Pediatric RESEARCH

POPULATION STUDY ARTICLE

Associations between *KCNQ1* and *ITIH4* gene polymorphisms and infant weight gain in early life

Yuanyuan Zhang[1], Hong Mei[2], Ke Xu[1], Chunan Li[1], Ruixia Chang[1], Haiqin Qi[1], Ya Zhang[1] and Jianduan Zhang[1]

BACKGROUND: An earlier meta-analysis of genome-wide association studies in Asian populations detected five novel body mass index-associated single-nucleotide polymorphisms (SNPs), including potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*) (rs2237892), *ALDH2/MYL2* (rs671, rs12229654), *ITIH4* (rs2535633), and *NT5C2* (rs11191580). Whether these SNPs take effect in early life, for example, affect infant rapid weight gain (RWG), is unclear.

METHODS: We obtained genomic DNA from 460 term infants with normal birth weight. RWG was defined as the change of weight-for-age standardized *Z*-score, calculated according to the Children Growth Standard released by the World Health Organization, from birth to 3 months of age >0.67. Using genetic models, associations between the candidate SNPs and infant RWG were examined, along with the interaction between the SNPs and the potential risk factors.

RESULTS: RWG was presented in 225 of 460 infants. SNP rs2535633 and rs2237892 were associated with the risk of RWG. Both additive and multiplicative interaction effects were found between infant delivery mode and rs2237892. The negative association between the rs2237892 T allele and infant RWG was only observed in vaginally delivered infants.

CONCLUSIONS: Obesity-related loci rs2535633 and rs2237892 are associated with infant RWG in the first 3 months of infancy. The relationship between rs2237892 and infant RGW might be moderated by cesarean delivery.

Pediatric Research (2022) 91:1290–1295; https://doi.org/10.1038/s41390-021-01601-8

IMPACT:

- Genetic predisposition is an essential aspect to understand infant weight gain.
- Obesity-related SNPs, rs2535633 and rs2237892, are associated with RWG in very early years of life.
- The negative association between rs2237892 T allele and RWG is only observed in infants delivered vaginally instead of cesarean section.

INTRODUCTION

Infant postnatal rapid weight gain (RWG) is most commonly defined as a change in weight-for-age *Z*-score (ΔWFA) >0.67.[1–3] For babies born preterm, low birth weight, or small-for-gestational age (SGA), catch-up growth provides immediate benefits as it, to some degree, erases the growth deficit via nutritional improvement and immunity enhancement. This, therefore, reduces morbidity and mortality in early childhood.[2] However, this kind of postnatal compensatory growth is not required for healthy term infants or for infants adequate for gestational age; rather, accelerated weight gain could be deemed harmful considering the long-term effects on obesity and related diseases.[4–6]

Results are inconclusive regarding which RWG periods (birth to 3, 6, 12, or 24 months) are most critical for future obesity and obesity-related diseases.[2,3,7–12] Multiple studies revealed the associations between infant RWG from birth to 12 or to 24 months and whole-life obesity.[2,3,12] In addition to these two periods, some studies also discussed the important role of RWG on the development of obesity at an earlier stage. For example, Helgeland et al. identified the effect of a variant in *LEPR* on infant body mass index (BMI) peaking at 6–12 months, but starting from 3 months.[9] Botton et al. found that the first 6 months postnatally comprise a sensitive window for the development of obesity.[8] Leunissen's team suggested that it was infant RWG in the first 3 months of life associated with an increased percentage of body fat, central adiposity, and insulin sensitivity in adults.[11] Although the sensitive period of infant RWG linking with obesity has not been conclusive, the importance of the duration from birth to 3 months of age, a very early period, could not be ignored considering its relationship with multiple adverse health outcomes.[7,10] Hence, understanding the origin of infant RWG in the first 3 months might help to prevent future obesity and related metabolic dysfunction early.

Genetic predisposition is an essential aspect to understand infant growth; however, the genetic profiles involved in the occurrence of RGW are less known. Thirty-two loci related to BMI were identified in a genome-wide association study (GWAS) meta-analysis that included 249,769 individuals of European ancestry.[13] To identify specific SNPs in the Asian population, Wen et al. conducted a two-staged meta-analysis of a GWAS for Asian

[1]Department of Woman and Child's Care and Adolescence Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China and [2]Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
Correspondence: Jianduan Zhang (jd_zh@hust.edu.cn)

