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Prenatal exposure to hyperglycemia and child growth trajectories in the first 3 years of life: a prospective birth cohort

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Abstract

Background Infants exposed to hyperglycemia in pregnancy (HIP) in utero are known to have higher risks of macrosomia at birth and obesity in adulthood, but longitudinal growth patterns in early childhood remain poorly characterized. This study aimed to examine HIP-associated differences in early childhood growth trajectories.

Methods In the population-based prospective Jiangsu Birth Cohort (JBC) study, 8780 children (23.3% HIP exposed) were included. Linear mixed models were used to assess the associations of maternal HIP with repeated growth measures in children. Latent class mixed models (LCMM) were used to identify trajectories for weight-for-age (WAZ), length/height-for-age (LAZ) and weight-for-length *z*-scores (WFL). Models were fitted to the full 0–36-month age range, with measurements at ages 0, 3, 6, 8, 12, 18, 24, 30, and 36 months, respectively. Adjusted associations between maternal HIP and child trajectory classes were evaluated with modified Poisson regression.

Results A higher proportion of LGA in the HIP-exposed group was observed. During the follow-up period from birth to 36 months, maternal HIP was associated with lower WAZ ($a\beta = -0.075$, 95% CI: −0.117, −0.034), LAZ ($a\beta = -0.054$, 95% CI: −0.099, −0.009), and WFL ($a\beta = -0.061$, 95% CI: −0.100, −0.022) in children. HIP was also correlated with reduced weight and body mass index (BMI) growth velocity at 0–3 and 6–8 months. Three distinct trajectory groups were identified, namely, moderate-stable, high-decreasing and low-increasing group. HIP exposed children were more likely to follow the high-decreasing WFL trajectory (aRR = 1.14, 95% CI: 1.01, 1.29).

Conclusions Maternal HIP was associated with slower growth in early childhood and an increased likelihood of following a high-decreasing growth trajectory, suggesting its potential long-term implications for child growth regulation.

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Keywords Cohort study, Infant growth trajectories, Hyperglycemia in pregnancy, Latent class mixed model, Catch-down growth

Background

In early gestation, the fetus relies on maternal glucose transferred through the placenta, which leads to a physiological decline in maternal blood glucose levels [1]. As pregnancy progresses into the second and third trimesters, placental hormones, such as human placental lactogen, cortisol, and progesterone, increase substantially, inducing insulin resistance [2]. In healthy pregnancies, this can be compensated by increased insulin secretion to maintain glucose homeostasis. When this compensatory mechanism is inadequate, maternal hyperglycemia develops [3]. This condition, referred to as hyperglycemia in pregnancy (HIP), is defined by World Health Organization (WHO), including both gestational diabetes mellitus (GDM) and pre-gestational diabetes (pGDM) [4]. GDM refers to abnormal blood glucose detected for the first time during pregnancy, but not yet reaching the diagnostic threshold for diabetes, while pGDM includes pre-existing diagnosed diabetes mellitus or blood glucose during pregnancy that meets the diagnostic threshold for adult diabetes mellitus. HIP has become a growing public health challenge worldwide. In terms of time trend, the average incidence rate has been increasing, with obvious regional differences [5]. Globally, it affects approximately 16.7% of pregnancies [5], whereas in China, the prevalence might be even higher, exceeding 21% [6].

Maternal HIP has been associated with a range of adverse perinatal outcomes and its influence extends beyond the neonatal period. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study revealed a positive association between maternal glycemic levels and birth weight [7]. Several studies further indicated that children exposed to maternal hyperglycemia are at a higher risk of developing obesity by the age of 7 to 11 years [8–10].

Accumulating evidence has linked maternal hyperglycemia, including GDM, type 1 diabetes (T1DM), and type 2 diabetes (T2DM), with altered childhood growth patterns [11–13]. Several longitudinal studies have documented the associations between HIP and accelerated or decelerated growth in early life. Importantly, infants born LGA often exhibit a compensatory "catch-down" growth trajectory during infancy [14], whereas those born small for gestational age (SGA) typically demonstrate "catch-up" growth [15]. These adaptations are thought to reflect metabolic regulation aimed at restoring growth toward genetically determined targets. Nevertheless, prior studies have reported inconsistent findings, with heterogeneity by population, timing of assessment, and analytic approach. Among studies focusing on single time point, a British study examining infant body composition reported that infants exposed to HIP had a 16% higher total adipose tissue volume at 2 months of age [16]. In contrast, an Australian study found that at 18 months, offspring in the HIP group exhibited lower mean values for weight, BMI, head circumference, and upper arm circumference [17]. In longitudinal studies, an Indian cohort of 630 mother-infant pairs revealed that newborns from the HIP group initially had significantly larger physical measurements than controls. However, these differences diminished over time and were no longer statistically significant at 1 year of age. Interestingly, at 2 years of age, the HIP affected offspring again demonstrated significant advantages in measures, such as parietal heel length and skinfold thickness [18]. Similarly, one cohort study involving 6684 mother–child pairs in China found that while higher maternal glycemia levels were associated with increased child BMI at birth, this relationship weakened by the age of two [19]. A meta-analysis also concluded that higher maternal glucose levels were not associated with offspring BMI *z*-scores during early childhood; however, they were linked to higher BMI *z*-scores during school age and later [20]. In particular, evidence regarding differential impacts on distinct growth patterns and longitudinal changes in weight and height from birth to 3 years remains inconsistent, and data from large, prospective Asian birth cohorts are scarce. Growth trajectories in infancy may be better predictors of long-term health outcomes than single cross-sectional measurements [21, 22], but few studies have conducted repeated measurements throughout infancy to capture growth trajectories in very early life. Based on our prior studies [23], we employed latent class mixed modeling (LCMM) to analyze data from a large, population-based prospective Chinese birth cohort, in which repeated anthropometric measurements were documented from birth to 36 months. This approach allowed us to comprehensively evaluate HIP-related differences in anthropometry, growth velocity, and distinct growth trajectories.

