Maternal serum branched-chain amino acids in early pregnancy and offspring growth patterns from 1 year to 8 years of age

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To the Editor: Childhood obesity has been demonstrated to persist into adulthood and be associated with many adverse health outcomes later in adulthood, including cardiovascular diseases and type 2 diabetes.[1] *In utero* exposure to "undernutrition" or "over-nutrition" plays an important role in obesity in childhood and diseases in adulthood.[2] It is established that high branched-chain amino acids (BCAAs) are associated with insulin resistance and gestational diabetes mellitus (GDM).[3] However, it is largely unknown whether *in utero* exposure to high BCAAs also plays a role in adverse childhood growth patterns. We used 8-year children follow-up data of a case-control study nested within a population-based prospective cohort of pregnant women in Tianjin, China, to examine associations between maternal BCAAs levels in early pregnancy and obesity-related growth patterns if any, in offspring at 1–8 years of age.

The study design and methods have been reported previously.[4] Briefly, 22,302 pregnant women were registered with primary care hospitals from 2010 to 2012. Between 24 gestational weeks and 28 gestational weeks, all pregnant women were offered a glucose challenge test (GCT) and women with GCT level ≥7.8 mmol/L were required to undergo a standard oral glucose tolerance test (OGTT). GDM was diagnosed based on the International Association of Diabetes and Pregnancy Study Group's criteria.

Of 22,302 pregnant women, 2991 women provided fasting blood samples in early pregnancy. After excluding 227 women without the results of GCT and OGTT if their GCT was ≥7.8 mmol/L, 243 women were diagnosed with GDM and 243 women without GDM matched on maternal age (±1 year) were selected as controls. Finally, we included the 243 pairs of GDM and non-GDM women in the study [Supplementary Figure 1, http://links.lww.com/CM9/B840]. This study was approved by the Ethics Committee of Tianjin Women and Children's Health Center (No. 2009-02) and all the participants signed the written informed consent forms.

At postpartum, 486 children of these included women were invited to participate in the follow-up study and were provided the health examinations to measure their height and weight each year from 1 year to 8 years of age. Finally, 401 children (17.5% loss to follow-up) attended at least one postpartum follow-up. We assumed an exposure rate of 15% in the control group. To detect an odds ratio (OR) of 2.40 at 80% power and 5% type I error needs a minimum sample size of 244.

PASS 15 (NCSS, LLC.Kaysville, Utah, USA) was performed to calculate the sample size. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was performed for all statistical analyses. All the tests were two-sided and statistical significance was defined as *P*-value <0.05. A group-based trajectory modeling method was performed to identify distinct body mass index (BMI) growth patterns from 1 year to 8 years of age. All parameter estimation and model fitting were

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performed using a maximum likelihood method. An optimal number of trajectory groups was determined based on the following criteria: (1) the model having the lowest Bayesian information criteria value; (2) the average posterior probability of assignment for each group ≥0.7; and (3) the minimum sample size in each of trajectory groups ≥5% of the total sample.

Continuous variables were represented as mean ± standard deviation or median (interquartile range) and compared using one-way analysis of variance (ANOVA) or Kruskal–Wallis test where appropriate. Categorical variables were represented as number (percentage) and compared using Chi-squared test or Fisher's exact test where appropriate.

Multinomial logistic regression was performed to obtain ORs and their 95% confidence interval (CI) of maternal BCAAs for adverse growth patterns in the offspring if any. The linearity of the associations between maternal BCAAs and the risk of offspring adverse growth patterns was tested using restricted cubic spline analysis. We made careful visual checking of the shapes of the OR curves of maternal BCAAs for offspring adverse growth patterns and identified the optimal cut-off values of BCAAs. We performed a structured adjustment scheme to control for confounding factors in the multinomial logistic regression. First, univariate analysis was performed to obtain unadjusted ORs and 95% CIs. Second, multivariate analysis was conducted to adjust for the potential risk factors, including maternal pre-pregnancy BMI, parity, smoking habit, gestational age at delivery, and child gender. Third, we further adjusted for GDM in addition to those risk factors to check the potential mediation effect of GDM between BCAAs and adverse growth patterns.

