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Association between birth weight and insulin resistance in US adolescents: A retrospective cohort study exploring the role of concurrent body mass index

Yubo Zhuo [a], Jieli He [a], Liangbing Wang [b], Chun Bong Chow [b], Frederick K. Ho [c,*]

[a] Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
[b] Department of Pediatrics, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
[c] School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom

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Abstract *Background and aims:* This study aimed to investigate the association between birth weight (BW) and abnormal HOMA-IR in US adolescents aged 12–15 years. The role of concurrent body mass index (BMI) in adolescence was also examined.
Methods and results: This retrospective cohort study included 3429 participants from NHANES with data in 1999–2020. HOMA-IR ≥2.3 was considered abnormal. Participants were classified as low (LBW; <2.5 kg), normal (NBW; 2.5–4.0 kg), or high (HBW; >4.0 kg) BW. Logistic regression was used to explore the association between BW and HOMA-IR. Mediation analysis was used to examine whether BMI z-score in adolescence mediated the association between BW and HOMA-IR. Compared with those in NBW, the odds ratios (95 % CI) of abnormal HOMA-IR in LBW and HBW groups were 1.26 (0.99–1.60), and 0.62 (0.47–0.83) respectively. The association between BW and abnormal HOMA-IR was consistent in all subgroups with no significant interactions. Mediation analysis showed that BW is associated with lower risk of HOMA-IR directly, but with higher risk indirectly via BMI in adolescence.
Conclusion: There was a negative linear relationship between BW and the prevalence of abnormal HOMA-IR in adolescents aged 12–15 independent of concurrent BMI. Children who were born with LBW but had high BMI in adolescence were of particularly higher risk of insulin resistance.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; HOMA-IR, The homeostasis model for the assessments of insulin resistance; BW, birth weight; NBW, normal birth weight; LBW, low birth weight; HBW, high birth weight; T2DM, Type 2 diabetes mellitus; PIR, Ratio of family income to poverty; BMI, body mass index; BP, Blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HTN, Hypertension; FSFA, Total saturated fatty acids; TG, Triglyceride; HDL-C, HDL-cholesterol; TC, Total cholesterol; FBG, Fasting blood glucose; HbA1C, Glycohemoglobin.

* Corresponding author. School of Health and Wellbeing, University of Glasgow, Glasgow G12 8TB, United Kingdom.
E-mail address: Frederick.Ho@glasgow.ac.uk (F.K. Ho).

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1. Introduction

In the last two decades, the prevalence of type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) in children and adolescents increased dramatically [1,2]. It is, therefore, important to find the possible etiological factors such as epigenetic, genetic and environmental factors so that interventions can be introduced.

While concurrent body mass index (BMI) remains a key risk factor for T2DM, emerging evidence has shown that low birth weight (LBW) to be associated with an increased risk of developing T2DM in adulthood [3–5]. The same was also suggested for early-onset T2DM in adolescence as the potential influence could have occurred earlier. One key risk factor for T2DM, MetS, and cardiovascular disease (CVD) is insulin resistance (IR) [6–8]. The homeostasis model for the assessments of insulin resistance (HOMA-IR) is commonly used in clinical research as it relates glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of IR and β cell function [9–11]. Previous literature has reported the relationship between BW and HOMA-IR inconsistent, with examples in U-shaped, negative linear, or even no association after adjusted for covariates [12–15]. The evidence regarding the association between BW and abnormal HOMA-IR, especially in the 12–15 years old, is limited.

Thus, this study aimed to investigate the association between BW and abnormal HOMA-IR in adolescents aged 12–15 in the USA, particularly in relation to concurrent body mass index (BMI) z-score.

2. Methods

2.1. Study population

This study is based on the data of participants aged 12–15 in The National Health and Nutrition Examination Survey (NHANES), 1999-2016, 2017-2020 (until March 2020) cycles. NHANES is a publicly available data that were designed to assess the health and nutritional status of adults and children in the United States by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC).

Data are available via the website of NHANES (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx) (accessed on 4 Dec 2022) [16]. It has obtained NCHS Ethics Review committee approval and all participants had signed informed consent forms before participation. Exemptions of human subjects research in NIH meet the criteria of involves the collection/study of data or specimens if publicly available, or recorded such that subjects cannot be identified [17].

