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Daily branched-chain amino acids intake and the risks of obesity and insulin resistance in children: a cross-sectional study

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Abstract

Objective: To investigate the association of daily branched-chain amino acids (BCAAs) intake with the risks of obesity and insulin resistance in children of mothers with gestational diabetes mellitus (GDM).

Methods: Daily BCAAs intake was calculated using a validated food frequency questionnaire in 996 children of mothers with GDM. The odds ratios (ORs) (95% confidence intervals) of childhood obesity and insulin resistance were obtained using logistic regression models.

Results: The multivariable-adjusted ORs for overweight and insulin resistance increased across quartiles of daily BCAAs intake (P for trend < 0.05). Multivariable-adjusted ORs for each 1 standard deviation increase in BCAAs intake were 1.37 (1.16–1.62) for overweight, and 1.19 (1.02–1.38) for insulin resistance. After additional adjustment of children's daily total energy intake, the OR was still significant for overweight risk but no longer significant for insulin

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resistance. There were positive associations of daily leucine, isoleucine and valine intake with the risks of overweight and insulin resistance.

Conclusions: Daily BCAAs intake was associated with increased risks of overweight and insulin resistance in children of mothers with GDM, but this association was not fully independent of children's daily energy intake. Restriction in dietary BCAAs may help prevent childhood obesity and insulin resistance.

Keywords

Obesity; Pediatrics; Insulin Resistance; Gestational Diabetes; Branched-Chain Amino Acids

Introduction

The branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, are essential amino acids for human beings (1). BCAAs are comparatively abundant in dietary proteins, constituting up to 15% - 20% of protein intake, which increase after intake of a meal containing proteins (1). A positive association was found between a BCAA-rich diet and metabolic health, including the regulation of body weight, muscle protein synthesis, and glucose homeostasis (2, 3). Moreover, some recent human studies found that elevated serum BCAA levels were associated with weight gain, insulin resistance and glucose metabolism abnormality in adults (4, 5). Increased serum BCAA levels were also associated with insulin resistance in a non-obese insulin-resistant fructose-fed rat model (6). A prospective study further demonstrated that serum BCAAs levels predicted the future risk of diabetes (7). In children, elevations in the circulating BCAAs levels were significantly associated with obesity in children and adolescents, which may independently predict future insulin resistance (8).

One meta-analysis reported that oral BCAA supplementation exerted modest influence on the circulating leucine profile, and the total BCAAs intake level was positively associated with the risk of type 2 diabetes (9). It was also reported that reduced dietary intake of BCAAs was associated with an improvement of glucose tolerance and body composition (10, 11). However, a study in young northern Chinese adults demonstrated that the dietary BCAA ratio was inversely associated with the risks of obesity, postprandial glucose and status of inflammation (12). Nevertheless, it is unclear whether excessive BCAAs intake is a risk factor for children's obesity and insulin resistance. We aimed to examine the association of daily BCAAs intake with the risks of overweight and insulin resistance among 996 children of mothers with gestational diabetes mellitus (GDM).

Methods

GDM screening process

Tianjin is the fourth largest city in China, only 30-min distance by train from Beijing. There are six central districts in Tianjin with about 4.3 million residents. In 1999, the Tianjin Women's and Children's Health Center launched an urban universal screening of GDM using the World Health Organization (WHO)'s criteria in all six central districts. The screening rate was reported to be >91% between 1999 and 2008 (13). We first invited all

pregnant women (at their 26–30 gestational weeks) to participate in a one-hour oral glucose tolerance test (OGTT) with 50-g glucose load in their community health centers. Then, those with glucose reading ≥7.8 mmol/L were referred to the Tianjin Women's and Children's Health Center to undergo a 2-hour OGTT with 75-g glucose load. If the pregnant women met the 1999 WHO's criteria of diabetes (fasting glucose ≥7 mmol/L or 2-h glucose ≥11.1 mmol/L) or impaired glucose tolerance (IGT) (2-h glucose ≥7.8 mmol/L and <11.1 mmol/L), they would be diagnosed as GDM (14).

Study Population

Totally 76,325 women were screened from 2005 to 2009, among whom 4644 women were diagnosed as GDM and 71,681 were free of GDM. We invited all 4644 GDM women to participate in the Tianjin Gestational Diabetes Mellitus Prevention Program (TGDMPP). From August 2009 to July 2011, a total of 1263 GDM women finished the baseline survey. A total of 996 children finished the follow-up survey, and had complete information of BMI and insulin resistance (Figure 1). The recruitment, inclusion and exclusion criteria have been described in detail elsewhere (15). We collected written informed consents from all participants, and this study was approved by the Human Subjects Committee of the Tianjin Women's and Children's Health Center.