Latent BMI trajectories of offspring from 1 year to 8 years of age. Among the 401 children who participated in the follow-up visits, four distinct BMI growth patterns were identified based on the group-based trajectory modeling approach. The four BMI trajectory patterns can be described as: (1) persistent lean growth pattern (PLGP, n = 110, 27.4%), characterized by a persistent low BMI over time; (2) normal growth pattern (NGP, n = 243, 60.6%), characterized by a middle and "normal" BMI over time; (3) persistent obesity growth pattern (POGP, n = 23, 5.7%), characterized by a high and persistent increased BMI over time; and (4) late obesity growth pattern (LOGP, n = 25, 6.2%), characterized by a normal BMI before 5 years of age and rapidly increased BMI after 5 years of age [Supplementary Figure 2, http://links.lww.com/CM9/B840].

Characteristics of offspring and mothers by different growth patterns. Compared to children with NGP or PLGP, children with POGP had a higher BMI from 1 year to 8 years of age while children with LOGP had a higher BMI after 5 years of age [Supplementary Table 1, http://links.lww.com/CM9/B840]. Their mothers of the POGP and LOGP children had a higher pre-pregnancy BMI and were more likely to smoke before and during pregnancy [Supplementary Table 2, http://links.lww.com/CM9/B840].

Associations of serum BCAAs with POGP and LOGP. Maternal valine was positively associated with the risk of POGP in the offspring in a non-linear manner while maternal valine was almost not associated with the risk of LOGP [Supplementary Figure 3, http://links.lww.com/CM9/B840]. Maternal valine ≥210.0 nmol/mL (i.e., high valine) was associated with markedly increased risk of POGP in the offspring in univariable and multivariable analyses (OR: 3.49, 95% CI: 1.49–8.21 and 2.76, 1.13–6.71). After further adjustment for GDM, the OR of high valine for POGP was slightly attenuated but its statistical significance persisted (2.70, 1.10–7.24). However, high valine was not significantly associated with the risk of LOGP [Supplementary Table 3, http://links.lww.com/CM9/B840].

Maternal leucine was associated with increased risk of POGP in the offspring in a U-shaped manner. Using 130.7–155.0 nmol/mL as the reference, maternal leucine ≥155.0 nmol/mL (i.e., high leucine) was associated with greatly increased risks of both POGP and LOGP in multivariable analysis (adjusted OR: 3.73, 1.14–12.19 and 3.13, 1.04–9.44), but maternal leucine <130.7 nmol/mL was not significantly associated with the risk of both POGP and LOGP. After further adjustment for GDM, high leucine was still significantly associated with increased risk of POGP (3.71, 1.14–12.11) while high leucine was no longer significantly associated with increased risk of LOGP (2.94, 0.97–8.90).

Maternal isoleucine was linearly associated with the risk of POGP in the offspring while maternal isoleucine was associated with the risk of LOGP in a non-linear manner. Maternal isoleucine ≥42.9 nmol/mL (i.e., high isoleucine) was associated with elevated risk of POGP but high isoleucine was not associated with the risk of LOGP (adjusted OR: 2.76, 1.05–7.24 and 1.70, 0.62–4.65). After further adjustment for GDM, the OR of high isoleucine for POGP was slightly attenuated but still significant (2.74, 1.04–7.20).

Among male infants, the ORs of maternal high *vs*. low levels of valine, leucine, and isoleucine for POGP were 2.80 (1.15–6.81), 4.08 (1.28–13.03), and 2.79 (1.07–7.24), respectively. Among other subgroups, maternal high valine, leucine, and isoleucine were also positively associated with the risk of POGP although not significantly [Supplementary Table 4, http://links.lww.com/CM9/B840]. After separately excluding multiparous and smoking women before and during pregnancy, high valine, leucine, and isoleucine remained significantly associated with increased risk of POGP [Supplementary Table 5, http://links.lww.com/CM9/B840].