The total number of participants aged between 12 and 15 years old was 9136. Participants were excluded from the analyses if there were missing data for BW (n = 457), fasting blood glucose (FBG) (n = 5236), fasting insulin (n = 92) and glycated hemoglobin (HbA1c) (n = 5); pregnant at the time (n = 3); or who had developed diabetes (doctor diagnosis, taking diabetic medications, or taking insulin) (n = 14). The final sample size for analysis was 3429 (summarized in the Supplementary Materials Fig. S1).

2.2. Birth weight

BW was retrospectively recalled by the parents or caregiver of the participants. Participants were classified as LBW (<2.5 kg), NBW (2.5–4.0 kg), and HBW (>4.0 kg).

2.3. HOMA-IR

HOMA-IR was calculated using the following standard formula: (fasting insulin in μU/ml) × (fasting glucose in mmol/l)/22.5. We use the cut-off point of HOMA-IR ≥ 2.3 according to a meta-analysis [18]. There were different threshold levels of HOMA-IR as its distribution varies according to the demographic characteristics [1,4,19–24]. We choose the minimal level of the threshold to be more inclusive.

2.4. Covariates

The following variables were collected and analyzed in the this study which were considered covariates determined by literature reported [1,15,22,25,26]: sex, age, race, the ratio of family income to poverty (PIR), mother's age when the child was born, maternal smoking during pregnancy, current weight, height, body mass index (BMI), waist circumference (WC), blood pressure (BP, including systolic and diastolic BP), dietary intake [by recall interview to obtain participants'24-hr nutritional information, included energy, carbohydrate, total fat, total saturated fatty acids (TSFA), cholesterol]. The information on diet yesterday compared with the usual (eat yesterday vs usual) were also obtained in this study.

The laboratory results included triglyceride (TG), HDL-cholesterol (HDL-c), total cholesterol (TC), fasting blood glucose (FBG), fasting insulin, glycohemoglobin (HbA1c).

BMI was defined overweight and obesity by using CDC criteria, which defined overweight as sex- and age-specific BMI ≥85th percentile and obesity as BMI ≥95th percentile [27]. BMI was also converted into age- and sex-specific z-scores in mediation analysis.

BP as sex-, age- and height-specific was defined normal BP, elevated BP and hypertension (HTN) by American Academy of Pediatrics (AAP) in 2017 [28]. Normal BP for aged 12 was SBP and DBP <90th percentile; For children aged 13–15 was SBP <120 and DBP <80 mmHg. Elevated BP for aged 12 was SBP and DBP ≥90th percentile to <95th percentile, or 120/80 mmHg to <95th percentile (whichever is lower). For children aged 13–15, the criteria was SBP 120 to 129 and DBP <80 mmHg. HTN for aged 12–15 was SBP and DBP ≥95th percentile, or ≥130/80 mmHg.

TG was considered to be acceptable if < 1 mmol/L, borderline if 1 to <1.5 mmol/L and high if ≥ 1.5 mmol/L; HDL-C was considered to be low if < 1 mmol/L, borderline if 1–1.2 mmol/L and acceptable if > 1.2 mmol/L; TC was considered to be acceptable if < 4.4 mmol/L, borderline if 4.4 to <5.2 mmol/L and high if ≥ 5.2 mmol/L [29].

Missing value management: We used multiple imputation, based on 5 replications and a chained equation approach method in the R with the mice package. We also performed sensitivity analyses using a complete-case analysis (We repeated all analyses with the complete data cohort for comparison).

Details of variables acquisition process was described at https://www.cdc.gov/nchs/nhanes/index.htm.

2.5. Statistical analyses

Analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software versions 1.7.1.

Data were categorized into continuous and categorical variables. Continuous variables based on the normality of their distribution were presented as the mean ± standard deviation (SD) or median (interquartile range), and categorical variables were presented by percentage. The statistical difference among BW groups were analyzed using one-way analyses of variance (normal distribution), Kruskal-Wallis tests (skewed distribution), and chi-square tests (categorical variables). Logistic regression models were used to determine the odds ratios (OR) and 95 % confidence intervals (CI) for the relationship between BW and HOMA-IR ≥2.3. Model 1 was adjusted for age, sex, race, PIR, mother's age when born, mother smoked when pregnant, dietary intake (energy, carbohydrate, total fat, total saturated fatty acids, cholesterol), eat yesterday vs usual, BMI z-score, Model 2 was additionally adjusted for BP and lipid variables.

