correlations between these variables were nearly identical after controlling for changes in pubertal status and VO$_2$ per kg of fat-free mass, suggesting that they did not influence these associations. These results disagree with cross-sectional studies that show positive relationships between pubertal

TABLE 1: Descriptive statistics (mean $\pm$ standard deviation) at baseline and follow-up two years later, presented for all participants.

	Baseline	Follow-up
n	120	
Sex (females, males)	62, 58	
Race (black, white, other)	58, 56, 6	
Age (years)	9.8 ± 1.0	11.6 ± 1.1
Median pubertal stage (range)	2 (1–4)	3 (1–5)
Body Mass (kg)	40.9 ± 12.2	51.4 ± 13.1
Height (cm)	141.3 ± 8.8	152.8 ± 9.5
BMI (kg/m^2)	20.2 ± 4.2	21.9 ± 4.4
Change in BMI (kg/m^2)	1.65 ± 2.49	
BMI percentile	75.4 ± 22.2	76.8 ± 21.9
VO$_2$/kg$_{FFM}$	47.4 ± 11.4	48.9 ± 11.0
Glucose (mmol/L)	5.1 ± 0.5	5.1 ± 0.5
Percent Δ Glucose	0.97 ± 12.1	
Insulin (pmol/L)	102.8 ± 61.1	102.1 ± 65.3
Percent Δ Insulin	10.8 ± 62.3	
HOMA-IR	3.4 ± 2.1	3.3 ± 2.4
Percent Δ HOMA-IR	13.4 ± 68.8	

status [5] and IR and negative relationships between fitness and IR in children and adolescents [16]. However, with regard to pubertal status, the changes in our participants were generally quite small which may explain their insignificant role in these relationships. The majority of participants (55%) increased by one pubertal stage over the two-year study period, while 28% did not change pubertal stage, 14% increased by two stages, and only 3 participants advanced three stages. Also, changes in fitness over the two-year period were small, ranging from -0.1 to 2.8 ml/kg$_{FFM}$/min. This likely explains why we failed to see a relationship between changes in fitness and IR, despite a previous investigation that reported a correlation of -0.41 between VO$_2$max in mL/kg$_{LBM}$/min and fasting insulin [16].

4.2. HOMA-IR versus Fasting Insulin. In general, the results of this investigation were nearly identical when either percent change in HOMA-IR or percent change in insulin was used as the dependent variable in the correlation analyses (Table 2). This suggests that insulin was the driving force behind HOMA-IR, and the influence of glucose was quite small. This was also evident in the weight group comparisons at baseline, as there were no group differences in glucose but the OO group had significantly higher insulin and HOMA-IR compared to all other groups. Our findings agree with previous research showing strong associations between fasting insulin and HOMA-IR [28]. In fact, the correlation between HOMA-IR and insulin was 0.98 at baseline and 0.99 at follow-up ($P < .05$), while the correlation between HOMA-IR and glucose was 0.51 and 0.24, respectively, ($P < .05$). Thus, in our apparently healthy participants, HOMA-IR did not yield stronger associations than insulin alone, and this agrees with results from previous research supporting the use of HOMA-IR [22, 29].

TABLE 2: Pearson correlations (95% confidence intervals) between z-score of change in BMI and percent change in HOMA-IR and insulin, before and after controlling for changes in pubertal status and VO_2/kg_{FFM}.[*]

	Sample size	z-score of Δ BMI	z-score of Δ BMI, controlling for changes in pubertal status and VO_2/kg_{FFM}
Percent Δ HOMA-IR: All participants	120	0.39 (0.22 to 0.53)	0.40 (0.23 to 0.54)
Percent Δ HOMA-IR: NO and ON groups	60	0.49 (0.26 to 0.66)	0.50 (0.28 to 0.67)
Percent Δ insulin: All participants	120	0.40 (0.24 to 0.54)	0.42 (0.25 to 0.55)
Percent Δ insulin: NO and ON groups	60	0.49 (0.26 to 0.66)	0.51 (0.29 to 0.68)

[*] All correlations were $P < .05$.

TABLE 3: Descriptive statistics (mean ± standard deviation) at baseline and follow-up two years later, presented by weight status group.