Using a group-based trajectory modeling analysis, this study identified four distinct childhood growth patterns, i.e., NGP, PLGP, POGP, and LOGP. We found that maternal high valine, leucine, and isoleucine in early pregnancy were associated with markedly increased risk of POGP in offspring; maternal high leucine was also associated with markedly increased risk of LOGP, only partially mediated via GDM.

In recent years, a few studies have attempted to explore associations of maternal BCAAs during pregnancy with newborn birth weight but their findings were inconsistent and inconclusive. Two independent birth cohorts in Spain found that maternal elevated BCAAs during late pregnancy were associated with greater birth weight in offspring.[5] However, another study observed that maternal fasting BCAAs were not associated with birth weight in offspring.[6] There is a lack of literature reporting risk associations of maternal BCAAs in early pregnancy with childhood obesity in offspring. In this study, we found that maternal high valine, leucine, and isoleucine in early pregnancy were associated with markedly increased risk of POGP in offspring and maternal high leucine was also associated with greatly elevated risk of LOGP in offspring.

High levels of BCAAs were able to active mammalian target of rapamycin and induce phosphorylation of insulin receptor substrate 1, leading to insulin resistance.[7] Due to increased insulin resistance, maternal excessive glucose and fatty acids could pass across the placental barrier and stimulate the excessive production of insulin and insulin-like growth factor 1 in the fetus.[8] They could contribute to the accumulation of adipose tissues and protein in the fetus, leading to a vicious intergenerational cycle of obesity.[9]

In conclusion, our study identified four distinct childhood growth patterns among the Chinese population. We found that maternal high valine, leucine, and isoleucine in early pregnancy were associated with greatly increased risk of POGP in offspring and maternal high leucine was also associated with greatly increased risk of LOGP in offspring. The latter may be partially mediated via GDM. Further studies are warranted to validate our findings, and mechanistic investigations are also needed to explore biological links from early life BCAAs exposure to adverse childhood growth patterns.

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Conflicts of interest

None.

References

1. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: A systematic review and meta-analysis. Obes Rev 2016;17:56–67. doi: 10.1111/obr.12316.
2. Zhou LY, Deng MQ, Zhang Q, Xiao XH. Early-life nutrition and metabolic disorders in later life: A new perspective on energy metabolism. Chin Med J 2020;133:1961–1970. doi: 10.1097/cm9.0000000000000976.
3. Li N, Li J, Wang H, Liu J, Li W, Yang K, *et al*. Branched-chain amino acids and their interactions with lipid metabolites for increased risk of gestational diabetes. J Clin Endocrinol Metab 2022;107:e3058–e3065. doi: 10.1210/clinem/dgac141.
4. Li J, Huo X, Cao YF, Li SN, Du Z, Shao P, *et al*. Bile acid metabolites in early pregnancy and risk of gestational diabetes in Chinese women: A nested case-control study. EBioMedicine 2018;35:317–324. doi: 10.1016/j.ebiom.2018.08.015.
5. Maitre L, Villanueva CM, Lewis MR, Ibarluzea J, Santa-Marina L, Vrijheid M, *et al*. Maternal urinary metabolic signatures of fetal growth and associated clinical and environmental factors in the INMA study. BMC Med 2016;14:177. doi: 10.1186/s12916-016-0706-3.
6. Kadakia R, Nodzenski M, Talbot O, Kuang A, Bain JR, Muehlbauer MJ, *et al*. Maternal metabolites during pregnancy are associated with newborn outcomes and hyperinsulinaemia across ancestries. Diabetologia 2019;62:473–484. doi: 10.1007/s00125-018-4781-1.
7. Yoon MS. The emerging role of branched-chain amino acids in insulin resistance and metabolism. Nutrients 2016;8:405. doi: 10.3390/nu8070405.
8. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci 2018;19:3342. doi: 10.3390/ijms19113342.
9. Schwartz R, Gruppuso PA, Petzold K, Brambilla D, Hiilesmaa V, Teramo KA. Hyperinsulinemia and macrosomia in the fetus of the diabetic mother. Diabetes Care 1994;17:640–648. doi: 10.2337/diacare.17.7.640.

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