



## Original Contribution

# Evaluating the Indirect Effect of Infant Weight Velocity on Insulin Resistance in Young Adulthood: A Birth Cohort Study From the Philippines

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The authors assessed the relation between infant weight velocity and adult insulin resistance, specifically evaluating whether adult size and body fat distribution mediated the association. Data were from the Cebu Longitudinal Health and Nutrition Survey (Cebu, the Philippines), in which a birth cohort was followed to age 22 years ( $n = 1,409$ ; 1983–2005). Insulin resistance was measured using homeostasis model assessment of insulin resistance (HOMA-IR). Weight velocity (g/month) from 0 to 4 months and from 0 to 24 months was assessed. The authors examined direct and total associations between early growth and adult HOMA-IR in linear regression models and used a nonparametric bootstrapping procedure to test indirect effects through adult body mass index (BMI; weight (kg)/height (m)<sup>2</sup>) and waist circumference. Infant weight velocity was positively associated with adult BMI and waist circumference, which positively predicted HOMA-IR. There were no total or direct effects of immediate postnatal weight velocity (0–4 months) on adult HOMA-IR, although indirect effects through BMI and waist circumference were significant. Weight velocity from 0 to 24 months positively predicted HOMA-IR among males only, while indirect effects were significant in both sexes. In a relatively lean sample of young adults from a population with rising rates of diabetes and cardiovascular disease, the authors found evidence for small indirect effects of infant weight velocity on adult insulin resistance mediated through adult BMI and waist circumference.

body mass index; growth; insulin resistance; waist circumference

Abbreviations: BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; SGA, small-for-gestational-age.

Longitudinal studies show that insulin resistance is strongly predictive of the development of type 2 diabetes (1). Small birth size and faster growth in infancy and childhood are associated with insulin resistance and type 2 diabetes (2–9). These findings have been interpreted as support for the “thrifty phenotype” hypothesis, which suggests that poor nutrition in early life produces physiologic and metabolic adaptations to ensure an adequate supply of nutrients to essential organs such as the brain at the expense of peripheral organs like the pancreas (10). Such changes during critical developmental periods are proposed to have permanent effects on insulin-glucose metabolism.

Although epidemiologic data support a relation between faster early growth and later insulin resistance, the underlying biologic mechanisms are still poorly understood. While

early growth may have irreversible effects on insulin-glucose metabolism, it is also known to influence the development of obesity (11), which itself is associated with insulin resistance (12, 13). As such, it is difficult to determine whether early growth affects later insulin resistance directly as a result of “programming” of insulin-glucose metabolism and/or affects it indirectly through its influence on adult body composition. It has been suggested that through mediation analysis, which allows partitioning of relations into direct and indirect pathways, epidemiologists may better describe the underlying mechanisms of observed associations (14).

Our objective in the current study was to use a mediation approach to assess the relation between infant weight velocity and adult insulin resistance, specifically evaluating whether

adult body mass index (BMI) and waist circumference mediate the association. Data were obtained from a large birth cohort of Filipinos who have been followed into young adulthood. Prior research in this sample has documented associations between birth size and blood pressure, lipid profiles, and inflammatory status, establishing a likely link between early nutrition or growth and adult cardiovascular disease risk (15–17). Here we extend these analyses by examining the association between early weight velocity and adult insulin resistance using methods capable of distinguishing the role of body composition and fat patterning as possible mediating influences. To clarify the importance of weight velocity at different ages, we examined the immediate post-natal period (0–4 months) as well as the infancy and early childhood periods combined (0–2 years).

## MATERIALS AND METHODS

### Study population

Data were from the Cebu Longitudinal Health and Nutrition Survey, a community-based cohort study of infants born in 1983–1984 in Metro Cebu, the second-largest metropolitan area in the Philippines (18). In 1983–1984, the Metro Cebu area was comprised of 243 administrative units; 33 (17 rural and 16 urban) were randomly selected. All pregnant women residing in these communities who gave birth during a 1-year period from 1983 to 1984 were invited to participate ( $n = 3,327$ ). The resulting child sample ( $n = 3,080$ ) was representative of singleton births in Metro Cebu. Data were collected during the last trimester of pregnancy, immediately following birth, and then bimonthly for 2 years. Seven follow-up surveys were conducted in 1991–1992, 1994, 1998, 2002, 2005, 2007, and 2009. In 2005, biomarker data were collected in the full sample. In the present analysis, we used data from the longitudinal survey (0–2 years) and the 2005 follow-up survey.

Of the 616 participants lost to follow-up from 0 to 24 months, 155 died (25%), while the remainder were not found or were no longer living in the study area. Of the 552 participants lost to follow-up between 24 months of age and the 2005 follow-up, 55 died (10%). The remaining losses were predominantly due to migration outside of the study area.

Because prematurity may influence insulin sensitivity, we excluded preterm births (<37 weeks' gestation;  $n = 119$ ) from the analytic sample. We also excluded women who reported being pregnant at the time of the 2005 survey ( $n = 81$ ). We compared baseline characteristics of the analytic sample with subjects who were in the sample at baseline. Birth weight and length did not differ between the 2 groups. Persons lost to follow-up were more likely to be urban residents and to have more highly educated mothers, but there were no significant differences in household assets, maternal height, maternal age, or maternal parity. Weight velocity from 0 to 4 months was greater among persons retained in the sample, which may have reflected slower growth among those who subsequently died during infancy.