Received: 24 September 2020 Revised: 17 April 2021 Accepted: 20 May 2021
Published online: 10 July 2021

ancestry. In addition to some SNPs previously identified in the European and Asian populations, eight novel SNPs were detected in the first stage, and these were further examined in the replication analysis (stage II), five of which were significant.[14] These five newly identified BMI-related SNPs, including SNPs near the potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*) (rs2237892), *ALDH2/MYL2* (rs671, rs12229654), *ITIH4* (rs2535633), and *NT5C2* (rs11191580) genes, were found to participate in pancreatic function and lipid metabolism. Evidence about the associations between these five SNPs and multiple obesity-related chronic diseases has also been previously reported.[15–18] Considering the relationship between infant RWG and metabolomic diseases, such as obesity, diabetes, or cardiovascular disease, the five SNPs might have potential effects on infant RWG.

In addition to genetic predisposition, socioeconomic, and demographic factors such as family monthly income, maternal educational level, and prenatal and perinatal factors, including maternal tobacco exposure, alcohol intake, maternal weight status before pregnancy, weight gain and morbidity in pregnancy, childbearing age, and neonatal factors including sex, delivery mode, and feeding patterns, also play important roles in the early growth of infants.[19–23] Multiple studies have suggested that these factors could modify an individual's predisposed genetic risk of adiposity, where genes, such as *FTO*, *LEPR*, and *MC4R*, among others, are commonly involved.[24–26] Although the five-targeted SNPs are less explored, there exists evidence suggesting their interactive effects with the factors aforementioned on adulthood obesity. For instance, *KCNQ1* (rs2237892) was reported to interact with the consumption of soft drinks on obesity,[27] and the effect of rs671 (*ALDH2*) on serum low-density lipoprotein cholesterol and triglycerides was found to be modified by the alcohol intake.[28] A growing body of research has indicated the early origins of obesity,[29] with one of the important focuses being the role of RWG in infancy.[30,31] For example, after systematically reviewing 17 related publications, Zheng et al. found that rapid weight gain during infancy endowed a four-fold increase of childhood obesity, and a two-fold increase in adult obesity.[3] Understanding what attributes to RWG has the potential to curtail the prevalence of obesity from the early stage of life.

In the current study, focusing on infants without growth deficit at birth, we aimed to first explore whether these five obesity-related SNPs, including *KCNQ1* (rs2237892), *ALDH2/MYL2* (rs671/rs12229654), *ITIH4* (rs2535633), and *NT5C2* (rs11191580), affect infant RWG from birth to 3 months of age. Second, we investigated the interaction effects between these SNPs and common risk factors on RWG. Such factors included socioeconomic and demographic factors like family monthly income, maternal educational level and childbearing age, maternal lifestyle exposures like tobacco and alcohol intake, and prenatal and perinatal factors including maternal weight status before pregnancy and gestational weight gain, and neonatal factors including sex, delivery mode, and feeding patterns.

METHODS

Subjects and design

A nested case–control study was conducted using data from a prospective birth cohort in Zhuhai, China, which enrolled pregnant women of estimated gestational age <13 weeks from January 2014 to June 2015 in Zhuhai, China. Newborns were actively followed until 3 years of age. More details about the original cohort could be referred to a previous publication.[32] The eligibility criteria in the current study were term infants who had no obvious genetic diseases, were non-SGA, had birthweight ≥2500 and <4000g, had Apgar scores ≥7 in both 1 and 5 min, had umbilical cord blood collected at birth, and were followed up at 1 and 3 months. In total, 460 mother–child pairs were included for the current analysis. The weights and lengths of children were measured by trained nurses using standard instruments and protocols. Weight-for-age (WFA) *Z*-scores were calculated according to the Children Growth Standard released by World Health Organization in 2006.[33] Infants exhibiting RWG were those with a ΔWFA-*Z* (the change of WFA Z-scores from birth to 3 months of age) >0.67 SD.[2] Those without RWG were recognized as controls.

Our study was approved by the Ethics Committees of the Tongji Medical College, Huazhong University of Science and Technology, and all the participants provided informed consent before study participation (IORG0003571).