Questionnaires and measurements

Mothers' information was collected by a self-administered questionnaire, including socio-demographic characteristics, such as age, marital status, education (< 13 years, 13–16 years, and ≥16 years), family income (<5000 yuan/month, 5000–8000 yuan/month, and ≥8000 yuan/month), and occupation; pregnancy outcomes (pre-pregnancy weight, weight gain during pregnancy, gestational age, and the number of births in the index pregnancy); and lifestyle in the past year, such as smoking status (non-smokers, former smokers, and current smokers), passive smoking, alcohol drinking status, sitting time and leisure-time physical activity (0 min/day, 1–29 min/day, and ≥30 min/day). Children's information was collected by another questionnaire completed by their mothers, including children's general information, such as gender, birth date, age, birth weight, birth length, lactation (exclusive formula, mixed or exclusive breast); history of diseases and medication; and routine activities (indoor and outdoor activities, screening watching time, and sleep duration) (16). A validated food frequency questionnaire to measure the children's frequency and quantity of intake of 35 major food groups and beverages during the past year was collected by children's mothers. The food frequency questionnaire asked these children about their frequency of "usual" consumption of 35 food categories, with response categories never, times/year, times/month, times/week, or times/day, and quantity of average consumption of gram or milliliter per time. The performance of the food frequency questionnaire has been validated in the China National Nutrition and Health Survey in 2002 [17]. Energy and daily BCAAs intake were calculated according to a food ingredient list published in 2002 (17). Children were divided into 4 groups according to BCAAs quartiles stratified by sex and age.

All mother-child pairs underwent a physical examination. Using the standardized protocol, all participants' height and weight were measured in light indoor clothing and without shoes by trained research doctors. Body mass index (BMI) was obtained by dividing weight in

kilograms by the square of height in meters. All mothers' pre-pregnancy BMI calculation used their self-reported pre-pregnancy weight and their measured height. Children's BMI calculation used their body weight and height examined at the study visit. Children's Z scores for BMI-for-age were calculated based on the WHO growth reference (18, 19). Children's BMI was classified as normal weight, BMI <85th percentiles; overweight, 85th percentile ≤ BMI <95th percentile; and obesity, BMI ≥95th percentile, according to the WHO age- and gender-specific growth reference (18, 19).

Whole blood specimens were collected from all participants after an overnight fast of at least 8 hours. Plasma glucose was measured using an automatic analyzer (TBA-120FR; Toshiba, Japan), and insulin was measured with chemiluminescence using a Siemens ADVIA Centaur CP Immunoassay System. The homeostatic model assessment was used to estimate insulin resistance (HOMA-IR) as previously described (20), and insulin resistance was defined as the upper quartile of HOMA-IR.

Statistical analysis

The general characteristics (continuous and categorical variables) of both mothers and children according to quartiles of children's daily BCAA intake levels were performed using the chi-square test or general linear model. Logistic regression models were used to estimate odds ratios of childhood overweight and insulin resistance according to children's daily different BCAA intake levels. BCAAs were evaluated in the following two ways: (1) as quartiles; and (2) as a continuous variable. All analyses were adjusted for maternal age, gestational age, education and smoking status, pre-pregnancy BMI and gestational weight gain, and children's sex, age, birth weight, and feeding status (categorical variables) (Model 1), and then children's lifestyles including outdoor physical activity time (continuous variables), screen watching time (continuous variables), and sleep time (categorical variables) (Model 2), as well as children's daily total energy intake (Model 3). All the statistical analyses were performed with the SPSS 25.0 for windows software package (IBM SPSS statistics 25). Two-sided P <0.05 was considered statistically significant.

Results

General characteristics of the study population are presented in Table 1. There were differences in sex composition, Z score for BMI-for-age, outdoor activity hour, daily energy intake, energy intake from fat, prevalence of overweight and insulin resistance among children with different daily BCAA intake levels (all P<0.05). Moreover, the linear regression analysis indicated that BCAAs and components were positively associated with HOMA-IR and BMI Z score (all P values <0.05, as shown in Table S1).