In addition we used a penalized cubic splines to assess the non-linear relationship between BW and abnormal HOMA-IR.

Furthermore, potential modifications of the relationship BW weight and abnormal HOMA-IR were analyzed, including the following variables: sex, race (Mexican American, Non-Hispanic White people, Non-Hispanic Black people, Other Race), BMI (<85th percentile, overweight, obesity), BP (Normal BP, Elevated BP and HTN), TG (acceptable-borderline-high), HDL-c (low-borderline-acceptable), TC (acceptable-borderline-high). Heterogeneity in subgroups was analyzed by multivariate logistic regression, and interactions between subgroups and birth weight were examined by likelihood ratio tests.

The relationship between BW and HOMA-IR was decomposed into natural direct effect (BW's effect on HOMA-IR independent of concurrent BMI z-score), and natural indirect effect (BW's effect on HOMA-IR via changes in concurrent BMI z-score). This was completed using the R package *CMAverse*.

3. Results

3.1. Baseline characteristics

The baseline characteristics of all subjects according to their BW is illustrated in Table 1. A total of 454 (13.2 %) were LBW (2.0 ± 0.4 kg), 2675 (78 %) were NBW (3.2 ± 0.3 kg), and 300 (8.7 %) were HBW (4.3 ± 0.3 kg), with an average weight of 3.1 ± 0.6 kg. according to the parental or proxy recall BW. The population factors showed that LBW tend to be female infants, Non-Hispanic Black, younger mothers, smoking during pregnancy and low PIR. HBW group and factors more likely to be male infants, Mexican American, older mothers, non-smoking during pregnancy. Adolescents in HBW group are taller, heavier, and bigger waist circumference, and higher daily carbohydrate intake. In addition, the LBW group had higher SBP, HDL-c and HbA1c values and more abnormal HOMA-IR (≥2.3).

The basic characteristics of the complete data cohort are shown in the Supplementary Materials (Table S1).

3.2. Relationship between BW and abnormal HOMA-IR

The univariate analysis demonstrated that BW groups, sex, race, PIR, BMI, BMI z-score and BMI groups, SBP and DBP, Diet intake (included energy/carbohydrate/total fat/total saturated fatty acids), some laboratory test (TG/TC/HDL-c) were associated with abnormal HOMA-IR (Table S2). Particularly, sex, race, BMI, BMI z-score, BMI groups, eat yesterday vs usual, TG, TC, HDL-c showed strong correlation in the univariate analysis (|OR-1| ≥0.20).

When BW was used as a continuous variable, each 1 kg increase in BW was associated with 21 % decrease in the prevalence of abnormal HOMA-IR (adjusted OR = 0.79, 95 % CI: 0.69−0.9). When BW was analyzed using three groups, it showed a significant association between BW and abnormal HOMA-IR after adjusting for covariates. Compared with those with NBW (2.5−4.0 kg), the adjusted odds ratios (OR) (95%Cl) with LBW (<2.5 kg) and HBW (>4.0 kg) were 1.26 (95 % Cl: 0.99−1.60) and 0.62 (95 % Cl: 0.47−0.83) respectively (*p* for trend <0.001) (Table 2). Figure 1 shows the dose-response association between BW and HOMA-IR. Regardless of the adjustment model, the associations exhibited a linear pattern.

3.3. Stratified analyses based on subgroups

The subgroups stratified by sex, race, BMI, BP, TG, TC, HDL-c were analyzed to assess any interactions. It was stable and had no significant interactions in different subgroups except TC (Fig. S2).

3.4. Sensitivity analysis using complete data analysis

After excluding all the missing data, 2900 participants were included, and the association between BW and abnormal HOMA-IR remained consistent. Compared with participants in NBW (2.5−4.0 kg), the adjusted odds ratios (OR) (95%Cl) among those with LBW (<2.5 kg) and HBW (>4.0 kg) were 1.42 (95 % Cl: 1.09−1.84) and 0.64 (95 % Cl: 0.47−0.87) (*P* for trend <0.001) (Table S3), respectively.