Risk factors/covariates

Information on maternal childbearing age, weight before pregnancy and before delivery, and morbidity in pregnancy, as well as infant sex and delivery mode, were acquired from medical records in Maternal and Child Health Information System. Information about family monthly income, maternal educational level, tobacco and alcohol exposure before pregnancy, and infants' feeding patterns at 3 months of age was collected using a self-administered questionnaire. Maternal childbearing age (<28 and ≥28 years), educational level (≤high school and >high school), and family monthly income (≤5000 and >5000 yuan) were set as dichotomized variables. Maternal prepregnancy BMI, calculated as weight (kg) divided by height (m) squared, was classified as underweight (prepregnancy BMI $< 18.5\ kg/m^2$), normal weight (prepregnancy BMI between 18.5 and $23.9\ kg/m^2$), and overweight/obesity (prepregnancy BMI $\geq 24\ kg/m^2$), according to the criterion of Working Group on Obesity in China.[34] Gestational weight gain was calculated as the difference between maternal prepregnancy weight and weight before delivery and was categorized into insufficient, adequate, and excessive based on the prepregnancy weight status, following the 2009 IOM criteria.[35] Maternal morbidity (yes/no) was defined as gestational diabetes, hypertension, thyroid disorder, anemia, or hyperemesis, or otherwise, as no morbidity. Exposure to tobacco (yes/no) either actively or passively was defined as tobacco exposure, or otherwise, as no exposure. Alcohol exposure was defined as drinking (liquor, beer, or wine) more than once per week. The delivery mode included a transvaginal and cesarean section (C-section). Feeding patterns at 3 months of age were dichotomized as exclusive breastfeeding and nonexclusive breastfeeding.[36]

Candidate SNPs and genotype

Newborn umbilical cord blood samples were collected at birth. Blood cells were isolated after centrifugation of whole blood at 3500 r/min for 5 min and then stored at −80 °C. Genomic DNA was extracted from blood cells using Bioteke DNA Investigator Kit AU18016 (Bioteke, Beijing, China) and concentrated by NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA). Five candidate SNPs in *KCNQ1* (rs2237892), *ALDH2/MYL2* (rs671, rs12229654), *ITIH4* (rs2535633), and *NT5C2* (rs11191580) genes were genotyped on the Sequenom MassARRAY platform (San Diego), following the manufacturer's protocol, BIO MIAO BIOLOGICAL Corporation (Beijing, China).

Statistical analysis

All the SNPs were filtered if the minor allele frequency (MAF) for Han Chinese in Beijing <10% (http://asia.ensembl.org/), the calling rate <95%, or the Hardy–Weinberg equilibrium (HWE) principles were not followed ($P < 0.05$). Genetic models, including codominant, dominant, recessive, and additive models, were used to examine the association between each SNP and infant RWG. Differences in the distribution of the aforementioned covariates between the cases and controls were compared using the χ^2 test. Considering the linkage disequilibrium between rs12229654 and rs671 reported previously,[14] rs671 was further adjusted for the genetic models of rs12229654, along with the confounding factors distributed differently between the case and control groups.

Both additive and multiplicative interaction effects of SNPs and potential risk factors were examined in the current analysis. The additive interaction effect was tested by the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI). RERI was defined as ($OR_{both} - OR_{SNP} - OR_{risk\_factor} + 1$), AP was calculated as RERI/OR_{both}, and SI was the ratio of ($OR_{both} - 1$) to (($OR_{SNP} - 1$) + ($OR_{risk\_factor} - 1$)).[37] The 95% confidence intervals (CIs) of RERI, AP, and SI were calculated using the delta method proposed by Hosmer and Lemeshow.[38] The multiplicative interaction effect was tested by the inclusion of an interaction term in the logistic model.

Variables with missing data, including maternal education, tobacco and alcohol exposure, and morbidity, were imputed multiple times using the random forest method ($N = 10$). Based on the ten imputed datasets, results of between-group comparison and interaction analysis involving the three variables with missing data were consolidated using Rubin's combination rules.[39] All the statistical analyses were conducted with R software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria), and the significance level was set as 0.05. The HWE test was performed with the *SNPassoc* package,[40] and multiple imputation was conducted with the *Mice* package for potential risk factors.[41]

RESULTS

In total, 460 infants were included in the current study, with 48.9% ($N = 225$) experiencing RWG in the first 3 months postpartum. There were some missing values for maternal variables, including maternal education level (12% missing), tobacco exposure (10% missing), alcohol exposure (1% missing), and morbidity (14%). Detailed information about the characteristics of the mothers and children is shown in Table 1. The imputations of the four maternal variables were used since there was no distributional difference between the imputed data and the original one ($P > 0.05$). A significant distributional difference in maternal childbearing age was found between the case and control group ($P = 0.044$).

All five SNPs were retained considering MAF, calling rate, and HWE result, which are shown in Supplementary Table S1. The distribution of genotype frequencies between the case and control groups is shown in Table 2. The results of the four genetic models are presented in Table 3. After the adjustment of maternal childbearing age, rs2535633 and rs2237892 were found to be significantly related to the infant RWG, whereas the other three SNPs, rs11191580, rs12229654, and rs671, showed no effect in any of the models.