Methods

Study design and participants

The present study was conducted within the Jiangsu Birth Cohort (JBC) Study, an ongoing population-based

prospective cohort study. The JBC collects detailed health-related information and biospecimens from both biological parents and their offspring through standardized procedures across all participating sites. Ethical approval was obtained from the Ethics Committee of Nanjing Medical University (NJMUIRB [2014] 248). Written informed consent was obtained from all participating mothers at recruitment, covering pregnancy assessments, delivery information, and all follow-up measurements of offspring growth and development. The consent explicitly stated that telephone follow-ups, questionnaire surveys, and biospecimen collection would be conducted during prenatal care, hospitalization, and subsequent child development. For follow-up participants under 16 years of age, written informed consent was obtained from a parent or legal guardian at each hospital visit and questionnaire administration.

Between 2014 and 2020, 14,969 women with singleton pregnancies were recruited from three hospitals in Jiangsu Province: the Women's Hospital Affiliated to Nanjing Medical University, Suzhou Hospital Affiliated to Nanjing Medical University, and Changzhou Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University. The overall response rate was 75.0%. We excluded 2463 women without HIP diagnostic data, 19 cases of neonatal death, and 3707 participants with fewer than three anthropometric measurements at the scheduled visits (1, 3, 6, 8, 12, 18, 24, 30, and 36 months). A total of 8780 mother–infant pairs were included in the final analysis (Additional file 1: Fig. S1). The study protocol has been approved by the Human Investigation Committees at Nanjing Medical University. Detailed research design and information collection have been described previously [23].

HIP assessment

Detailed clinical diagnosis of HIP was extracted from medical records. As part of routine prenatal care, the oral glucose tolerance test (OGTT) is recommended for all pregnancies [4]. According to the WHO diagnostic criteria [4], HIP is diagnosed if one or more of the following conditions are met: (1) fasting blood glucose (FBG) $\geq$ 5.1 mmol/L; (2) 1-h plasma glucose $\geq$ 10.0 mmol/L following a 75-g oral glucose load; (3) 2-h plasma glucose $\geq$ 8.5 mmol/L following a 75 g oral glucose load; or (4) random plasma glucose $\geq$ 11.1 mmol/L with diabetes symptoms. Among them, those with FBG $\geq$ 7.0 mmol/L or a 2-h plasma glucose $\geq$ 11.1 mmol/L were classified as pGDM, while the remainder were diagnosed with GDM.

Outcome variables

Offspring birth weight and anthropometric measurements at birth, 1, 3, 6, 8, 18, 24, and 30 months were extracted from medical records. At 12 and 36 months of age, anthropometric measurements were conducted at the child health care departments of the birth hospitals as part of routine follow-up. Undressed weight was measured using calibrated scales to the nearest 0.1 kg. Recumbent length (for children < 24 months) or standing height ($\geq$ 24 months) was measured to the nearest 0.1 cm using calibrated stadiometers or length boards. Primary outcomes included age- and sex-specific *z*-scores for weight-for-age (WAZ), length/height-for-age (LAZ), and weight-for-length (WFL) calculated according to the 2006 WHO growth reference standards [24] and growth trajectories of each index. Growth trajectories were derived from LCMM fitted to all available repeated measurements from birth to 36 months. Extreme outliers (> 5 or < −5 for WAZ and WFL; > 6 or < −6 for LAZ) without plausible explanation were excluded [25], accounting for < 1% of all measurements. Secondary outcomes were growth velocities. Growth velocity was calculated as the change in raw anthropometric measurements between two consecutive visits, divided by the interval in months.