3.5. Mediation analysis

Table 3 shows the mediation analysis results decomposing the association between BW and HOMA-IR, via BMI z-

Table 1 Baseline characteristics of the study participants.

Variables	Total	Low birth weight	Normal birth weight	High birth weight	*P* value
	(n = 3429)	(n = 454, 13.2 %)	(n = 2675, 78 %)	(n = 300, 8.7 %)	
Birth weight, (kg)	3.1 ± 0.6	2.0 ± 0.4	3.2 ± 0.3	4.3 ± 0.3	<0.001
Sex, n (%)					<0.001
Male	1762 (51.4)	213 (46.9)	1352 (50.5)	197 (65.7)	
Female	1667 (48.6)	241 (53.1)	1323 (49.5)	103 (34.3)	
Age, (ys)	13.5 ± 1.1	13.4 ± 1.1	13.5 ± 1.1	13.4 ± 1.2	0.94
Race, n (%)					<0.001
Mexican American	985 (28.7)	105 (23.1)	770 (28.8)	110 (36.7)	
Non-Hispanic White	919 (26.8)	90 (19.8)	743 (27.8)	86 (28.7)	
Non-Hispanic Black	990 (28.9)	189 (41.6)	746 (27.9)	55 (18.3)	
Other Race	535 (15.6)	70 (15.4)	416 (15.6)	49 (16.3)	
PIR	1.6 (0.9, 3.1)	1.5 (0.8, 3.0)	1.6 (0.9, 3.1)	1.8 (0.9, 3.5)	0.025
Mothers' age when the child was born, (ys)	25.8 ± 6.1	25.3 ± 6.4	25.8 ± 6.1	26.9 ± 5.8	0.002
Maternal smoking during pregnancy, n (%)					<0.001
No	2942 (86.4)	360 (80.4)	2307 (86.8)	275 (92)	
Yes	462 (13.6)	88 (19.6)	350 (13.2)	24 (8)	
Weight, (kg)	60.8 ± 17.6	58.2 ± 15.9	60.6 ± 17.5	66.1 ± 20.5	<0.001
Hight, (cm)	162.3 ± 9.5	160.6 ± 9.3	162.3 ± 9.4	165.3 ± 10.0	<0.001
BMI, (kg/m^2)	22.9 ± 5.6	22.4 ± 5.1	22.8 ± 5.6	24.0 ± 6.5	<0.001
BMI z-score	0.7 (−0.1, 1.5)	0.6 (−0.1, 1.4)	0.7 (−0.1, 1.5)	0.9 (0.1, 1.7)	0.003
BMI groups, n (%)					0.013
<85th	2109 (61.9)	290 (64.4)	1656 (62.3)	163 (55.1)	
Over weight	579 (17.0)	77 (17.1)	454 (17.1)	48 (16.2)	
Obesity	718 (21.1)	83 (18.4)	550 (20.7)	85 (28.7)	
Waist circumference, (cm)	78.8 ± 14.2	76.8 ± 12.9	78.8 ± 14.1	82.3 ± 16.0	<0.001
Blood pressure					
SBP, (mmHg)	107.7 ± 9.5	108.8 ± 9.2	107.5 ± 9.5	107.8 ± 9.9	0.022
DBP, (mmHg)	59.1 ± 11.6	58.7 ± 11.0	59.2 ± 11.7	58.7 ± 11.7	0.553
Categorical BP					0.77
Normal BP	2916 (88.5)	388 (88.8)	2276 (88.6)	252 (87.2)	
Elevated BP and HTN	380 (11.5)	49 (11.2)	294 (11.4)	37 (12.8)	
Dietary intake					
Energy, (kcal)	1934.0 (1383.0, 2573.0)	1926.0 (1372.0, 2426.0)	1929.0 (1380.0, 2572.0)	2003.0 (1474.0, 2729.0)	0.133
Carbohydrate, (gm)	254.5 (183.0, 348.3)	242.8 (180.6, 327.6)	254.5 (182.0, 348.5)	269.2 (204.1, 387.7)	0.014
Total fat, (gm)	69.7 (47.1, 100.6)	73.3 (48.9, 101.1)	68.5 (46.8, 100.3)	74.5 (47.7, 103.6)	0.171
TSFA, (gm)	23.6 (15.3, 34.7)	24.1 (15.5, 35.1)	23.3 (15.2, 34.4)	25.3 (16.0, 37.0)	0.165
Cholesterol, (mg)	179.0 (105.0, 295.0)	171.0 (101.8, 287.5)	178.0 (106.0, 296.0)	196.0 (109.0, 301.6)	0.345
Eat yestoday. Vs. Usual, n (%)					0.616
Usual	1965 (59.5)	264 (60.6)	1539 (59.7)	162 (56.4)	
Much more than usual	612 (18.5)	74 (17)	476 (18.5)	62 (21.6)	
Much Less than usual	723 (21.9)	98 (22.5)	562 (21.8)	63 (22)	
TG, (mmol/L)	0.8 (0.6, 1.1)	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.202
TC, (mmol/L)	4.0 ± 0.8	4.1 ± 0.8	4.0 ± 0.7	4.1 ± 0.8	0.112
HDL-C, (mg/dL)	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	0.009
FBG, (mmol/L)	5.2 ± 0.5	5.2 ± 0.6	5.2 ± 0.4	5.2 ± 0.4	0.202
Insulin, (uU/mL)	11.6 (8.1, 17.3)	11.9 (8.2, 18.6)	11.6 (8.1, 17.0)	10.7 (7.5, 17.5)	0.183
HbA1C, (%)	5.2 ± 0.3	5.2 ± 0.4	5.2 ± 0.3	5.2 ± 0.3	0.002
HOMA-IR, n (%)					0.041
<2.3	1378 (40.2)	167 (36.8)	1073 (40.1)	138 (46)	
≥2.3	2051 (59.8)	287 (63.2)	1602 (59.9)	162 (54)	