### Infant anthropometric measures

Infant weight was measured using hanging scales (CMS Weighing Equipment Ltd., London, United Kingdom) to the

nearest 10 g (model HIW10; 10-kg capacity), progressing to the nearest 100 g (model HIW25; 25-kg capacity) as infants aged. Infants were weighed with minimal clothing and without diapers, shoes, or blankets. Weight velocity (kg/month) from 0 to 4 months and from 0 to 24 months was calculated as the change in weight (kg) between 2 measurements divided by the time interval (months) between those measurements. We chose the 0- to 4-month interval in an effort to capture the first months of life, a period hypothesized to be critical for the development of obesity (19). We chose the 0- to 2-year interval for comparability with other studies.

### Adult anthropometric measures

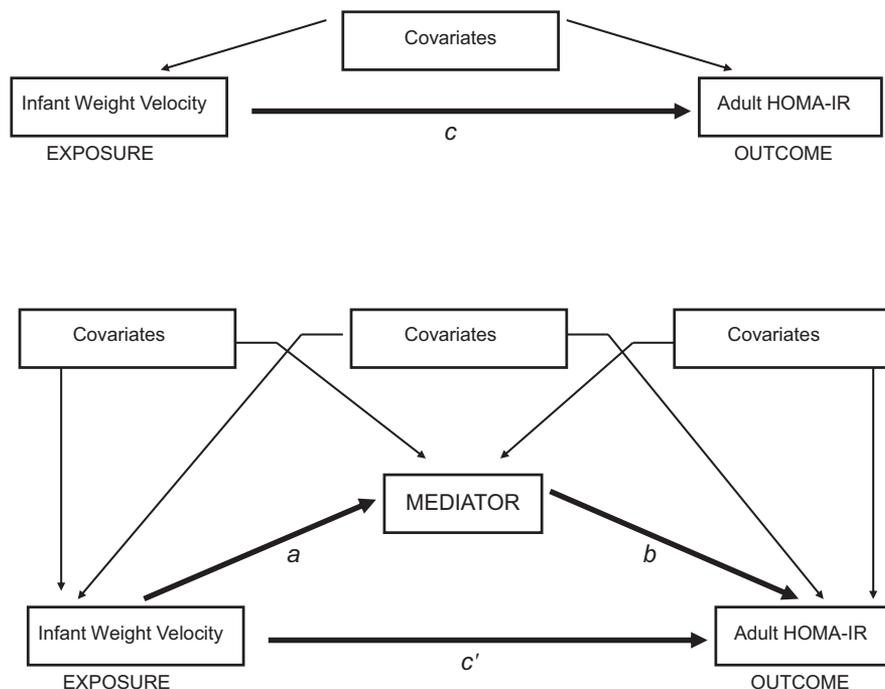
BMI was calculated (weight (kg)/height (m)<sup>2</sup>) from measured weight and height in 2005. Adults were weighed in light clothing using portable spring balance scales. Heights were measured without shoes using portable stadiometers. Waist circumference was measured at the midpoint between the bottom of the ribs and the top of the iliac crest. Data on BMI and waist circumference were log-transformed; therefore, geometric mean values and standard deviations are presented for these variables.

### Laboratory analyses

Participants were asked to fast overnight, and blood samples were collected by venipuncture the following morning using ethylenediaminetetraacetic acid-coated tubes. After mixing to inhibit clotting, a sterile disposable pipette was used to remove several drops of blood for immediate photometric measurement of glucose based on a glucose dehydrogenase method, using the OneTouch Ultra Blood Glucose Monitoring System (Lifescan; Johnson and Johnson, Milpitas, California). After separation, plasma samples were frozen and shipped on dry ice to the clinical laboratory facility at Northwestern University Hospital (Evanston, Illinois) for analysis of insulin levels using a commercially available enzyme immunoassay protocol (DY1065; R&D Systems, Minneapolis, Minnesota). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as  $22.5/(\text{insulin} \times \text{glucose})$  (20). The distributions of fasting insulin and HOMA-IR were skewed, so the values were log-transformed; geometric means and standard deviations are presented for these variables. Insulin resistance was defined as  $\text{HOMA-IR} > 4.65$  (21).

### Covariates

Gestational age was estimated from the mother's report of the date of her last menstrual period. In cases where this date was unknown, where pregnancy complications occurred, or where the infant weighed less than 2.5 kg at birth, gestational age was determined by nurses using the method of Ballard et al. (22). Small-for-gestational age (SGA) birth was defined as birth weight below the 10th percentile of individually customized birth weight percentiles, calculated according to the method described by Gardosi (23). In brief, this approach calculates an individually customized gestation-specific optimal birth weight by adjusting for physiologic variables such as maternal size, parity, and ethnicity



**Figure 1.** Conceptual model for a mediation analysis of the relation between infant weight velocity and adult insulin resistance. Using data from Cebu, the Philippines (1983–2005), the authors used linear regression analysis to examine the relations between infant weight velocity and adult body mass index and waist circumference (path *a*), the relations between body mass index and waist circumference and homeostasis model assessment of insulin resistance (HOMA-IR) (path *b*), and the relation between infant weight velocity and adult HOMA-IR (the direct effect; path *c'*). Path *c* (the total effect) is the path from infant weight velocity to adult HOMA-IR in a model with no mediator. Covariates on the left include participant's adult age, small-for-gestational-age status, mother's height, parity, urbanicity, and socioeconomic status.

while not adjusting for pathologic variables known to affect growth and birth weight.