SNP rs2535633 (*ITIH4*) was found to be associated with RWG of infants in the codominant or dominant model. In the codominant model, infants with the heterozygote CG genotype had a lower RWG risk compared to that in infants with the CC genotype (odds ratio (OR) = 0.62; 95% confidence interval (CI), 0.42–0.93; $P = 0.020$), whereas the effect of homozygote GG was insignificant (OR = 0.88; 95% CI, 0.49–1.55; $P = 0.651$). In the dominant model, compared to the infant with homozygote CC genotype, those who had CG/GG genotype had lower RWG risk (OR = 0.68; 95% CI, 0.47–0.98; $P = 0.040$). The dominant model of SNP rs2237892 (*KCNQ1*) suggested a negative relationship between it and infant RWG. Infants carrying the minor allele T (homozygous or heterozygous) had a lower risk of RWG than those with homozygous major allele C (OR = 0.66; 95% CI, 0.45–0.96; $P = 0.031$).

We further explored the additive and multiplicative interactions between these two significant SNPs, that is, rs2535633 and rs2237892, with other potential risk factors on infant RWG. Both significant additive and multiplicative interaction effects were detected between delivery type and rs2237892 in the dominant model, with a RERI of 0.55 (95% CI, 0.17–0.94), AP of 1.05 (95% CI, 0.20–1.91), and *P* value of multiplicative interaction term <0.05. No interaction effects were observed between rs2237892 and other factors such as family income level, maternal educational level, weight status, tobacco and alcohol exposure before pregnancy, gestational weight gain, childbearing age, and morbidity in pregnancy as well as infant sex and feeding pattern; the results are shown in the Supplementary Table S2. The effects of rs2237892 on RGW under different delivery modes are presented in Fig. 1, with the negative association between the T allele in rs2237892 and infant RWG only detected in transvaginal infants (OR = 0.51; 95% CI, 0.32–0.82; $P = 0.005$).

Table 1. Characteristic description of 460 infants (*N* (%)).

Variable	Class	Control ($N = 235$)	Case ($N = 225$)	*P* value
Maternal childbearing age				
	<28 y	94 (40.00)	112 (49.78)	0.044[a]
	≥28 y	141 (60.00)	113 (50.22)	
Maternal education level				
	≤High school	58 (28.16)	46 (23.23)	0.309
	>High school	148 (71.84)	152 (76.77)	
Maternal tobacco exposure before pregnancy				
	No	50 (23.58)	43 (21.39)	0.678
	Yes	162 (76.42)	158 (78.61)	
Maternal alcohol exposure before pregnancy				
	No	217 (93.94)	213 (95.52)	0.589
	Yes	14 (6.06)	10 (4.48)	
Household income/ monthly				
	≤5000 yuan	97 (41.28)	81 (36.00)	0.287
	>5000 yuan	138 (58.72)	144 (64.00)	
Maternal prepregnancy BMI (kg/m^2)				
	18.5–23.9 (normal)	151 (64.26)	156 (69.33)	0.058
	<18.5 (low)	54 (22.98)	55 (24.44)	
	≥24 (overweight/obese)	30 (12.77)	14 (6.22)	
Maternal gestational weight gain				
	Adequate	115 (48.94)	106 (47.11)	0.140
	Insufficient	35 (14.89)	49 (21.78)	
	Excessive	85 (36.17)	70 (31.11)	
Maternal morbidity in pregnancy				
	No	181 (88.73)	171 (88.60)	1
	Yes	23 (11.27)	22 (11.40)	
Delivery type				
	Transvaginal	144 (61.28)	157 (69.78)	0.069
	Cesarean	91 (38.72)	68 (30.22)	
Infant sex				
	Female	105 (44.68)	111 (49.33)	0.365
	Male	130 (55.32)	114 (50.67)	
Feeding pattern at 3 months				
	Nonexclusive breastfeeding	199 (84.68)	176 (78.22)	0.096
	Exclusive breastfeeding	36 (15.32)	49 (21.78)	

[a]There were significant differences in the distribution of maternal childbearing age between the case and control group.

DISCUSSION

In this study, we identified for the first time the impacts of rs2535633 (*ITIH4*), rs2237892 (*KCNQ1*), and the interaction between rs2237892 and delivery mode on infant RWG from birth

Table 2. Genotype descriptions of the five SNPs (*N* (%)).