As shown in Table 2 and Figure S1, elevated levels of daily BCAA intake (assessed by quartiles) were associated with an increased risk of childhood overweight (P for trend<0.01). The multivariable-adjusted (maternal age at delivery, gestational age at delivery, education, current smoking, and children's age, sex, birth weight, feeding status, outdoor physical activity time, screen watching time, and sleep time - Model 2) odds ratios (ORs) of childhood overweight associated with each 1 standard deviation (SD) increase in daily intake of BCAAs, isoleucine, leucine and valine were 1.37 (95% confidence interval [95%

CI 1.16–1.62]), 1.38 (95% CI 1.16–1.63), 1.36 (95% CI 1.15–1.61), and 1.36 (95% CI 1.15–1.61), respectively. The association of daily intake of BCAAs, isoleucine, and leucine with the risk of childhood overweight attenuated but was still significant after further adjustment of children's daily energy intake (multivariable-adjusted Model 3).

Multivariable-adjusted ORs of childhood insulin resistance across quartiles of daily intake of total BCAAs were 1.00, 1.39, 1.52, and 1.71 (P for trend 0.018), respectively (Model 2, Table 3; Figure S2). There were positive associations of daily intake of isoleucine, leucine and valine with the risk of childhood insulin resistance. Multivariable-adjusted (Model 2) ORs of childhood insulin resistance associated with each 1 SD increase in daily intake of BCAAs, isoleucine, leucine and valine were 1.19 (95% CI 1.02–1.38), 1.19 (95% CI 1.03–1.39), 1.19 (95% CI 1.02–1.38), and 1.19 (95% CI 1.02–1.39), respectively. The positive associations of daily intake of BCAAs, isoleucine, leucine and valine with the risk of childhood insulin resistance were no longer significant after further adjustment of children's daily energy intake (multivariable-adjusted Model 3).

Discussion

The present study indicated that daily intake of BCAAs, leucine, isoleucine and valine was associated with increased risks of overweight and insulin resistance among children of mothers with GDM; however, this association was not fully independent of children's daily energy intake, especially for the risk of childhood insulin resistance.

The prevalence of pediatric obesity increased rapidly in recent decades worldwide (21). Many factors accounted for the rapid increase in pediatric obesity, including congenital and acquired factors. Maternal pre-pregnancy overweight and obesity, excess gestational weight gain were risk factors for the children's obesity; other childhood factors such as elevated energy intake, elevated screen time, reduced outdoor activity were also risk factors for childhood obesity(22–24). The present study indicated that daily dietary intake of BCAAs was independently associated with increased risks of childhood overweight and insulin resistance after adjustment of these major risk factors. However, the positive association of daily dietary intake of BCAAs with the risk of childhood insulin resistance was not independent of children's daily energy intake.

Low-fat diet or low-carbohydrate diet has been accepted as an effective intervention way for metabolic disorders (25). Recently, it is reported that protein restricted diet could help improve metabolic indexes, including obesity and insulin resistance in humans (10). Several recent studies further indicated that BCAA restriction may largely recapitulate the metabolic effects induced by the restriction of proteins (10, 26, 27). Cummings et al. pointed out that the restriction of dietary BCAAs significantly decreased body weight and adiposity, increased energy expenditure, and improved glucose tolerance and insulin sensitivity in animal experiments (28). There were very few studies on the effects of dietary BCAA restriction on metabolism in humans (29). In the present study, our data indicated dietary BCAAs intake was independently associated with childhood obesity and insulin resistance, however, this association was not fully independent of children's daily energy intake, especially for the risk of childhood insulin resistance. Large human clinical trials are needed

to assess whether dietary BCAA restriction can lose weight and improve metabolism among both adults and children, and whether above association is independent of daily energy intake.