Low birth weight was defined as a birth weight less than 2.5 kg. Maternal height (cm) was selected to represent the child's genetic size potential. Parity was reported by mothers at baseline. A multicomponent urbanicity scale (24) was chosen as an indicator of the community environment in which the child was raised. Socioeconomic status was represented by a summary assets score including 10 key household assets (home ownership, air conditioner, quality of home construction materials, television, tape recorder, refrigerator, electric fan, jeepny (minivan-type vehicle), automobile, and electricity).

All data were collected by project staff during in-home interviews. Quality control measures included extensive training and periodic interobserver reliability assessments. All procedures were reviewed and approved by the institutional review board of the University of North Carolina at Chapel Hill.

### Statistical analysis

Statistical analyses were performed using Stata, version 11.0 (StataCorp LP, College Station, Texas) and SPSS 17.0 for Windows (SPSS, Inc., Chicago, Illinois). Statistical significance was set at  $P < 0.05$ . Given the known sex differences in early growth and in the development of insulin resistance, all models were sex-stratified (25). While the

focus was on weight velocity in the first months of life (0–4 months), weight velocity from 0 to 2 years was also examined for comparability with other studies that examined longer intervals.

The INDIRECT macro in SPSS (26) was used to test the mediation hypotheses. The macro combines linear regression models with a bootstrapping method (26) to calculate indirect effects. Weight velocity, HOMA-IR, BMI, and waist circumference were modeled as continuous variables. Potential mediators were examined in separate models.

The conceptual model for the mediation analysis is illustrated in Figure 1. The INDIRECT macro incorporates several regression equations to obtain path coefficients for each relation. Linear regression was used to examine the relations between infant weight velocity and adult BMI and waist circumference (path *a*), between adult BMI and waist circumference and adult HOMA-IR (path *b*), and between infant weight velocity and adult HOMA-IR (the direct effect; path *c'*). The total effect (path *c*) is the association of infant weight velocity with adult HOMA-IR without the inclusion of mediators in the model.

The indirect effect was quantified using a bootstrapping method (with  $n = 5,000$  bootstrap resamples) recommended by MacKinnon (27) and further elaborated by Preacher and Hayes (26). There is a nonparametric approach to effect-size estimation and hypothesis-testing that makes no assumptions about the shape of the distributions of the variables or the sampling distribution of the statistic. Bias-

corrected and accelerated 95% confidence intervals were calculated (28), and point estimates of indirect effects were considered significant if zero was not contained in the confidence intervals.

For all models, separate interactions between infant weight velocity and SGA birth and low birth weight were tested. Since no interactions were found, these interaction terms were not included in the final models. Covariates hypothesized to be confounders of the relation between infant weight velocity and adult insulin resistance and the relations between adult BMI and waist circumference and adult insulin resistance included participant's adult age, mother's height, parity, urbanicity, and socioeconomic status (Figure 1). These same factors, along with SGA status, were considered as confounders of the relation between infant weight velocity and adult BMI and waist circumference.

## RESULTS

In infancy, the sample was generally undernourished. The prevalence of underweight (weight-for-age  $z$  score  $< -2$ ) at birth was 10% for males and 6% for females and substantially increased with age, such that by 2 years of age, 35% of sample infants were underweight (Table 1). The prevalence of stunting (length-for-age  $z$  score  $< -2$ ) at birth was 6% for males and 8% for females and substantially increased with age, such that by 2 years of age, 59% of sample infants were stunted (Table 1). The sample was relatively young and lean in adulthood (Table 1).

Table 2 presents results from regression models of the effect of infant weight velocity (0–4 months and 0–24 months) on adult BMI and waist circumference (Figure 1, path *a*). Weight velocity was positively associated with adult BMI and waist circumference. Adult BMI and waist circumference were positively associated with adult HOMA-IR (Figure 1, path *b*) (Table 3). Total and direct effects of infant weight velocity on adult HOMA-IR (Figure 1, paths *c* and *c'*) are shown in Table 4. In the models without mediators (total effect; Figure 1, path *c*), weight velocity from 0 to 4 months was not associated with adult HOMA-IR, while weight velocity from 0 to 24 months was positively associated with HOMA-IR among males only. In the models with mediators (direct effects; Figure 1, path *c'*), weight velocity was not associated with HOMA-IR.