Abbreviations: PIR, Ratio of family income to poverty; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; TG, Triglyceride; HDL-C, HDL-cholesterol; TC, Total cholesterol; FBG, Fasting blood glucose; HbA1C, Glycohemoglobin; HOMA-IR, The homeostasis model for the assessments of insulin resistance.

score. Assuming causality conditional on the covariates, BW has a negative effect on the risk of abnormal HOMA-IR, independent of concurrent BMI. However, BW also increased BMI z-score in adolescence which in turn increased the risk of abnormal HOMA-IR. These two contrasting pathways indicate that children who had a large amount LBW and high BMI in adolescence were at the highest risk of abnormal HOMA-IR.

Table 2 Association between BW and abnormal HOMA-IR.

Variable	Number	Number of Event (%)	Not adjusted		Model 1		Model 2	
			Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
BW, (kg)	3429	2051 (59.8)	0.91 (0.82−1.01)	0.076	0.78 (0.69−0.89)	<0.001	0.79 (0.69−0.90)	<0.001
BW groups								
LBW	454	287 (63.2)	1.15 (0.94−1.41)	0.18	1.29 (1.02−1.63)	0.031	1.26 (0.99−1.60)	0.056
NBW	2675	1602 (59.9)	1 (Ref)		1 (Ref)		1(Ref)	
HBW	300	162 (54.0)	0.79 (0.62−1.00)	0.049	0.64 (0.49−0.85)	0.002	0.62 (0.47−0.83)	0.001
P for Trend	3429	2051 (59.8)		0.014		<0.001		<0.001

Model 1: Adjust for sex, age, race, PIR, mother's age when the child was born, maternal smoking during pregnancy, total dietary energy intake, dietary intake from carbohydrate, total fat, TSFA, cholesterol, eat yesterday vs usual, and concurrent BMI z-score.
Model 2: Adjust for Model 1, and additionally categorical BP, TG, TC, HDL-c.
Abbreviations: HOMA-IR, The homeostasis model for the assessments of insulin resistance; BW, birth weight; NBW, normal birth weight; LBW, low birth weight; HBW, high birth weight; PIR, Ratio of family income to poverty; BMI, body mass index; WC, Waist circumference; FSFA, Total saturated fatty acids; TG, Triglyceride; TC, Total cholesterol; HDL-C, HDL-cholesterol; HbA1C, Glycohemoglobin.