The mechanisms mediating BCAAs and metabolic disorders were complicated. First, BCAA supplementation was shown to increase the activation of mammalian target of rapamycin (mTOR) and subsequent ribosomal protein S6 kinase (S6K) phosphorylation, which was coupled with insulin receptor substrate (IRS)-1 Ser-307 phosphorylation and decreased insulin-induced phosphoinositide 3-kinase (PI3K) activity, resulting in impaired insulin signaling (30, 31). Second, the metabolites of BCAAs were associated with the risks of obesity and insulin resistance. Researchers pointed out that 3-hydroxyisobutyrate dehydrogenase in the muscle tissue of rats decreased 50%, resulting in an elevation of catabolic intermediate of valine 3-hydroxyisobutyrate (3-HIB) (32, 33). In animals, 3-HIB is secreted from muscle cells, activates endothelial FA transport, stimulates muscle fatty acid uptake in vivo, and promotes muscle lipid accumulation and insulin resistance (34). In human studies, 3-HIB was shown to be related to insulin resistance in individuals with overweight and obesity, and changes in 3-HIB were associated with metabolic improvements with weight loss (35). Finally, Leucine supplementation led to abnormal catabolism of BCAA and the incompletely oxidized lipid species contributed to mitochondrial dysfunction in skeletal muscle in high fat diet-fed rats (36). BCAAs could also stimulate metabolic stress in islet β cells in animals (10). Impaired BCAAs catabolism may result in increased circulating levels of BCAAs that enhance their pathological effects on obesity and insulin resistance (6).

There were some strengths in our study. Our study enrolled a large sample of children of mothers with GDM. Data on a variety of confounding variables, such as the parameters of mothers before and during pregnancy; and indices of the children, including birth weight, lifestyles factors, and anthropometric indexes were collected and used in the final analysis. There were also some limitations in our study. This was a cross-sectional study, and more prospective studies should be warranted in the future. Moreover, the study samples in the present study were restricted to children of mothers with GDM, and the extrapolation of the conclusion to the whole children population should be scrupulous.

Conclusion

The present study indicated that dietary BCAAs intake was associated with increased risks of obesity and insulin resistance in children of mothers with GDM, however, the association of dietary BCAAs intake with the risk of insulin resistance was not independent of children’s daily energy intake. Thus, dietary BCAAs restriction may prevent these children from obesity and insulin resistance, and more clinical trials are needed to further verify this issue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

What is already known about this subject?

Several studies have reported a positive association of branched-chain amino acids via diet or plasma with the risks of obesity and insulin resistance in adults.

Question:

It is uncertain whether excessive branched-chain amino acid intake increases the risks of obesity and insulin resistance in children.

Findings:

Daily intake of branched-chain amino acids was associated with increased risks of overweight and insulin resistance in children of mothers with gestational diabetes mellitus.

What does your study add?

Our data indicated that excessive branched-chain amino acid intake increased the risks of obesity and insulin resistance in children, so restriction in nutrition ingredients such as branched-chain amino acids may be important to prevent childhood obesity and insulin resistance.