Table 5 shows the indirect effects of infant weight velocity on HOMA-IR as mediated through adult BMI and waist circumference. The point estimates represent the product of coefficients (Figure 1, paths  $a \times b$ ), which is the amount HOMA-IR is expected to change for a 1-kg/month increase in weight velocity, indirectly through BMI or waist circumference. All models revealed significant, positive indirect effects of infant weight velocity on HOMA-IR through adult BMI and waist circumference. Indirect effects were slightly stronger via waist circumference than via BMI and among males as compared with females.

## DISCUSSION

To our knowledge, this is the first study to explicitly examine adult BMI and waist circumference as potential

mediators of the relation between infant weight gain and adult HOMA-IR in a young adult population with a low prevalence of overweight and obesity. Weight velocity both in the immediate postnatal period (0–4 months) and through early childhood (0–24 months) was positively associated with adult BMI and waist circumference, which were both positively associated with HOMA-IR. There were no total or direct effects of immediate postnatal weight velocity on young adult HOMA-IR, although small indirect effects mediated through adult BMI and waist circumference were observed. Weight velocity over a longer interval (0–24 months) was positively associated with HOMA-IR among males only (total effects; Figure 1, path *c'*), and indirect effects mediated through adult BMI and waist circumference were significant in both sexes.

Consistent with previous studies, infant weight gain was positively associated with adult BMI (29, 30) and waist circumference (9, 31–33). Understanding the relation between postnatal weight gain and adult BMI and waist circumference is important given the well-recognized relations between central obesity and insulin resistance (12, 13). As expected, adult BMI and waist circumference were both positively associated with adult HOMA-IR.

Although immediate postnatal weight velocity (0–4 months) was positively associated with adult BMI and waist circumference, there were no total effects on adult HOMA-IR (Figure 1, *c* paths). In the literature on developmental origins of health and disease, a number of investigators have reported that they found significant associations between early-life size and adult outcomes only after adjusting for current body size (34). Because we hypothesized that adult size lay in the causal pathway from infant weight velocity to adult HOMA-IR, we examined the indirect effects of weight velocity (0–4 months) on adult HOMA-IR as mediated through adult BMI and waist circumference. Significant, though small, positive indirect effects of immediate postnatal weight velocity on HOMA-IR through adult BMI and waist circumference were established. For example, for a 1-standard-deviation increase in weight velocity from 0 to 4 months (0.170 kg/month for males and 0.160 kg/month for females), HOMA-IR was expected to increase 3.4% and 3.2% among males and females, respectively, indirectly through waist circumference. Increases in HOMA-IR of this magnitude would only increase the percentage of insulin-resistant (HOMA-IR  $> 4.65$ ) adult males and females in the sample from 5.15% to 5.89% (0.74 percentage points) and from 7.75% to 7.81% (0.06 percentage points), respectively.

Overweight and insulin resistance were still relatively rare in the young adult sample. It is possible that the long-term effects of infant weight velocity on insulin-glucose metabolism are not yet evident. Future research conducted as the population ages may reveal a strengthening of the effects documented here, or perhaps long-term effects not yet apparent.

Notably, while not statistically significant, direct effects (Figure 1, *c'* paths) were all negative. Negative direct effects may explain our findings of significant indirect effects in the absence of total effects, suggesting masking of the total effect estimate by opposing direct and indirect effects of

**Table 1.** Selected Characteristics of Participants With Infant and Young Adult Measures, Cebu, the Philippines, 1983–2005<sup>a</sup>

Measurement	No. Missing From Full Sample (n = 1,409)	Males (n = 777)	Females (n = 632)	P Value <sup>b</sup>
<i>Infancy</i>				
Weight, kg				
0 months	0	3.04 (0.41)	2.97 (0.40)	<0.01
4 months	0	6.39 (0.76)	5.91 (0.69)	<0.001
2 years	54	10.09 (1.11)	9.47 (1.09)	<0.001
WAZ <sup>c</sup>				
0 months	0	−0.82 (0.88)	−0.68 (0.85)	<0.01
4 months	0	−0.88 (1.04)	−0.77 (0.97)	0.03
2 years	54	−1.69 (0.97)	−1.67 (0.99)	0.73
Weight velocity, kg/month				
0–4 months	0	0.86 (0.17)	0.75 (0.16)	<0.001
0–24 months	54	0.29 (0.01)	0.27 (0.01)	<0.001
% underweight (WAZ < −2)				
0 months	0	9.91	6.33	0.02
4 months	0	13.51	8.86	<0.01
2 years	54	35.33	34.71	0.81
LAZ <sup>c</sup>				
0 months	0	−0.44 (1.02)	−0.59 (1.02)	<0.01
4 months	0	−0.84 (1.02)	−1.06 (1.08)	<0.01
2 years	58	−2.32 (1.06)	−2.41 (1.10)	0.12
% stunted (LAZ < −2)				
0 months	0	6.01	8.38	0.09
4 months	0	11.23	18.58	<0.01
2 years	58	57.75	60.80	0.25
Gestational age, weeks	0	39.12 (1.61)	39.32 (1.69)	0.02
Household assets <sup>d</sup>	0	5.21 (2.05)	5.33 (1.92)	0.25
Household urbanicity <sup>e</sup>	0	40.90 (13.62)	41.10 (13.03)	0.79
Mother's education, years	0	7.47 (3.67)	7.38 (3.64)	0.67
Mother's age at child's birth, years	0	26.50 (5.94)	26.68 (5.88)	0.55
Mother's height, cm	0	150.61 (4.94)	150.51 (5.01)	0.72
Parity	0	2.25 (2.22)	2.25 (2.16)	0.99
<i>Adulthood</i>				
Age, years	0	21.47 (0.30)	21.46 (0.31)	0.61
Height, cm	0	163.00 (5.70)	151.15 (5.32)	<0.001
Weight, kg	0	55.79 (8.89)	46.46 (8.13)	<0.001
Body mass index <sup>f,g</sup>	0	20.78 (0.10)	20.09 (0.12)	<0.001
% overweight <sup>h</sup>	0	18.79	15.66	0.12
Waist circumference, cm <sup>g</sup>	0	71.70 (0.25)	67.65 (0.28)	<0.001
Fasting insulin level, µg/mL <sup>g</sup>	0	6.47 (0.13)	8.21 (0.19)	<0.001
HOMA-IR <sup>g,i</sup>	0	1.62 (0.03)	2.01 (0.05)	<0.001
% insulin-resistant <sup>j</sup>	0	5.15	7.75	<0.05