Covariates

Questionnaires were completed through face-to-face interviews at recruitment and follow-up visits. Demographic characteristics, including maternal age at delivery (continuous, years), area of residence (rural or urban), household income (< 10,0000, 10,0000–20,0000 and > 20,0000 CNY), maternal and paternal education (< 12 years or $\geq$ 12 years) and lifestyle habits (including passive smoking or drinking during pregnancy) were obtained. Pre-pregnancy BMI was calculated by dividing pre-pregnancy weight (kg) by height (m) squared. At delivery, mothers' history of gestation, parity (nulliparous or multiparous), hypertensive disorders in pregnancy, birth weight (continuous, grams), maternal weight gain during pregnancy (continuous, kilograms), gestational age at delivery (continuous, weeks), and sex of newborns (boys or girls) were extracted from the medical record. At 1 year and 3 years of age, mothers and children would be invited to complete a structured questionnaire collection data on offsprings' feeding patterns, sleep patterns and diseases.

A directed acyclic graph (DAG) was utilized to represent our priori causal hypotheses regarding the relationships between the HIP and child growth trajectories and to guide the variable selection approach [26]. Based on the DAG and available data, we finally included pre-pregnancy BMI, parity, maternal education, maternal age at delivery, passive smoking during pregnancy, area

of residence, household income and child sex as minimal adjustment sets (Additional file 1: Fig. S2), which were adjusted in the main analysis. To account for any residual confounding, sensitivity models were further adjusted for gestational weight gain and delivery method.

Statistical methods

The study population characteristics were shown with continuous variables being displayed as means ± standard deviations, and categorical variables being presented in numbers (percentage). Linear regressions were used to examine the association between HIP and offspring growth at specified time points. Linear mixed models (LMM) were used to evaluate the association between HIP and repeated offspring growth measures, adjusting for within-individual and between-individual variations [27]. Afterwards, to identify patterns of child growth trajectories from birth to 3 years old, we used LCMM based on their anthropometries measured at ages of 1, 3, 6, 8, 12, 18, 24, 30, and 36 months. This is a specialized form of finite mixture modeling and is designed to identify latent classes of individuals following similar progressions over time or with age [28]. The LCMM package in R was used to estimate latent class mixed models in a maximum likelihood framework. Unlike conventional longitudinal regression models, which may overlook the complex and heterogeneous nature of growth, LCMM enables the identification of distinct subgroups allowing for the assumption that growth trajectories are not parallel [29]. LCMM is a data-driven approach to identify similar patterns of change in longitudinal data. To determine the optimal number of groups, the following criteria should be fitted: (1) a Bayesian information criterion (BIC, requiring data as close to 0 as possible), (2) the threshold of the mean posterior probability of membership (reaching ≥ 0.7 for each trajectory subgroup), and (3) a reasonable distribution of the participants (class size ≥ 2% of the population) [30, 31]. To facilitate interpretability, we assigned labels to the trajectories on the basis of their modeled graphic patterns. For interpretative clarity, the biological implications of each trajectory group are described in the Results section and figure legends. Models were fitted to the set of repeated measurements from birth to 36 months (0, 3, 6, 8, 12, 18, 24, 30, and 36 months). Associations between HIP with trajectory classes were evaluated with modified Poisson regression.

Based on the existing evidence on the sex differentiation in offspring growth [32], we first conducted sex stratified analysis to explore whether any factor might modify the effect of maternal hyperglycemia. Additionally, given that evidence suggests a link between breastfeeding duration and child growth, we replicated the main analysis stratified by the duration of breastfeeding (less than 6 months *vs.* 6 months or longer) to evaluate the variations on the study's association [33]. The heterogeneity test was performed to assess the consistency of results among different sub-groups. To address potential bias from metabolic disorders before and during pregnancy, we performed sensitivity analysis by excluding participants with hypertensive disorders during pregnancy ($n = 430$). Additionally, to account for differences in growth velocity of IVF/ICSI conception and preterm birth, we performed analysis restricted to spontaneously conceived ($n = 6952$) and term-born infants ($n = 8404$).

All the statistical analysis were conducted in R Software Version 4.3.1 (The R Foundation). A two-sided P value less than 0.05 was considered statistically significant.