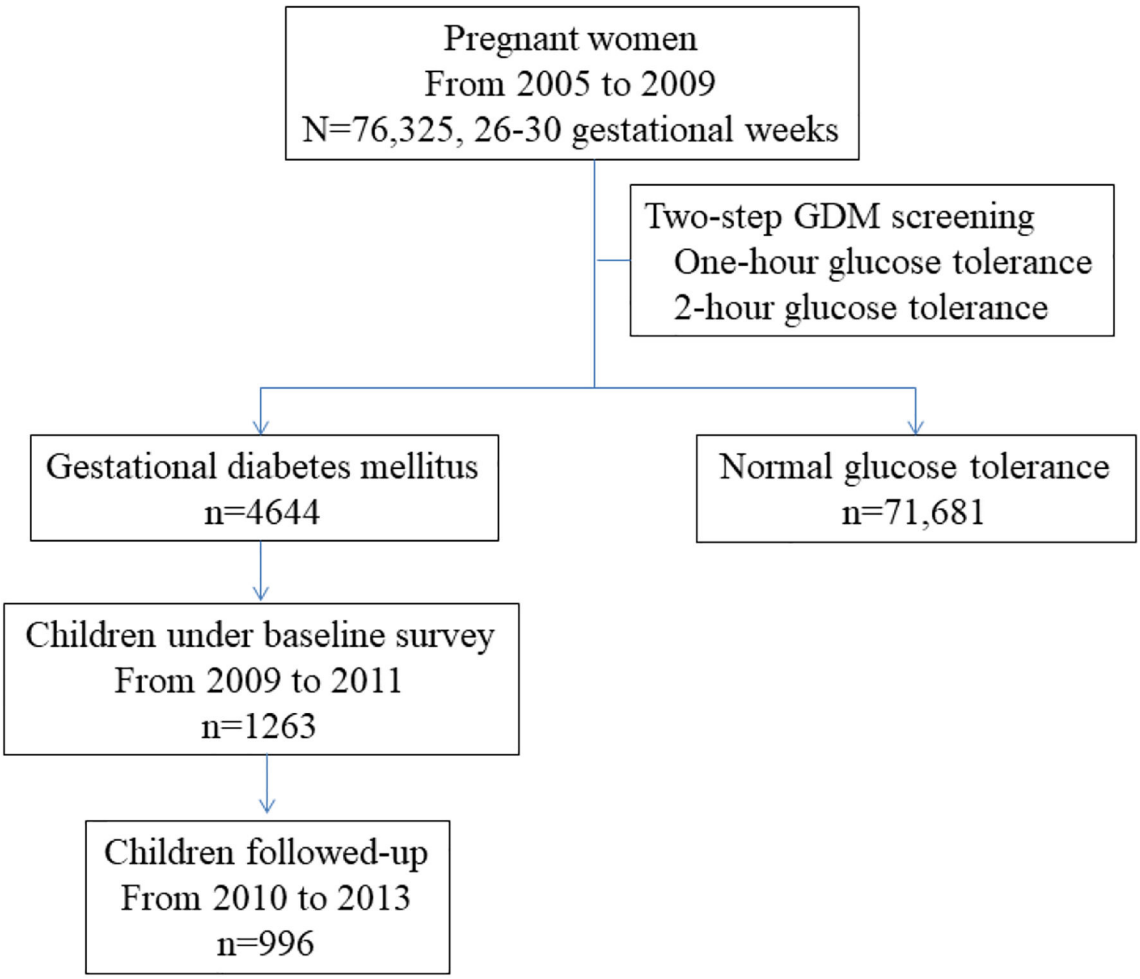

Figure 1.
Flow chart of subjects enrollment.
Abbreviation: *GDM* gestational diabetes mellitus

Table 1.

Clinical feature in children with different levels of daily branched-chain amino acids intake

	Quartiles of branched-chain amino acids				P value
	1	2	3	4	
No. of subjects	249	249	249	249	
Maternal characteristics					
Delivery age, years	31.3 ± 3.64	30.6 ± 3.4	31.4 ± 3.52	30.7 ± 3.56	0.027
Gestational age at delivery, weeks	39.0 ± 1.49	39.2 ± 1.34	39.1 ± 1.52	38.9 ± 1.63	0.19
Pre-pregnancy BMI, kg/m^2	23.2 ± 3.32	22.7 ± 3.19	23.2 ± 3.19	23.3 ± 3.49	0.24
Gestational weight gain, kg	16.8 ± 6.02	16.2 ± 5.51	16.9 ± 6.00	16.8 ± 6.37	0.56
Current smoker, %	0	1.2	1.6	3.2	0.004
Education, %					0.71
<13 years	23.3	18.9	24.5	21.3	
13–16 years	69.1	75.1	67.9	69.9	
≥16 years	7.6	6.0	7.6	8.8	
Child characteristics					
Boy, %	47.8	50.6	50.6	64.3	<0.001
Age, years	3.07 ± 1.04	3.08 ± 1.08	3.01 ± 1.02	3.14 ± 1.09	0.58
Birth weight, gram	3540±513	3503±492	3557 ± 552	3571 ± 542	0.51
Mode of infant feeding, %					0.76
Exclusive breastfeeding	45.4	42.6	38.6	47.0	
Exclusive formula feeding	39.4	48.2	45.4	37.8	
Mixed feeding	15.3	9.2	16.1	15.3	
BMI, kg/m^2	15.4 ± 1.22	15.6 ± 1.6	15.9 ± 1.54	16.2 ± 2.09	<0.001
BMI-for-age z-score	−0.07 ± 0.91	0.03 ± 1.12	0.24 ± 1.07	0.47 ± 1.33	<0.001
Prevalence of overweight, %	10.0	17.3	18.1	24.5	<0.001
Fasting plasma glucose, mmol/l	4.31 ± 0.4	4.33 ± 0.39	4.36 ± 0.35	4.38 ± 0.39	0.22
HOMA-IR *	−0.44 ± 0.35	−0.42 ± 0.36	−0.42 ± 0.36	−0.37 ± 0.38	0.14
Insulin resistance, %	18.9	24.5	25.3	28.5	0.015
Outdoor activity, hours	1.69 ± 0.83	1.61 ± 0.89	1.54 ± 0.88	1.73 ± 0.86	0.07
Screen watching time, hours	1.3 ± 1.04	1.24 ± 1.02	1.25 ± 1.05	1.39 ± 1.04	0.33
Sleeping time, %					0.58
≤8 hours/day	3.6	1.6	1.2	1.6	
9–10 hours/day	43.4	45.4	47.4	49.8	
≥11 hours/day	53.0	53.0	51.4	48.6	
Daily nutrition intake					
Energy, kcal	686 ± 138	836 ± 131	953 ± 138	1157 ± 237	<0.001
Energy intake from protein, %	13.8 ± 2.20	15.7 ± 2.22	16.6 ± 2.18	17.9 ± 2.72	<0.001
Energy intake from carbohydrate, %	53.7 ± 8.47	52.2 ± 7.34	51.6 ± 6.86	51.4 ± 7.00	0.002
Energy intake from fat, %	32.5 ± 8.26	32.1 ± 7.17	31.8 ± 6.64	30.6 ± 6.4.	0.028
Branched chain amino acids, mg/day	3893 ± 702	5428 ± 322	6591 ± 363	8595 ± 1353	<0.001
Isoleucine, mg/day	1021 ± 186	1419 ± 86	1718 ± 97	2238 ± 349	<0.001