SNP	Genotype	Control	Case
rs11191580	TT	128 (54.47)	118 (53.64)
	CT	91 (38.72)	94 (42.73)
	CC	16 (6.81)	8 (3.64)
rs12229654	TT	139 (59.66)	145 (65.91)
	GT	81 (34.76)	70 (31.82)
	GG	13 (5.58)	5 (2.27)
rs2237892	CC	89 (38.36)	107 (47.98)
	CT	114 (49.14)	99 (44.39)
	TT	29 (12.50)	17 (7.62)
rs2535633	CC	93 (39.91)	112 (50.22)
	CG	109 (46.78)	80 (35.87)
	GG	31 (13.30)	31 (13.90)
rs671	GG	138 (59.23)	137 (62.84)
	GA	75 (32.19)	70 (32.11)
	AA	20 (8.58)	11 (5.05)

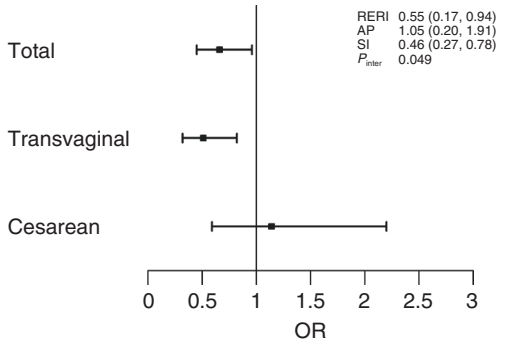

Fig. 1 Odds ratios of rs2237892 on RWG under different delivery modes in the dominant model. RERI (relative excess risk due to interaction), AP (attributable proportion due to interaction), and SI (synergy index) were used to test the additive interaction effect between delivery mode and rs2237892 on infant RWG. P_{inter} denoted as the *P* value of interaction term of delivery mode and rs2237892 (delivery mode × rs2237892) in the logistic model reflected the significance of multiplicative interaction effect.

Table 3. The associations between the five candidate SNPs and infant RWG[a].

SNP	Codominant$_1$ [b]		Codominant$_2$ [c]		Dominant		Recessive		Additive	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
rs11191580	1.13 (0.77, 1.65)	0.543	0.57 (0.23, 1.38)	0.211	1.04 (0.72, 1.51)	0.818	0.54 (0.22, 1.29)	0.165	0.95 (0.70, 1.29)	0.739
rs12229654	0.83 (0.56, 1.23)	0.356	0.36 (0.12, 1.03)	0.057	0.76 (0.52, 1.12)	0.168	0.38 (0.13, 1.09)	0.073	0.74 (0.53, 1.03)	0.070
rs2237892	0.70 (0.48, 1.04)	0.079	0.49 (0.25, 0.96)	0.036*	0.66 (0.45, 0.96)	0.031*	0.59 (0.31, 1.11)	0.102	0.70 (0.53, 0.94)	0.017*
rs2535633	0.62 (0.42, 0.93)	0.020*	0.88 (0.49, 1.55)	0.651	0.68 (0.47, 0.98)	0.040*	1.10 (0.64, 1.89)	0.725	0.84 (0.64, 1.10)	0.197
rs671	0.95 (0.63, 1.42)	0.787	0.55 (0.25, 1.20)	0.132	0.86 (0.59, 1.26)	0.445	0.56 (0.26, 1.21)	0.139	0.83 (0.62, 1.12)	0.227

RWG rapid weight gain, *OR* odds ratio, *CI* confidence interval.
**P* value is <0.05.
[a] Maternal childbearing age was adjusted in the genetic models.
[b]Codominant$_1$ represented heterozygote versus wild homozygote.
[c]Codominant$_2$ represented mutant homozygote versus wild homozygote.

to 3 months of age in a Chinese population. Our findings suggest that infants carrying the homozygous major allele C in SNP rs2237892 had a higher risk of RWG than those carrying the minor allele T (homozygous or heterozygous). SNP rs2237892 is located in the intron region of the *KCNQ1* gene. *KCNQ1* encodes a voltage-gated potassium channel, which is pivotal for the cardiac action potential repolarization, and water and salt transportation in epithelial tissues.[42,43] *KCNQ1* was also found to be expressed in pancreatic islets and cultured insulin-secreting INS-1 cell.[44] The association between rs2237892 (*KCNQ1*) and type 2 diabetes (T2D) was previously identified by a GWAS in East Asian adults and was replicated in populations of Japanese, Korean, Chinese (Hong Kong and Singapore), and European ancestry.[45,46] Individuals carrying the C allele of rs2237892 had a higher risk of T2D with lower fasting insulin levels and a reduced insulin secretion in adulthood.[47] Previous studies also reported the association between infant RWG and T2D-related metabolism. For example, the Netherlands Cohort Study demonstrated that infant RWG during the first 3 months was significantly associated with reduced insulin sensitivity in early adulthood (β, −0.223; 95% CI, −0.386 to −0.060),[11] which was later replicated in Danish adolescents.[48] Considering the correlations among rs2237892, RWG, and T2D, we inferred that, on the one hand, the occurrence of RWG and T2D might share some similar genetic background and biological pathways, and, on the other hand, infant rapid weight gain might serve as a mediator between the association between rs2237892 (*KCNQ1*) and the T2D risk.