Results

Description of the population

Baseline characteristics of the study participants are presented in Table 1. The mean (SD) BMI of HIP-exposed mothers before pregnancy was 22.6 (3.4), and their mean age at delivery was 31.4 (4.0), compared to 29.7 (3.8) for non-exposed mothers. Additionally, 1699 (82.9%) of HIP-exposed mothers resided in urban or suburban areas. Mothers in the HIP group also had a higher percentage of passive smoking and cesarean deliveries compared to those in the non-exposed group. In the HIP group, 1165 infants (56.9%) were boys, with a mean birth weight of 3372.6 ± 495.5 g. The classification of infant size for gestational age varied by HIP exposure, with a higher percentage of infants exposed to HIP being LGA compared to the non-exposed group (17.2% *vs.* 11.8%), and a lower percentage being SGA (3.8% *vs.* 4.2%). Infant anthropometric indexes from birth to 36 months were shown in Additional file 1: Fig. S3 and Fig. S4. WAZ, LAZ and WFL showed a rapid increase in the first 6 months, stabilizing thereafter. Mean weight at birth, 1 year and 3 years were 3.36 (0.45), 10.14 (1.16) and 15.06 (1.89), respectively. Body length at 1 and 3 years was 76.38 (2.70) and 97.77 (3.64) cm. The sample size at each time points and other details of anthropometric index's *z*-scores were displayed in Additional file 2: Table S1. The rate of weight gain in the first month of life differed significantly between the groups, with mean values of 1.35 ± 0.46 kg/month and 1.39 ± 0.47 kg/month, respectively ($P = 0.013$).

The rate change in BMI also differed significantly between the groups at 6–8 months of age, with values of − 0.08 ± 0.47 kg/m^2·month in the non-HIP group and − 0.11 ± 0.47 kg/m^2·month in the HIP group (Additional file 2: Table S2). Covariates with missing data were

Table 1 Baseline characteristics of mothers and their children according to mothers' HIP status

Characteristics	Non-HIP exposed	HIP exposed	*P*[a]
Maternal characteristics	6731	2049	
Age at delivery, years	29.7 ± 3.8	31.4 ± 4.0	< 0.001
Pre-pregnancy BMI, kg/m^2	21.1 ± 2.8	22.6 ± 3.4	< 0.001
Pre-pregnancy BMI category (kg/m^2, %)	1056 (15.7)	171 (8.4)	< 0.001
< 18.5	1056 (15.7)	171 (8.4)	
18.5–23.9	4729 (70.3)	1277 (62.4)	
24–27.9	761 (11.3)	446 (21.8)	
≥ 28	166 (2.5)	150 (7.3)	
Area of residence (*n*, %)			< 0.001
Rural	1616 (24.0)	350 (17.1)	
Urban/sub-urban	5115 (76.0)	1699 (82.9)	
Household income (CNY, %)			< 0.001
< 100,000	2127 (31.9)	581 (28.6)	
100,000–200,000	2864 (43.0)	863 (42.5)	
> 200,000	1677 (25.2)	587 (28.9)	
Maternal education (years, %)			< 0.001
≤ 12	1027 (15.3)	388 (18.9)	
> 12	5694 (84.7)	1661 (81.1)	
Parity (*n*, %)			0.002
Nulliparous	5293 (78.6)	1542 (75.3)	
Multiparous	1421 (21.1)	505 (24.7)	
Passive smoking (*n*, %)	2192 (33.3)	756 (37.5)	0.002
Drinking (*n*, %)	90 (1.3)	21 (1.0)	0.369
Hypertensive disorders in pregnancy [b] (*n*, %)	279 (4.2)	151 (7.4)	< 0.001
Mode of delivery (*n*, %)			< 0.001
Cesarean	2510 (37.3)	1016 (49.6)	
Vaginal delivery	4206 (62.5)	1029 (50.2)	
Infant characteristics			
Sex (%)			0.002
Boys	3537 (52.6)	1165 (56.9)	
Girls	3193 (47.4)	883 (43.1)	
Gestational age, weeks	39.5 ± 1.4	39.2 ± 1.5	< 0.001
Preterm birth [c] (*n*, %)	257 (3.8)	119 (5.8)	< 0.001
Birth weight, g	3360.4 (439.8)	3372.6 (495.5)	0.286
Birth weight category (*n*, %)			< 0.001
LBW	171 (2.5)	74 (3.6)	
Normal	6137 (91.2)	1809 (88.3)	
Macrosomia	397 (5.9)	164 (8.0)	
Birth weight *z*-score	0.3 ± 0.9	0.4 ± 1.0	< 0.001
Fetal size (*n*, %)			< 0.001
SGA	279 (4.2)	78 (3.8)	
AGA	5639 (83.8)	1612 (78.7)	
LGA	794 (11.8)	353 (17.2)	
Breastfeeding duration (months, %)			0.261
< 6	1259 (18.7)	380 (18.6)	
≥ 6	5411 (80.4)	1658 (80.9)	
Number of measurements, times	7.2 ± 1.4	7.2 ± 1.5	0.074

Data represent the number (percentage) or mean ± standard deviation

Abbreviations: *BMI* body mass index, *CNY* Chinese yuan, *LBW* low birth weight, *SGA* small for gestational age, *AGA* appropriate for gestational age, *LGA* large for gestational age

[a] *P* value was calculated using chi-square test for proportions and ANOVA F test for means

[b] Hypertension disorders in pregnancy includes chronic, gestational and pre-eclampsia

[c] The cutoff point to distinguish preterm and term children is 37 gestational weeks

rare (< 5% for each; Additional file 2: Table S3). We conducted complete-case analysis without imputation, as the low level of missingness was unlikely to bias the results.