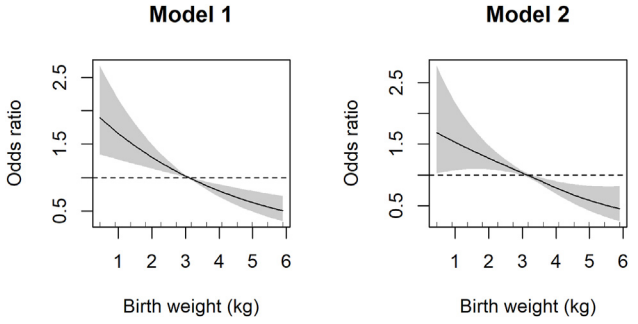

Figure 1 Association between BW and abnormal HOMA-IR. **Model 1:** Adjust for sex, age, race, PIR, mother's age when the child was born, maternal smoking during pregnancy, total dietary energy intake, dietary intake from carbohydrate, total fat, TSFA, cholesterol, eat yesterday vs usual, and concurrent BMI z-score. **Model 2:** Adjust for Model 1, and additionally categorical BP, TG, TC, HDL-c. **Abbreviations:** HOMA-IR, The homeostasis model for the assessments of insulin resistance; BW, birth weight; NBW, normal birth weight; LBW, low birth weight; HBW, high birth weight; PIR, Ratio of family income to poverty; BMI, body mass index; FSFA, Total saturated fatty acids; BP, blood pressure; TG, Triglyceride; TC, Total cholesterol; HDL-c, HDL-cholesterol.

Table 3 Mediation analysis from BW to HOMA-IR via BMI z-score.

	Model 1		Model 2	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Natural direct effect	0.67 (0.55−0.85)	<0.001	0.69 (0.58−0.83)	<0.001
Natural indirect effect	1.32 (1.22−1.43)	<0.001	1.23 (1.17−1.33)	<0.001

Model 1: Adjust for sex, age, race, PIR, mother's age when the child was born, maternal smoking during pregnancy, total dietary energy intake, dietary intake from carbohydrate, total fat, TSFA, cholesterol, eat yesterday vs usual, and concurrent BMI z-score.
Model 2: Adjust for Model 1, and additionally categorical BP, TG, TC, HDL-c.
Abbreviations: HOMA-IR, The homeostasis model for the assessments of insulin resistance; BW, birth weight; NBW, normal birth weight; LBW, low birth weight; HBW, high birth weight; PIR, Ratio of family income to poverty; BMI, body mass index; FSFA, Total saturated fatty acids; BP, blood pressure; TG, Triglyceride; TC, Total cholesterol; HDL-c, HDL-cholesterol.

4. Discussion

The present study utilized the population-based data from the NHANES to investigate the association between BW and abnormal HOMA-IR in adolescents aged 12−15 years. While the association between BW and HOMA-IR was previously reported, it was the first time, to our knowledge, that the role of concurrent BMI was considered. Our study showed a negative linear relationship between BW and the prevalence of abnormal HOMA-IR after adjusted for covariates. The results were consistent in subgroups defined by sex, race, BMI, BP, TG, and HDL-c. The mediation analysis indicated there could be two contrasting pathways between BW and HOMA-IR. On one hand, LBW could lead to lower BMI in adolescence, which is associated with lower risk of abnormal HOMA-IR. On the other hand, independent of BMI in adolescence, LBW was associated with higher risk of HOMA-IR. These two pathways indicate that children who were born LBW but had high BMI in adolescence to be of particularly high risk for IR.