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; LAZ, length-for-age z score; WAZ, weight-for-age z score; WHO, World Health Organization.

<sup>a</sup> Values are means and standard deviations unless otherwise indicated.

<sup>b</sup> P value for comparison between the sexes.

<sup>c</sup> Calculated from the 2006 WHO growth standards (49).

<sup>d</sup> Socioeconomic status was represented by a summary assets score including 10 key household assets (home ownership, air conditioner, quality of home construction materials, television, tape recorder, refrigerator, electric fan, jeepny (minivan-type vehicle), automobile, and electricity). The total score could range from 1 to 11, as the score for household construction materials ranged from 0 to 2 (light, strong, or heavy).

<sup>e</sup> A multicomponent urbanicity scale (24) was chosen as an indicator of the child's community environment. The scale ranged from 0 to 70.

<sup>f</sup> Weight (kg)/height (m)<sup>2</sup>.

<sup>g</sup> Geometric mean and standard deviation.

<sup>h</sup> Body mass index > 23 (WHO-recommended cutpoint for Asian populations (50)).

<sup>i</sup> HOMA-IR was calculated as 22.5/(insulin × glucose) (20).

<sup>j</sup> Insulin resistance was defined as HOMA-IR > 4.65 (21).

**Table 2.** Regression Coefficients From Separate Regression Models of the Effect of Infant Weight Velocity on Adult Body Mass Index and Waist Circumference, Cebu, the Philippines, 1983–2005

Weight Velocity Measure (kg/month) and Variable <sup>a</sup>	Males			Females		
	No. of Subjects	$\beta^{b,c}$	95% CI	No. of Subjects	$\beta^{b,c}$	95% CI
0–4 months						
Adult BMI <sup>d</sup>	777	0.15*	0.09, 0.20	632	0.10*	0.02, 0.17
Adult WC, cm	777	0.11*	0.07, 0.15	632	0.07*	0.02, 0.12
0–24 months						
Adult BMI	750	1.01*	0.79, 1.23	605	0.64*	0.33, 0.94
Adult WC, cm	750	0.71*	0.55, 0.87	605	0.45*	0.24, 0.67

Abbreviations: BMI, body mass index; CI, confidence interval; WC, waist circumference.

\*  $P < 0.05$ .

<sup>a</sup> Data were log-transformed.

<sup>b</sup> Because adult BMI and WC were log-transformed variables, the  $\beta$  coefficients are interpreted as the percent change in BMI or WC expected with a 1-kg/month increase in weight velocity.

<sup>c</sup> Adjusted for participant’s adult age, small-for-gestational-age status, parity, mother’s height, urbanicity, and socioeconomic status.

<sup>d</sup> Weight (kg)/height (m)<sup>2</sup>.

early growth. Negative direct effects are biologically plausible. Immediate postnatal weight gain may have greater effects on lean mass as compared with fat mass (35), which would be expected to improve insulin sensitivity. Significant total effects of weight velocity over a longer period (0–24 months) on adult HOMA-IR in males are consistent with previous studies demonstrating a positive relation between infant and early childhood growth and insulin resistance in childhood (36, 37) and adulthood (9). Among sample males, for a 1-standard-deviation increase in weight velocity from 0 to 24 months (42.77 g/month), HOMA-IR was expected to increase 6% (total effect, without potential mediators). Considering the indirect effects mediated through waist circum-

ference, for the same 1-standard-deviation increase in weight velocity, HOMA-IR was expected to increase 7.3%. Increases of this magnitude would only increase the percentage of insulin-resistant (HOMA-IR > 4.65) adult males in the sample from 5.15% to 6.67% (1.52 percentage points). Many previous investigators pooled male and female data. An important addition to the literature is the finding that among females, weight velocity in the first 2 years was not directly associated with HOMA-IR.