To our knowledge, this study provides the first evidence for a negative association between the T allele in rs2237892 (*KCNQ1*) on infant RWG during the first 3 months. Previous studies have shown inconsistent results of the effect of rs2237892 on lipid metabolic traits. For example, the minor alleles rs2237892 (T) were found to decrease the triglyceride level according to the results from a meta-analysis based on Uyghur and Han adults.[49] However, meta-analysis of GWASs conducted by Wen et al. reported a contradictory result, indicating that the C allele of rs2237892 was associated with lower BMI in adulthood.[14] The underlying mechanisms of RWG–obesity association might be complex, and further studies on the effect of rs2237892 on obesity-related traits are needed.

In our study, we found that the negative effect of the T allele of rs2237892 on RWG was only observed in transvaginal instead of cesarean deliveries. An earlier study reported a positive relationship between cesarean delivery and infant weight gain in the first year.[50] Another study reported different microbiota structure and composition in infants with a different delivery mode in the transitional stool at 3 days postnatally. For example, in comparison with vaginally delivered neonates, C-section-delivered neonates had lower proportions of the genera *Bacteroides*, *Parabacteroides*, and *Clostridium* in their microbiota, which led to a different

predicted abundance of microbial genes and related metabolic characteristics.[51] An animal experiment also demonstrated that the gut microbiota changes found in the C-section-born mice might explain the causal relationship between C-section and increased body weight.[52] We hypothesized that for infants delivered via C-section, the negative effect of the T allele in rs2237892 on the overnutritional growth of infants might be compromised due to the metabolomic changes programmed by the pioneering gut microbiota in the early life.

SNP rs2535633, an intron of the *ITIH4* gene, was found to be associated with infant RWG in our study, and infants with the heterozygote CG genotype instead of homozygote GG genotype had a lower RWG risk compared to that in infants with the CC genotype. However, each copy of the G allele of rs2535633 was associated with 0.0288 increased BMI in East Asian-ancestry adults, according to the findings suggested in a GWAS meta-analysis.[14] The inconsistency might trigger further questions on whether the impacts of SNP such as rs2535633 vary in relation to obesity traits at different ages, in addition to whether rapid weight gain in early years and obesity in later life share a common genetic background. More research is needed to answer these questions.

Some limitations of the current study are worth mentioning. First, there were some missing data on covariates such as maternal educational level, tobacco and alcohol exposure, and morbidity in pregnancy. However, there were no significant distributional differences between the initial and imputed datasets. Moreover, the MAF of rs12229654 was relatively small, especially in the case group; however, it might, to some degree, affect the robustness of the results of the recessive genetic model. Further studies with a large sample size are warranted for more robust results.

In conclusion, among a Chinese population, we identified the significant effects of rs2237892 and rs2535633 on RWG, as well as the moderating effect of delivery type on the rs2237892–RWG association in early infancy. Our findings suggested that specific SNPs could affect RWG in very early years of life, which might predispose children to a different risk of metabolomic diseases in the future. However, such effects could also be affected by environmental factors, for example, the negative association between T allele in rs2237892 and RWG could be compromised by cesarean delivery.

ACKNOWLEDGEMENTS

This study was supported by grants from the National Natural Science Foundation of China (grant numbers 81373017 and 81673182). We thank all the participants and their families as well as the medical staff involved in our study for the time and efforts.

AUTHOR CONTRIBUTIONS

Substantial contributions to conceptions and design, acquisition of data, or analysis and interpretation of data: Y.Z., H.M., K.X., C.L., R.C., H.Q., Y.Z., and J.Z. Drafting the article or revising it critically for important intellectual content: Y.Z. and J.Z. Final approval of the version to be published: all the authors.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-021-01601-8.

Competing interests: The authors declare no competing interests.