BW have been shown to affect IR and adiposity in animal models. Prenatal intrauterine malnutrition or stunting during fetal development can affect some pathways regulating insulin sensitivity. This may have a permanent impact on the fetal metabolism, increasing the risk of T2DM and MetS. Wang et al. [30] found LBW mice compared with NBW mice, exhibited IR and worse lipid metabolism when exposed to high-fat diets, with increased expression of peroxisome proliferator-activated receptor gamma (PPARγ), as well as elevated upstream CD36, downstream SCD1 and PCK1 of the PPARγ in the adipose tissue, and suggested that CD36/PPARγ/SCD1 and CD36/PPARγ/PCK1 pathways activation may induce adipose dysfunction and cause increased susceptibility of insulin resistance. Clinical research also found that fetus with LBW had increased prevalence of T2DM, MetS and cardiovascular disease in adults and children. Giapros et al. reported [31] that LBW was independently correlated with HOMA-IR at 12 months infants. Ruiz Narváez et al. had the same results in African American women aged 21−69 years [32]. In our study, it showed that each 1 unit increase in BW was associated with 21 % decrease in the prevalence

of abnormal HOMA-IR among adolescents aged 12−15 in USA and was consistent with these studies.

Some previous studies showed no differences in the levels of HOMA-IR profiles later in adolescence regardless of BW status, but our findings were on the contrary suggested BW was strongly relevant to abnormal HOMA-IR. Oliveira-Santos et al. [26] adjusted age, pubertal stage, BMI, fat mass, socioeconomic status, KIDMED index (Mediterranean Diet Quality Index for children and adolescents) of 415 Portuguese adolescents in their study, and suggested that high BMI from an early age was consistently associated with IR in adolescence but had no relation with BW. Ranke et al. [33] have not adjusted any covariables in 141 pre-pubertal school children of Tuebingen reported that short children with a history in very low birth weight or small for gestational age when compared with normal height did not observe any dissimilarities. Their smaller sample size and population characteristics (including concurrent BMI in adolescence) could contributed to their findings different to this study.

Additionally, some other studies had suggested that BW had a U-shaped relations with HOMA-IR in children [34,35]. This U-shaped correlation, conversely, has not been replicated in adolescents in our research. The U-shaped trend in TC groups of our study is unexpected and warrant further exploration.

One main novel finding of our study is the contrasting pathways from BW to HOMA-IR. This suggested adolescents born with LBW but had overcompensated catch-up growths were of particular higher risk of IR. The latest evidence suggested rapid growth and high HOMA-IR was associated in children older than 6 years especially in full-term history but did not in LBW subjects [36]. Further studies will be required to disentangled these complex relationships.

Limitations of our study are as follows: first there was no information on gestation age at birth, the growth patterns followed-up between birth and adolescence and family diabetes history of this aged groups in NHANES. This prevented us from analyzing the interaction of prenatal factors and adiposity rebound of the investigated individuals. The second one is physical activity data used different definitions in different survey waves. This restricted us from harmonizing these variables for analysis. Third, although multiple regression models, stratified analyses, and sensitivity analysis were used, unmeasured or unknown confounding could not be ruled out entirely. Fourth, cut-off points of HOMA-IR was affected by multiple factors, and the optimal threshold of adolescent was not well defined. Fifth, BW was obtained by parental or proxy recall and may be subject to recall bias. But parental recall of BW have been reported to be an accurate proxy for recorded birth weight, which was within 50 g of the child's documented weight in 75 % of parents recalling up to 16 years after delivery [37] and there was no evidence showing the recall accuracy is dependent on adolescents' health.

In summary, abnormal HOMA-IR was found to be more prevalent among adolescents with a history of LBW compared with those with NBW and HBW, independent of BMI z-score and other covariates. Prevention of LBW could potentially reduce the risk of IR. Particular attention should be paid to adolescents who were born with LBW but obese in adolescence, as they are particularly vulnerable to IR.

5. Conclusion

There was a negative linear relationship between BW and the prevalence of abnormal HOMA-IR ($\geq$2.3) in 12−15 yr old adolescents independent of concurrent BMI.

Author contributions

Yubo Zhuo contributed to the study conceptualization, data curation, formal analysis, methodology, writing-original draft, critical revision of manuscript for important intellectual content. Frederick Ho contributed to data curation, formal analysis, methodology, writing-original draft, critical revision of manuscript for important intellectual content. Liangbing Wang contributed to methodology, analysis and interpretation of data, and preparation of tables. Jieli He contributed to writing-original draft and edited the manuscript. Chung Bong Chow contributed to methodology, critical revision of manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.11.016.

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