Associations were larger in males than in females. The sex differences are not surprising, since sex hormones may have important influences on early-life growth and the development of body composition (38), as well as the risk of type 2 diabetes (39). Additionally, prior work in this sample has found that birth weight is inversely related to blood pressure and adverse lipid profiles measured in adolescence, with effects being stronger in males or, in some instances, being present only in males (15, 17). The present findings extend evidence for sex differences in long-term health effects in the Cebu Longitudinal Health and Nutrition Survey sample to the outcome of insulin resistance in early adulthood.

A focus of the critiques of mediation analysis by epidemiologists is the potential for biased estimates of the direct and indirect effects if confounding of the mediator-disease relation is not adjusted for (40, 41). The Cebu Longitudinal Health and Nutrition Survey includes a breadth of measurements that allow for inclusion of covariates known to be confounders of the mediator-disease relation, representing a major strength of the study. However, while we included many known confounders of the relation between adult size and HOMA-IR, the possibility of residual confounding or other unmeasured confounders which might create “collider bias” and inflate our estimates of the indirect effects (42) cannot be ruled out.

This analysis adds to the ongoing debate in the literature on developmental origins of health and disease regarding

**Table 3.** Regression Coefficients From Separate Regression Models of the Effect of Infant Weight Velocity on Adult Body Mass Index and Waist Circumference, Using HOMA-IR as the Dependent Variable and Body Mass Index and Waist Circumference as Independent Variables, Cebu, the Philippines, 1983–2005<sup>a</sup>

	Males (n = 777)		Females (n = 632)	
	$\beta^{b,c}$	95% CI	$\beta^{b,c}$	95% CI
Adult body mass index <sup>d</sup>	1.50*	1.20, 2.51	1.63*	1.34, 2.77
Adult waist circumference, cm	2.28*	1.87, 3.87	2.49*	2.08, 4.29

Abbreviations: CI, confidence interval; HOMA-IR, homeostasis model of insulin resistance.

\*  $P < 0.05$ .

<sup>a</sup> Data on all variables were log-transformed.

<sup>b</sup> Because data on both the independent variables and the dependent variable were log-transformed, the  $\beta$  coefficients are interpreted as the percent change in HOMA-IR expected with a 1% change in adult body mass index or waist circumference.

<sup>c</sup> Adjusted for participant’s adult age, parity, mother’s height, urbanicity, and socioeconomic status.

<sup>d</sup> Weight (kg)/height (m)<sup>2</sup>.

**Table 4.** Regression Coefficients for Total<sup>a</sup> and Direct<sup>b</sup> Effects of Infant Weight Velocity on Adult HOMA-IR<sup>c</sup>, Cebu, the Philippines, 1983–2005

Weight Velocity Measure (kg/month) and Effect Measure	Males			Females		
	No. of Subjects	$\beta^{d,e}$	95% CI	No. of Subjects	$\beta^{d,e}$	95% CI
0–4 months						
Total effect	777	0.12	–0.13, 0.37	632	–0.002	–0.30, 0.30
Direct effect (including BMI <sup>f</sup> )	777	–0.11	–0.35, 0.13	632	–0.17	–0.44, 0.10
Direct effect (including WC, cm)	777	–0.12	–0.36, 0.11	632	–0.16	–0.43, 0.12
0–24 months						
Total effect	750	1.41*	0.38, 2.45	605	0.76	–0.47, 1.99
Direct effect (including BMI)	750	–0.05	–1.09, 0.99	605	–0.38	–1.50, 0.74
Direct effect (including WC, cm)	750	–0.18	–1.20, 0.83	605	–0.30	–1.44, 0.83

Abbreviations: BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model of insulin resistance; WC, waist circumference.

\*  $P < 0.05$ .

<sup>a</sup> The total effect (Figure 1, path *c*) is the association of infant weight velocity with adult HOMA-IR with no mediators in the model.

<sup>b</sup> The direct effect (Figure 1, path *c'*) is the association of infant weight velocity with adult HOMA-IR with mediators in the model.

<sup>c</sup> Data on HOMA-IR were log-transformed.

<sup>d</sup> Because adult HOMA-IR was a log-transformed variable, the  $\beta$  coefficients are interpreted as the percent change in HOMA-IR expected with a 1-kg/month increase in weight velocity.

<sup>e</sup> Adjusted for participant's adult age, small-for-gestational-age status, parity, mother's height, urbanicity, and socioeconomic status.

<sup>f</sup> Weight (kg)/height (m)<sup>2</sup>.

how best to account for current size when modeling the relation between early growth and adult outcomes. While in most studies researchers have simply adjusted for adult size, others have questioned this approach, suggesting that it results in the statistical paradoxes known as “Simpson’s

paradox,” “Lord’s paradox,” and “suppression,” whereby the association between 2 variables can be reversed, diminished, or enhanced when another variable is statistically controlled for (43). The analytic approach used in this study accounts for current size by explicitly modeling the

**Table 5.** Indirect Effects of Infant Weight Velocity on Adult HOMA-IR as Mediated Through Adult Body Mass Index and Waist Circumference in 5,000 Bootstrap Samples<sup>a</sup>, Cebu, the Philippines, 1983–2005

Indirect Effects of Infant Weight Velocity, kg/month	Males			Females		
	No. of Subjects	Point Estimate <sup>b</sup>	BCA <sup>c</sup> 95% CI	No. of Subjects	Point Estimate <sup>b</sup>	BCA <sup>c</sup> 95% CI
0–4 months						
BMI <sup>d</sup>	777	0.23	0.14, 0.35	632	0.16	0.04, 0.29
WC, cm	777	0.24	0.14, 0.37	632	0.17	0.05, 0.31
0–24 months						
BMI	750	1.46	1.03, 2.10	605	1.06	0.57, 1.67
WC, cm	750	1.60	1.13, 2.28	605	1.15	0.63, 1.75

Abbreviations: BCA, bias-corrected and accelerated; BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model of insulin resistance; WC, waist circumference.