Informed consent: All the participants provided informed consent before study participation.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. Andrea, S. B. et al. Does the association between early life growth and later obesity differ by race/ethnicity or socioeconomic status? A systematic review. *Ann. Epidemiol.* **27**, 583–592.e585 (2017).
2. Ong, K. K. & Loos, R. J. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr.* **95**, 904–908 (2006).
3. Zheng, M. et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. *Obes. Rev.* **19**, 321–332 (2018).
4. Jain, V. & Singhal, A. Catch up growth in low birth weight infants: striking a healthy balance. *Rev. Endocr. Metab. Disord.* **13**, 141–147 (2012).
5. Marinkovic, T. et al. Early infant growth velocity patterns and cardiovascular and metabolic outcomes in childhood. *J. Pediatr.* **186**, 57–63.e54 (2017).
6. Sutharsan, R. et al. Rapid growth in early childhood associated with young adult overweight and obesity–evidence from a community based cohort study. *J. Health Popul. Nutr.* **33**, 13 (2015).
7. Bansal, N. et al. Effects of early growth on blood pressure of infants of British European and South Asian origin at one year of age: the Manchester children's growth and vascular health study. *J. Hypertens.* **26**, 412–418 (2008).
8. Botton, J. et al. Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls. *Am. J. Clin. Nutr.* **87**, 1760–1768 (2008).
9. Helgeland, Ø. et al. Genome-wide association study reveals dynamic role of genetic variation in infant and early childhood growth. *Nat. Commun.* **10**, 4448 (2019).
10. Kerkhof, G. F. et al. Health profile of young adults born preterm: negative effects of rapid weight gain in early life. *J. Clin. Endocrinol. Metab.* **97**, 4498–4506 (2012).
11. Leunissen, R. W., Kerkhof, G. F., Stijnen, T. & Hokken-Koelega, A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. *JAMA* **301**, 2234–2242 (2009).
12. Wang, G. et al. Weight gain in infancy and overweight or obesity in childhood across the gestational spectrum: a Prospective Birth Cohort Study. *Sci. Rep.* **6**, 29867 (2016).
13. Speliotes, E. K. et al. Association analyses of 249,796 individuals reveal eighteen new loci associated with body mass index. *Nat. Genet.* **42**, 937–948 (2010).
14. Wen, W. et al. Meta-analysis of genome-wide association studies in East Asian-ancestry populations identifies four new loci for body mass index. *Hum. Mol. Genet.* **23**, 5492–5504 (2014).
15. Miyake, Y., Tanaka, K. & Arakawa, M. ITIH3 and ITIH4 polymorphisms and depressive symptoms during pregnancy in Japan: the Kyushu Okinawa Maternal and Child Health Study. *J. Neural Transm.* **125**, 1503–1509 (2018).
16. Heo, S. G. et al. Male-specific genetic effect on hypertension and metabolic disorders. *Hum. Genet.* **133**, 311–319 (2014).
17. Zhang, W. et al. Variant rs2237892 of KCNQ1 is potentially associated with hypertension and macrovascular complications in type 2 diabetes mellitus in a Chinese Han Population. *Genomics Proteom. Bioinform.* **13**, 364–370 (2015).
18. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* **43**, 969–976 (2011).
19. Graulau, R. E. et al. Amount, preparation and type of formula consumed and its association with weight gain in infants participating in the WIC Program in Hawaii and Puerto Rico. *Nutrients* **11**, 695 (2019).
20. Pesch, M. H. et al. Mother and infant predictors of rapid infant weight gain. *Clin. Pediatr.* **58**, 1515–1521 (2019).
21. Ventura, A. K. & Thompson, K. Predictors of resilience among infants at risk for rapid weight gain. *Obesity* **27**, 130–136 (2019).
22. Yang, S. et al. Risks of maternal prepregnancy overweight/obesity, excessive gestational weight gain, and bottle-feeding in infancy rapid weight gain: evidence from a cohort study in China. *Sci. China Life Sci.* **62**, 1580–1589 (2019).
23. Mihrshahi, S., Battistutta, D., Magarey, A. & Daniels, L. A. Determinants of rapid weight gain during infancy: baseline results from the NOURISH randomised controlled trial. *BMC Pediatr.* **11**, 99 (2011).
24. Zhang, M. et al. Age- and sex-dependent association between FTO rs9939609 and obesity-related traits in Chinese children and adolescents. *PLoS ONE* **9**, e97545 (2014).
25. Wei, B. L. et al. The MC4R SNPs, their haplotypes and gene-environment interactions on the risk of obesity. *Mol. Med.* **26**, 77 (2020).
26. Marcos-Pasero, H. et al. The Q223R polymorphism of the leptin receptor gene as a predictor of weight gain in childhood obesity and the identification of possible factors involved. *Genes* **11**, 560 (2020).
27. Li, L. et al. Identification of genetic and environmental factors predicting metabolically healthy obesity in children: data from the BCAMS Study. *J. Clin. Endocrinol. Metab.* **101**, 1816–1825 (2016).
28. Sasakabe, T. et al. Modification of the associations of alcohol intake with serum low-density lipoprotein cholesterol and triglycerides by ALDH2 and ADH1B polymorphisms in Japanese men. *J. Epidemiol.* **28**, 185–193 (2018).