Association between HIP and anthropometric measures at different time points

As shown in Fig. 1, across the entire follow-up period from birth to 36 months, HIP was significantly associated with reduced WAZ, LAZ and WFL during the first 3 years (WAZ: a$\beta = -0.065$ [95% CI: −0.105, −0.026]; LAZ: a$\beta = -0.054$ [95% CI: −0.099, −0.009]; WFL: a$\beta = -0.061$ [95% CI: −0.100, −0.022]). These estimates were derived from linear mixed models that accounted for repeated measurements across time points. As to birth size, HIP was associated with a higher risk of LGA infants (Additional file 1: Table S4, aRR = 1.17, 95% CI: 1.01, 1.36; $P = 0.035$).

Significant associations between HIP and lower LAZ were observed at 3 months (a$\beta = -0.090$, 95% CI: −0.156, −0.025), 6 months (a$\beta = -0.089$, 95% CI: −0.153, −0.025), and 8 (a$\beta = -0.081$, 95% CI: −0.143, −0.019) months of age. Moreover, HIP was consistently linked to lower WAZ, starting as early as the first month of life. Furthermore, from 8 months onwards, HIP was associated with a decline in WFL (at 8 months: a$\beta = -0.085$, 95% CI: −0.145, −0.026; at 12 months: a$\beta = -0.106$, 95% CI: −0.158, −0.055; at 18 months: a$\beta = -0.066$, 95% CI: −0.116, −0.015; at 24 months: a$\beta = -0.124$, 95% CI: −0.175, −0.073; at 30 months: a$\beta = -0.071$, 95% CI: −0.130, −0.012; at 36 months: a$\beta = -0.083$, 95% CI: −0.136, −0.030), reflecting potential growth challenges relative to weight and length (Additional file 2: Table S5).

In the stratified analysis of infant sex and duration of breastfeeding (less than 6 months versus 6 months or longer), we observed results consistent with the main analysis (Additional file 1: Fig. S5 and Additional file 2: Table S6). Although the association with WAZ and WFL in girls were not statistically significant at 12 months, the effect size of association still remained. In the sensitivity analysis, when restricted to infants unexposed to maternal hypertensive disorders during pregnancy, those conceived spontaneously, term-born infants, infants born to mothers with a BMI ≤ 24 kg/m^2, or mothers without pre-pregnancy diabetes, although some changes were observed, the overall results were consistent with our main analysis (Additional file 1: Fig. S6 and Additional file 2: Table S7).

HIP was also significantly associated with reduced weight growth velocity between 0 to 3 (Table 2, a$\beta = -0.022$, 95% CI: −0.036, −0.008) and 6 to 8 months of age (a$\beta = -0.017$, 95% CI: −0.032, −0.002). Similarly, lower BMI growth velocity was observed between 6 to 8 months in the HIP group (a$\beta = -0.042$, 95% CI: −0.078, −0.006).

Trajectories for anthropometric measures

Using LCMM, three distinct trajectory groups were identified for WAZ, LAZ, and WFL. Figure 2 illustrates these trajectory groups to reflect growth trends, which were labeled as "low-increasing," "moderate-stable," and "high-decreasing" based on its initial values (low, moderate or high) and trends (increasing, stable or decreasing). Dashed lines around the solid lines represent the confidence intervals for the calculated trajectories. Low-increasing was characterized by lower baseline *z*-scores