<sup>a</sup> In all models, results were controlled for participant's adult age, small-for-gestational-age status, parity, mother's height, urbanicity, and socioeconomic status.

<sup>b</sup> Point estimates represent the amount HOMA-IR is expected to change for a 1-kg increase in infant weight velocity, indirectly through BMI or WC.

<sup>c</sup> Confidence intervals include corrections for both median bias and skewness (28). Confidence intervals containing zero are interpreted as not significant.

<sup>d</sup> Weight (kg)/height (m)<sup>2</sup>.

hypothesized pathways linking early growth with insulin resistance *through* adult size rather than *adjusting for* adult size.

No total or direct effects of faster immediate postnatal weight velocity on adult HOMA-IR were detected; only small indirect effects were observed. Notably, there was no interaction between infant weight velocity and SGA status, indicating that in the study sample, faster postnatal growth had similar effects in participants born SGA and those who were not. These results suggest that in lower-income contexts where undernutrition and small birth size are common, the promotion of compensatory growth will not have substantial long-term negative consequences for insulin resistance if excess development of body fat and central obesity can be prevented. Faster weight gain in later childhood and adolescence has been more clearly associated with increased adult adiposity and central adiposity, as well as increased risk of impaired glucose tolerance and type 2 diabetes (35, 44). In making recommendations about early growth, it is important to consider both the short- and long-term consequences. We emphasize that in infancy the sample was generally undernourished, and the prevalence of underweight increased with the introduction of complementary foods when exposure to pathogens and diarrheal illness was more common (45). Past work in this sample suggests that improving infant nutrition would probably reduce short-term morbidity and increase infant survival (46, 47) while having positive effects on adult achievement and productivity (48). The present finding of minimal associations between immediate postnatal weight velocity and adult insulin resistance suggests that any deleterious long-term consequences of improved early-life nutrition on adult diabetes risk might be comparatively small.

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## REFERENCES

- Lillioja S, Mott DM, Spraul M, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J Med*. 1993;329(27):1988–1992.
- Crowther NJ, Cameron N, Trusler J, et al. Association between poor glucose tolerance and rapid post natal weight gain in seven-year-old children. *Diabetologia*. 1998;41(10):1163–1167.
- Jaquet D, Deghmoun S, Chevenne D, et al. Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth. *Diabetologia*. 2005;48(5):849–855.
- Barker DJ, Hales CN, Fall CH, et al. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia*. 1993;36(1):62–67.
- Newsome CA, Shiell AW, Fall CH, et al. Is birth weight related to later glucose and insulin metabolism?—a systematic review. *Diabet Med*. 2003;20(5):339–348.
- Eriksson JG, Forsen TJ, Osmond C, et al. Pathways of infant and childhood growth that lead to type 2 diabetes. *Diabetes Care*. 2003;26(11):3006–3010.
- Ong KK, Dunger DB. Birth weight, infant growth and insulin resistance. *Eur J Endocrinol*. 2004;151(suppl 3):U131–U139.
- Ravelli AC, van der Meulen JH, Michels RP, et al. Glucose tolerance in adults after prenatal exposure to famine. *Lancet*. 1998;351(9097):173–177.
- Fall CH, Sachdev HS, Osmond C, et al. Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of BMI gain during infancy: data from the New Delhi birth cohort. *Diabetes Care*. 2008;31(12):2349–2356.
- Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull*. 2001;60:5–20.
- Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr*. 2006;95(8):904–908.
- Felber JP, Golay A. Pathways from obesity to diabetes. *Int J Obes Relat Metab Disord*. 2002;26(suppl 2):S39–S45.
- Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444(7121):840–846.
- Hafeman DM, Schwartz S. Opening the Black Box: a motivation for the assessment of mediation. *Int J Epidemiol*. 2009;38(3):838–845.
- Adair LS, Kuzawa CW, Borja J. Maternal energy stores and diet composition during pregnancy program adolescent blood pressure. *Circulation*. 2001;104(9):1034–1039.
- McDade TW, Rutherford J, Adair L, et al. Early origins of inflammation: microbial exposures in infancy predict lower levels of C-reactive protein in adulthood. *Proc Biol Sci*. 2010;277(1684):1129–1137.
- Kuzawa CW, Adair LS. Lipid profiles in adolescent Filipinos: relation to birth weight and maternal energy status during pregnancy. *Am J Clin Nutr*. 2003;77(4):960–966.
- Adair LS, Popkin BM, Akin JS, et al. Cohort profile: the Cebu Longitudinal Health and Nutrition Survey [published online ahead of print May 27, 2010]. *Int J Epidemiol*. (doi: 10.1093/ije/dyq085).
- Gillman MW. The first months of life: a critical period for development of obesity. *Am J Clin Nutr*. 2008;87(6):1587–1589.
- Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. *Diabetes Care*. 1997;20(7):1087–1092.
- Stern SE, Williams K, Ferrannini E, et al. Identification of individuals with insulin resistance using routine clinical measurements. *Diabetes*. 2005;54(2):333–339.