	Quartiles of branched-chain amino acids				P value
	1	2	3	4	
Leucine, mg/day	1717 ± 310	2404 ± 152	2931 ± 169	3833 ± 618	<0.001
Valine, mg/day	1155 ± 211	1605 ± 98	1942 ± 111	2523 ± 391	<0.001

BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin resistance.

BMI-for-age Z score, and overweight in children were evaluated according to the age- and sex-specific growth reference issued by World Health Organization.

*Data were log-transformed.

Table 2.

Odds ratios of overweight by different dietary intake levels of branched-chain amino acid, isoleucine, leucine, and valine

	No. of participants	No. of cases	Odds ratios (95% confidence intervals)		
			Model 1	Model 2	Model 3
Branched-chain amino acids					
Quartile 1	249	25	1	1	1
Quartile 2	249	43	2.11 (1.22 – 3.65)	2.19 (1.26 – 3.82)	2.07 (1.13 – 3.82)
Quartile 3	249	45	1.97 (1.15 – 3.39)	2.06 (1.19 – 3.57)	1.74 (0.88 – 3.43)
Quartile 4	249	61	2.76 (1.63 – 4.67)	2.81 (1.65 – 4.78)	2.21 (1.05 – 4.64)
P value for trend			<0.001	<0.001	0.11
One SD increase			1.38 (1.17 – 1.63)	1.37 (1.16 – 1.62)	1.31 (1.01 – 1.70)
Isoleucine					
Quartile 1	250	24	1	1	1
Quartile 2	249	49	2.57 (1.50 – 4.43)	2.63 (1.52 – 4.56)	2.38 (1.31 – 4.34)
Quartile 3	250	43	1.85 (1.06 – 3.22)	1.89 (1.08 – 3.32)	1.51 (0.76 – 3.00)
Quartile 4	247	58	2.93 (1.71 – 5.00)	2.90 (1.69 – 4.99)	2.08 (0.99 – 4.40)
P value for trend			0.001	0.001	0.25
One SD increase			1.38 (1.17 – 1.63)	1.38 (1.16 – 1.63)	1.30 (1.01 – 1.69)
Leucine					
Quartile 1	249	26	1	1	1
Quartile 2	249	43	2.07 (1.20 – 3.56)	2.18 (1.26 – 3.78)	2.02 (1.10 – 3.68)
Quartile 3	250	45	1.86 (1.09 – 3.18)	1.93 (1.12 – 3.33)	1.56 (0.80 – 3.04)
Quartile 4	248	60	2.62 (1.55 – 4.41)	2.66 (1.57 – 4.52)	1.99 (0.96 – 4.12)
P value for trend			0.001	0.001	0.18
One SD increase			1.38 (1.17 – 1.63)	1.36 (1.15 – 1.61)	1.32 (1.02 – 1.70)
Valine					
Quartile 1	249	25	1	1	1
Quartile 2	249	43	2.12 (1.23 – 3.66)	2.17 (1.25 – 3.77)	2.05 (1.11 – 3.82)
Quartile 3	249	45	1.92 (1.11 – 3.30)	2.03 (1.17 – 3.52)	1.70 (0.85 – 3.39)
Quartile 4	249	61	2.77 (1.63 – 4.69)	2.81 (1.65 – 4.79)	2.21 (1.04 – 4.67)
P value for trend			0.001	<0.001	0.12

	No. of participants	No. of cases	Odds ratios (95% confidence intervals)		
			Model 1	Model 2	Model 3
One SD increase			1.37 (1.16 – 1.61)	1.36 (1.15 – 1.61)	1.29 (0.99 – 1.67)

Model 1 adjusted for maternal age at delivery, gestational age at delivery, education, current smoking, pre-pregnancy BMI and gestational weight gain, and children's age, sex, birth weight, and feeding status.