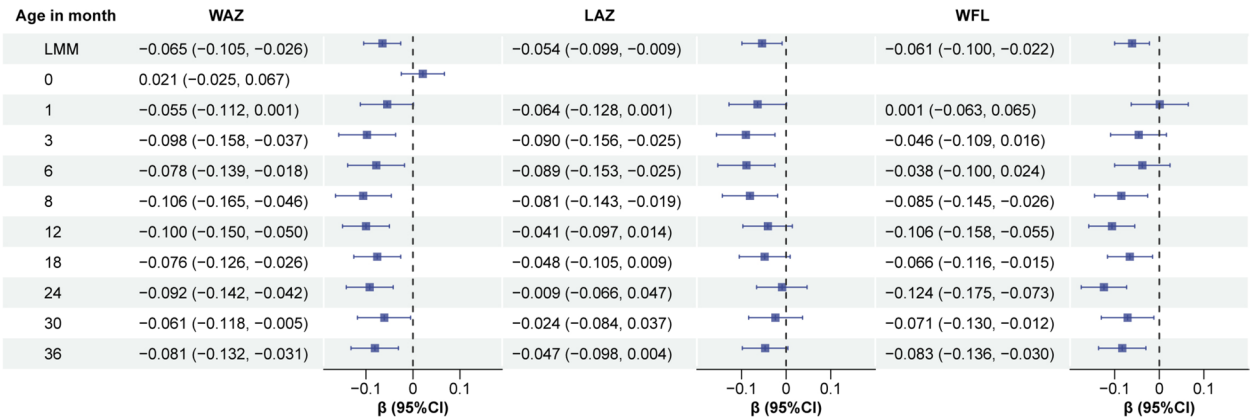

Fig. 1 Forest plot of the association between maternal HIP and infant anthropometric *z*-scores at ten time points from birth to 3 years. β and 95% CI for each anthropometrical measures according to maternal HIP in general linear models. All models were adjusted for pre-pregnancy BMI, parity, maternal education, maternal age at delivery, passive smoking during pregnancy, area of residence, household income and child sex. Abbreviations: HIP, hyperglycemia in pregnancy; BMI, body mass index; CI, confidence interval; LAZ, length/height-for-age *z*-score; WAZ, weight-for-age *z*-score; WFL, weight-for-length *z*-score

Table 2 Association between maternal HIP and growth velocity of anthropometric indicators at different periods

Period (month)	Weight (kg/month)			Length/height (cm/month)			BMI (kg/m^2·month)		
	Mean (SD)	β (95% CI)[a]	P[a]	Mean (SD)	β (95% CI)[a]	P[a]	Mean (SD)	β (95% CI)[a]	P[a]
0–3	1.16 (0.24)	−0.022 (−0.036, −0.008)	0.003	-	-	-	-	-	-
3–6	0.56 (0.19)	−0.001 (−0.016, 0.013)	0.864	2.00 (0.57)	−0.015 (−0.057, 0.027)	0.487	0.21 (0.41)	0.017 (−0.014, 0.048)	0.280
6–8	0.34 (0.20)	−0.017 (−0.032, −0.002)	0.031	1.49 (0.66)	0.030 (−0.020, 0.080)	0.238	−0.08 (0.47)	−0.042 (−0.078, −0.006)	0.021
8–12	0.24 (0.15)	−0.001 (−0.014, 0.012)	0.888	1.27 (0.41)	0.003 (−0.031, 0.038)	0.852	−0.16 (0.29)	0.009 (−0.016, 0.033)	0.496
12–18	0.21 (0.11)	0.000 (−0.009, 0.010)	0.923	1.10 (0.28)	−0.001 (−0.025, 0.023)	0.943	−0.14 (0.18)	0.008 (−0.008, 0.023)	0.337
18–24	0.22 (0.12)	−0.002 (−0.011, 0.007)	0.693	0.98 (0.28)	0.013 (−0.009, 0.034)	0.246	−0.03 (0.17)	−0.006 (−0.020, 0.007)	0.330
24–30	0.20 (0.13)	0.005 (−0.007, 0.017)	0.410	0.84 (0.28)	−0.004 (−0.029, 0.021)	0.755	−0.06 (0.16)	0.012 (−0.003, 0.026)	0.119
30–36	0.19 (0.14)	−0.009 (−0.023, 0.004)	0.188	0.67 (0.29)	−0.020 (−0.049, 0.009)	0.177	−0.05 (0.16)	−0.002 (−0.018, 0.014)	0.811

[a] Adjusted for pre-pregnancy BMI, parity, maternal education, maternal age at delivery, passive smoking during pregnancy, area of residence, household income and child sex

at birth, followed by a gradual increase over time, indicating potential catch-up growth. High-decreasing was characterized by higher baseline *z*-scores at birth, followed by a marked decline during infancy, suggesting early growth deceleration or "catch-down" growth. The "moderate-stable" trajectory served as the reference group for all measures, as it included a largest portion of the population and maintained a mean *z*-score near zero. The BIC values and other details of the model are presented in Additional file 2: Table S8 and Additional file 2: Table S9 presents the baseline characteristics of mothers and their children across the WFL trajectory groups identified by latent class mixed modeling. Compared with the moderate-stable group, mothers in both high-decreasing and low-increasing groups were more likely to be diagnosed with HIP.

Association between HIP and growth trajectories

Offspring exposed to maternal hyperglycemia exhibited a 14% higher risk of following ahigh-decreasing WFL trajectory compared to unexposed children (aRR = 1.14; 95% CI, 1.01–1.29; $P = 0.031$). No significant associations were observed for other growth indices (Table 3). Similarly, within the low-increasing trajectory group, no significant associations were identified. Association analysis between HIP subtypes and WFL trajectories revealed that GDM was linked to a higher likelihood of infants following a high-decreasing WFL growth trajectory (Additional file 2: Table S10, aRR = 1.16; 95% CI, 1.03–1.30; $P = 0.015$).

To further explore potential risk groups in smaller samples [31], WFL trajectory patterns were classified into two to five groups, as illustrated in Additional file 2: Fig. S7. When classified into four groups, a distinct "high-increasing" growth pattern ($n = 116$) emerged. In this group, HIP exposure was significantly associated in the crude model (Additional file 1: Table S11, aRR = 1.85; 95% CI, 1.25–2.73; $P = 0.002$). However, this association became marginally significant after adjusting for confounders (aRR = 1.56; 95% CI, 0.95–2.54; $P = 0.076$).