22. Ballard JL, Novak KK, Driver M. A simplified score for assessment of fetal maturation of newly born infants. *J Pediatr*. 1979;95(5):769–774.
23. Gardosi J. New definition of small for gestational age based on fetal growth potential. *Horm Res*. 2006;65(suppl 3):15–18.
24. Dahly DL, Adair LS. Quantifying the urban environment: a scale measure of urbanicity outperforms the urban-rural dichotomy. *Soc Sci Med*. 2007;64(7):1407–1419.
25. Regitz-Zagrosek V, Lehmkuhl E, Mahmoodzadeh S. Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gen Med*. 2007;4(suppl B):S162–S177.
26. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods*. 2008;40(3):879–891.
27. MacKinnon D. Contrasts in multiple mediator models. In: Rose J, Chassin L, Presson C, et al, eds. *Multivariate Applications in Substance Use Research: New Methods for New Questions*. Mahwah, NJ: Lawrence Erlbaum Associates; 2000:141–160.
28. Efron B. Better bootstrap confidence intervals. *J Am Stat Assoc*. 1987;82(397):171–185.
29. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life—a systematic review. *Obes Rev*. 2005;6(2):143–154.
30. Ong KK. Size at birth, postnatal growth and risk of obesity. *Horm Res*. 2006;65(suppl 3):65–69.
31. Euser AM, Finken MJ, Keijzer-Veen MG, et al. Associations between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm. *Am J Clin Nutr*. 2005;81(2):480–487.
32. González DA, Nazmi A, Victora CG. Growth from birth to adulthood and abdominal obesity in a Brazilian birth cohort. *Int J Obes (Lond)*. 2010;34(1):195–202.
33. Corvalán C, Gregory CO, Ramirez-Zea M, et al. Size at birth, infant, early and later childhood growth and adult body composition: a prospective study in a stunted population. *Int J Epidemiol*. 2007;36(3):550–557.
34. Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet*. 2002;360(9334):659–665.
35. Sachdev HS, Fall CH, Osmond C, et al. Anthropometric indicators of body composition in young adults: relation to size at birth and serial measurements of body mass index in childhood in the New Delhi birth cohort. *Am J Clin Nutr*. 2005;82(2):456–466.
36. Ong KK, Petry CJ, Emmett PM, et al. Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. *Diabetologia*. 2004;47(6):1064–1070.
37. Crowther NJ, Cameron N, Trusler J, et al. Influence of catch-up growth on glucose tolerance and  $\beta$ -cell function in 7-year-old children: results from the Birth to Twenty study. *Pediatrics*. 2008;121(6):e1715–e1722.
38. Lampl M, Thompson AL, Frongillo EA. Sex differences in the relationships among weight gain, subcutaneous skinfold tissue and saltatory length growth spurts in infancy. *Pediatr Res*. 2005;58(6):1238–1242.
39. Ding EL, Song Y, Malik VS, et al. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2006;295(11):1288–1299.
40. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3(2):143–155.
41. Cole SR, Hernán MA. Fallibility in estimating direct effects. *Int J Epidemiol*. 2002;31(1):163–165.
42. Hafeman DM. A sufficient cause based approach to the assessment of mediation. *Eur J Epidemiol*. 2008;23(11):711–721.
43. Tu YK, Gunnell D, Gilthorpe MS. Simpson's paradox, Lord's paradox, and suppression effects are the same phenomenon—the reversal paradox. *Emerg Themes Epidemiol*. 2008;5:2. (doi: 10.1186/1742-7622-5-2).
44. Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N Engl J Med*. 2004;350(9):865–875.
45. Popkin BM, Adair L, Akin JS, et al. Breast-feeding and diarrheal morbidity. *Pediatrics*. 1990;86(6):874–882.
46. Mendez MA, Adair LS. Severity and timing of stunting in the first two years of life affect performance on cognitive tests in late childhood. *J Nutr*. 1999;129(8):1555–1562.
47. Martorell R, Horta BL, Adair LS, et al. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries. *J Nutr*. 2010;140(2):348–354.
48. Victora CG, Adair L, Fall C, et al. Maternal and child under-nutrition: consequences for adult health and human capital. *Lancet*. 2008;371(9609):340–357.
49. World Health Organization. WHO child growth standards based on length/height, weight and age. *Acta Paediatr Suppl*. 2006;450:76–85.
50. World Health Organization, International Association for the Study of Obesity, and International Obesity Task Force. *The Asia Pacific Perspective: Redefining Obesity and Its Treatment*. Sydney, Australia: Health Communications; 2000.