Model 2 adjusted for variables in Model 1 plus children's outdoor physical activity time, screen-watching time, and sleep time.

Model 3 adjusted for variables in Model 2 plus children's daily energy intake.

Abbreviation: standard deviation, SD.

Table 3.

Odds ratios of insulin resistance by different dietary intake levels of branched-chain amino acid, isoleucine, leucine, and valine

	No. of participants	No. of cases	Odds ratios (95% confidence intervals)		
			Model 1	Model 2	Model 3
Branched-chain amino acids					
Quartile 1	249	47	1	1	1
Quartile 2	249	61	1.37 (0.88 – 2.14)	1.39 (0.89 – 2.17)	1.26 (0.77 – 2.07)
Quartile 3	249	63	1.49 (0.96 – 2.32)	1.52 (0.97 – 2.37)	1.28 (0.74 – 2.24)
Quartile 4	249	71	1.74 (1.12 – 2.69)	1.71 (1.10 – 2.66)	1.43 (0.76 – 2.67)
P value for trend			0.014	0.018	0.31
One SD increase			1.20 (1.03 – 1.39)	1.19 (1.02 – 1.38)	1.12 (0.89 – 1.42)
Isoleucine					
Quartile 1	250	45	1	1	1
Quartile 2	249	64	1.60 (1.03 – 2.50)	1.61 (1.03 – 2.52)	1.48 (0.9 – 2.41)
Quartile 3	250	63	1.55 (0.99 – 2.42)	1.55 (0.99 – 2.42)	1.32 (0.76 – 2.31)
Quartile 4	247	70	1.82 (1.17 – 2.84)	1.79 (1.15 – 2.79)	1.49 (0.79 – 2.8)
P value for trend			0.014	0.019	0.33
One SD increase			1.20 (1.04 – 1.40)	1.19 (1.03 – 1.39)	1.13 (0.89 – 1.43)
Leucine					
Quartile 1	249	47	1	1	1
Quartile 2	249	61	1.41 (0.90 – 2.20)	1.44 (0.92 – 2.25)	1.31 (0.8 – 2.15)
Quartile 3	250	60	1.37 (0.88 – 2.14)	1.38 (0.89 – 2.17)	1.18 (0.68 – 2.05)
Quartile 4	248	74	1.83 (1.18 – 2.83)	1.81 (1.17 – 2.81)	1.55 (0.83 – 2.87)
P value for trend			0.011	0.014	0.24
One SD increase			1.20 (1.03 – 1.39)	1.19 (1.02 – 1.38)	1.12 (0.89 – 1.41)
Valine					
Quartile 1	249	46	1	1	1
Quartile 2	249	60	1.38 (0.88 – 2.16)	1.40 (0.89 – 2.19)	1.31 (0.79 – 2.18)
Quartile 3	250	66	1.67 (1.07 – 2.59)	1.70 (1.09 – 2.65)	1.53 (0.87 – 2.71)
Quartile 4	248	70	1.83 (1.18 – 2.86)	1.81 (1.16 – 2.82)	1.65 (0.87 – 3.14)
P value for trend			0.005	0.006	0.13

	No. of participants	No. of cases	Odds ratios (95% confidence intervals)		
			Model 1	Model 2	Model 3
One SD increase			1.20 (1.03 – 1.39)	1.19 (1.02 – 1.39)	1.12 (0.88 – 1.43)

Model 1 adjusted for maternal age at delivery, gestational age at delivery, education, current smoking, pre-pregnancy BMI and gestational weight gain, and children's age, sex, birth weight, and feeding status.

Model 2 adjusted for variables in Model 1 plus children's outdoor physical activity time, screen-watching time, and sleep time.

Model 3 adjusted for variables in Model 2 plus children's daily energy intake.

Abbreviation: standard deviation, SD.