Discussion

We identified distinct early-life growth trajectories and found that exposure to maternal HIP increased the likelihood of following a "high-decreasing" WFL pattern, consistent with a catch-down growth profile. This trajectory-level finding was supported by our longitudinal *z*-score analysis, which showed that HIP-exposed children had consistently lower weight, length, and WFL *z*-scores at multiple time points from birth to 3 years.

Although HIP exposure was associated with a higher proportion of LGA births [7], this pattern did not persist into infancy. Our findings align with previous studies. For example, a Danish register-based study reported growth deceleration at 5 and 12 months among HIP-exposed children [34], and research in Pima Indian populations found higher weight-for-age *z*-scores at birth that were no longer evident by 1.5 years compared to unexposed peers [35]. Together, these results suggest that the impact of maternal hyperglycemia on offspring growth may be age-specific, with critical time windows in early life.

There are several potential explanations for the associations observed in our study. First, during the intrauterine

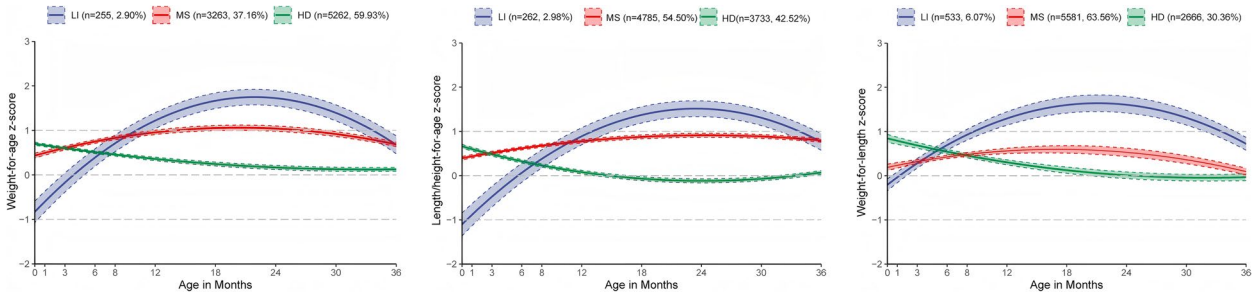

Fig. 2 Developmental trajectories for weight-for-age *z*-score, length/height-for-age *z*-score and weight-for-length *z*-score from birth to 36 months of age in Jiangsu Birth Cohort, Jiangsu, China, recruited from 2014 to 2020. The groups are labeled according to the initial value and following trend (LI: low-increasing; MS: moderate-stable; HD: high-decreasing). The LI trajectory reflects potential catch-up growth from a low baseline, the HD trajectory reflects early growth deceleration from a high baseline, and the MS trajectory indicates maintenance of intermediate growth status. The solid line indicates predicted trajectory and the shaded areas around represent the 95% confidence intervals for the calculated trajectories

developmental stage, maternal glucose freely crosses the placenta, while insulin cannot. Elevated maternal blood glucose stimulates fetal pancreatic islet cell proliferation and enhances insulin synthesis, resulting in increased fetal insulin and insulin-like growth factor (IGF) secretion [36]. The upregulation of the insulin/IGF axis promotes fetal growth and development [37, 38]. After birth, these infants may develop early insulin resistance, contributing to slower postnatal growth [39, 40]. Second, evidence also suggests that offspring exposed to maternal hyperglycemia may exhibit smaller kidneys with fewer nephrons and impaired renal endocrine function [41, 42]. This may result in reduced growth hormone activity and slower growth during early childhood [43]. Third, a recent US-based cohort study identified associations between gestational diabetes, breast milk metabolites, and infant growth and body composition [44]. Specifically, three of the nine milk metabolites significantly associated with GDM were also linked to infant growth and body composition measures. Notably, the abundance of 2-hydroxybutyric, a metabolite linked to lipid metabolism, was higher in participants with GDM and negatively associated with the change in infant body fat percentage from 1 to 3 months. This suggests that breastfeeding may be another pathway through which maternal diabetes impairs infant growth.