	NN ($n = 35$)		NO ($n = 35$)		ON ($n = 25$)		OO ($n = 25$)	
	Baseline	Follow-up	Baseline	followup	Baseline	followup	Baseline	followup
Sex (females, males)	17, 18		17, 18		14, 11		14, 11	
Race (black, white, other)	21, 13, 1		21, 13, 1		8, 15, 2		8, 15, 2	
Age (years)[*]	9.8 ± 0.9	11.7 ± 0.9	9.2 ± 1.0	11.1 ± 1.0	10.2 ± 1.0	12.0 ± 1.0	10.1 ± 1.1	12.0 ± 1.1
Median pubertal stage (range)	2 (1–4)	3 (1–5)	2 (1–4)	3 (1–4)	2 (1–4)	4 (2–4)	2 (1–4)	3 (1–5)
Body mass (kg)[†]	34.2 ± 5.3	42.8 ± 6.5	34.9 ± 5.6	49.8 ± 7.6	45.9 ± 8.8	51.6 ± 6.3	53.6 ± 16.1	65.2 ± 18.9
Height (cm)[*]	141.0 ± 7.3	152.4 ± 8.1	137.0 ± 8.2	148.4 ± 8.9	145.8 ± 8.7	158.5 ± 9.6	143.4 ± 9.1	153.9 ± 9.2
BMI (kg/m^2)[†]	17.1 ± 1.6	18.4 ± 1.7	18.5 ± 1.1	22.5 ± 1.8	21.4 ± 2.3	20.5 ± 0.9	25.7 ± 5.3	27.2 ± 6.0
BMI change z-score[^^]	−0.07 ± 0.24		0.55 ± 0.40		−0.60 ± 0.55		−0.07 ± 0.47	
BMI percentile[‡]	50.8 ± 24.4	51.8 ± 23.1	76.0 ± 8.0	90.2 ± 3.1	89.2 ± 2.9	75.3 ± 9.3	95.3 ± 3.9	94.4 ± 4.2
VO_2/kg_{FFM}[^]	51.5 ± 10.9	53.8 ± 9.7	47.9 ± 10.4	47.9 ± 10.0	45.9 ± 12.0	47.2 ± 9.4	42.2 ± 11.9	43.4 ± 10.1
Glucose (mmol/L)	4.9 ± 0.5	5.1 ± 0.4	5.0 ± 0.4	5.1 ± 0.5	5.2 ± 0.4	5.0 ± 0.3	5.3 ± 0.5	5.0 ± 0.5
Percent Δ Glucose[††]	5.1 ± 12.9		2.4 ± 11.2		−2.3 ± 10.0		3.6 ± 12.3	
Insulin (pmol/L)[**]	84.0 ± 71.5	75.0 ± 56.9	92.4 ± 49.3	116.0 ± 78.5	100.0 ± 31.9	93.8 ± 53.5	144.5 ± 67.4	127.8 ± 55.6
Percent Δ Insulin[§]	−2.8 ± 42.8		43.8 ± 84.8		−7.2 ± 38.2		1.6 ± 52.2	
HOMA-IR[**]	2.7 ± 2.4	2.5 ± 2.1	3.0 ± 1.8	3.9 ± 3.0	3.3 ± 1.1	3.0 ± 1.9	4.9 ± 2.4	4.1 ± 1.8
Percent Δ HOMA-IR[§]	2.1 ± 48.5		49.7 ± 93.5		−7.7 ± 43.0		−0.8 ± 55.5	

[*] $P < .05$; NO < all other groups at baseline, [§] $P < .05$; NO versus NN, ON, and OO, [†] $P < .05$; NN and NO < ON < OO at baseline, [‡] $P < .05$; NN < NO < ON and OO at baseline, [^] $P < .05$; NN < OO at baseline, [††] $P < .05$; NN versus ON and OO, [**] $P < .05$; NN, NO, and ON < OO at baseline, [^^] $P < .05$, ON < NN and OO < NO.

As with any investigation, there are inherent strengths and limitations. One of the strengths of this study is the inclusion of participants who changed their weight status favorably and unfavorably as well as participants who did not change weight status. Likewise, this study is one of the few to describe the natural progression of the HOMA-IR in youth who underwent favorable changes in weight status by moving from overweight to normal weight, as the majority of research focuses on youth who move from normal weight to overweight status. A final strongpoint of this investigation is the consideration of pubertal status and aerobic fitness, as it is likely that they are related to weight status and HOMA-IR in youth.

Some limitations of this investigation include the relatively small sample sizes in each of the weight groups and the breadth of BMI values in the overweight category ($\geq$85th percentile). If more participants were included, the overweight groups may have been divided further, into the "at risk for overweight" and "overweight" groups, as described by the CDC [23]. Another limitation is the use of self-report measures of pubertal status. While some research has reported high correlations ($r = 0.82$) among self- and physician-generated ratings of Tanner stage in adolescent girls [30], other studies have weaker relationships [31]. Also, there were slight inequities for age and race, which may have impacted HOMA-IR values in this investigation, as research shows that black females had higher insulin and HOMA-IR values compared to White girls, regardless of pubertal stage [24]. Additionally, cut-points ranging from 3.16 to 4.0 for HOMA-IR have been used to classify IR in children and adolescents, yet there is no universally accepted value for use in youth [2, 22]. This complicates the interpretation of

results, as different conclusions can be formulated depending upon which cut-point is used. As a result, we did not dichotomize individuals as insulin resistant or not. Once a consensus is reached regarding these cut-points, normal and overweight participants could be compared using these insulin resistance classifications. The weight group analysis could be considered both a strength, as mentioned above, or a weakness. As a weakness, the groups have limited power, which could skew our findings. Also, although determined a priori, the criteria for allocation to a group were artificial. There is no reason why a person in the normal group cannot have a large change in BMI; yet because they do not cross the cut-point, they do not enter the "overweight" group. Thus our grouping does not allow for any conclusions regarding a large change in BMI, without a change in categorization. Finally, we are unable to determine temporality of these relationships using the current design. As a result, we cannot determine if changes in weight status caused changes in HOMA-IR or vice versa and instead can only comment upon their associations.

5. Conclusion

In youth, changes in BMI z-score and percent change in HOMA-IR over two years are positively related. Specifically, participants who underwent natural increases in weight status and became overweight had substantial increases in HOMA-IR, and the magnitude of these changes was greater than those for youth who decreased or maintained their weight status. These results reinforce the importance of preventing overweight during childhood.

Acknowledgment

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