29. Hoffman, D. J., Powell, T. L., Barrett, E. S. & Hardy, D. B. Developmental origins of metabolic disease. *Physiol. Rev.* **101**, 739–795 (2020).
30. Gillman, M. W. Early infancy - a critical period for development of obesity. *J. Dev. Orig. Health Dis.* **1**, 292–299 (2010).
31. Brands, B., Demmelmair, H. & Koletzko, B. How growth due to infant nutrition influences obesity and later disease risk. *Acta Paediatr.* **103**, 578–585 (2014).
32. Huang, Y. et al. Effect of maternal glycemia and weight status on offspring birth measures and BMI-z among Chinese population in the first year. *Sci. Rep.* **7**, 16030 (2017).
33. World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. https://www.who.int/childgrowth/standards/technical_report/en/ (2020).
34. Li, N. et al. Maternal prepregnancy body mass index and gestational weight gain on offspring overweight in early infancy. *PLoS ONE* **8**, e77809 (2013).
35. Institute of Medicine and National Research Council. *Weight Gain During Pregnancy: Reexamining the Guidelines* (National Academies Press (US), 2009).
36. Abouelfettoh, A. M. et al. Cup versus bottle feeding for hospitalized late preterm infants in Egypt: a quasi-experimental study. *Int. Breastfeed. J.* **3**, 27 (2008).
37. Andersson, T. et al. Calculating measures of biological interaction. *Eur. J. Epidemiol.* **20**, 575–579 (2005).
38. Hosmer, D. W. & Lemeshow, S. Confidence interval estimation of interaction. *Epidemiology* **3**, 452–456 (1992).
39. Sterne, J. A. et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* **338**, b2393 (2009).
40. Gonzalez, J. R. et al. SNPassoc: an R package to perform whole genome association studies. *Bioinformatics* **23**, 644–645 (2007).
41. Buuren SV & Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. *J. Stat. Softw.* **45** (2011).
42. Jespersen, T., Grunnet, M. & Olesen, S. P. The KCNQ1 potassium channel: from gene to physiological function. *Physiology* **20**, 408–416 (2005).
43. Henrion, U. et al. Long QT syndrome-associated mutations in the voltage sensor of I(Ks) channels. *Cell Physiol. Biochem.* **24**, 11–16 (2009).
44. Ullrich, S. et al. Effects of I(Ks) channel inhibitors in insulin-secreting INS-1 cells. *Pflug. Arch.* **451**, 428–436 (2005).
45. Yasuda, K. et al. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat. Genet.* **40**, 1092–1097 (2008).
46. Unoki, H. et al. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat. Genet.* **40**, 1098–1102 (2008).
47. Hu, C. et al. Variations in KCNQ1 are associated with type 2 diabetes and beta cell function in a Chinese population. *Diabetologia* **52**, 1322–1325 (2009).
48. Fabricius-Bjerre, S. et al. Impact of birth weight and early infant weight gain on insulin resistance and associated cardiovascular risk factors in adolescence. *PLoS ONE* **6**, e20595 (2011).
49. Chen, X. D. et al. Several polymorphisms of KCNQ1 gene are associated with plasma lipid levels in general Chinese populations. *PLoS ONE* **7**, e34229 (2012).
50. Mueller, N. T. et al. Does cesarean delivery impact infant weight gain and adiposity over the first year of life? *Int. J. Obes.* **43**, 1549–1555 (2019).
51. Mueller, N. T. et al. Delivery mode and the transition of pioneering gut-microbiota structure, composition and predicted metabolic function. *Genes* **8**, 364 (2017).
52. Martinez, K. A. 2nd et al. Increased weight gain by C-section: functional significance of the primordial microbiome. *Sci. Adv.* **3**, eaao1874 (2017).