Our findings also suggest potential sex differences in the effects of HIP. Boys in our study appeared more sensitive to HIP exposures, showing stronger negative associations between HIP and both WAZ and WFL compared to girls. Other studies have reported sex-specific effects of HIP on fetal or childhood growth inconsistently. For example, some studies on offspring of mothers with GDM found boys to be at higher risk of obesity in childhood and adolescence compared to girls [45], whereas others suggested that girls could be more vulnerable [46]. A recent study found that sons of women with poorly controlled GDM are characterized by increased and longer-acting activation of the reproductive axis, and faster growth of male genital organs in infancy [47]. The sex differences observed in our study and others may be attributed to postnatal sex steroid production during the so-called mini-puberty [48]. This phase is characterized by a testosterone surge in boys during the first month of

Table 3 Association between HIP and growth trajectories

Outcome	Growth indices	*n/N* (%)	Crude model		Model [a]		Model [b]	
			RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Low-increasing	WAZ	72/819 (8.79%)	1.34 (1.01, 1.79)	0.043	1.09 (0.80, 1.48)	0.591	1.08 (0.79, 1.49)	0.633
	LAZ	70/1205 (5.81%)	1.19 (0.90, 1.57)	0.234	1.02 (0.75, 1.39)	0.893	0.99 (0.72, 1.36)	0.963
	WFL	133/1382 (9.62%)	1.15 (0.94, 1.41)	0.184	0.96 (0.77, 1.20)	0.707	0.98 (0.78, 1.24)	0.876
High-decreasing	WAZ	1223/1970 (62.08%)	1.02 (0.92, 1.13)	0.726	1.08 (0.97, 1.20)	0.183	1.08 (0.97, 1.22)	0.170
	LAZ	837/1972 (42.44%)	0.93 (0.84, 1.03)	0.154	0.97 (0.87, 1.09)	0.635	0.96 (0.86, 1.07)	0.473
	WFL	660/1909 (34.57%)	1.14 (1.03, 1.27)	0.016	1.15 (1.02, 1.29)	0.018	1.14 (1.01, 1.29)	0.031

RR risk ratio, *CI* confidence interval, *LAZ* length/height-for-age *z*-score, *WAZ* weight-for-age *z*-score, *WFL* weight-for-length *z*-score

[a] Adjusted for pre-pregnancy BMI, parity, maternal education, maternal age at delivery, passive smoking during pregnancy, area of residence, household income and child sex

[b] Additionally adjusted for gestational weight gain and delivery model

life, while girls exhibit higher estrogen levels, potentially influencing hormone-sensitive metabolic organs differently [49].

Not all infants grow exactly as these LCMM patterns showed but these are identifiable trends. Using LCMM, we saw that infants exposed to HIP were more likely to be in the high-decreasing WFL group across the first 3 years of life. Growth trajectory curves that follow this downward trend in growth percentiles have been termed as "catch-down growth" in previous literature [50]. For example, a recent cohort from Ohio found that infants exposed to HIP accumulated less fat during the first year of life [11]. This growth pattern may reflect a compensatory response to early overnutrition, or it could signal underlying abnormalities in metabolic programming. However, the long-term clinical implications of this pattern remain unclear and warrant further follow-up. We also observed that infants born with lower birth weight exhibit typical catch-up growth, which we labeled as the "low-increasing" pattern. Since excessive catch-up growth is a well-established risk factor for obesity and metabolic disorders later in life [51], these findings warrant the concern over the long-term health influence of prenatal HIP exposure. We hypothesize that the natural biological processes may support self-rehabilitation of prenatal impairments during early postnatal life. However, this intrauterine 'programmed' vulnerability may resurface later in life under the influence of environmental stressors. The differences observed early in life might be likely to persist or track into later childhood, which warrant enhanced monitoring and intervention in offspring of HIP mothers.

Our study has several strengths: Our study has several strengths: (1) the multi-centered prospective cohort design with repeated anthropometric assessments across ten time points, providing a unique opportunity to investigate long-term HIP effects on offspring growth while adjusting for key confounders; (2) dense monitoring of postnatal physical growth ensuring the reliability of trajectory data; (3) comprehensive data collection from interviews and medical records, accounting for multiple confounders; and (4) the use of LCMM to identify subgroup-specific growth patterns that may be missed in studies relying on heterogeneous or cross-sectional data. This approach allows us to determine if there are underlying commonalities in growth trends and if HIP is associated with a certain underlying growth trend.

However, several limitations must be noted. First, the small number of pre-existing diabetes cases limited power to detect modest HIP-type differences in trajectory membership; larger or pooled cohorts are needed to delineate heterogeneity by HIP type. Second, information on HIP treatment modality (e.g., diet-controlled and insulin-treated) was not available. Given that treatment intensity can influence fetal growth and subsequent postnatal trajectories, this represents a limitation. In our cohort, HIP management followed national guidelines, with diet and lifestyle advice as the first-line approach and insulin prescribed if glycemic targets were unmet. Future studies with detailed treatment data are warranted to disentangle the effects of HIP severity and its management on child growth patterns. Third, despite adjusting for multiple confounders, there might still be residual confounding factors (e.g., genetics, parental/sibling development, glycemic control). Life-course studies using diverse methodologies are needed [52]. Moreover, body composition measures were not collected during infancy and early childhood, which limits the ability to directly assess adiposity in the interpretation of weight-for-length *z*-scores. However, these measures are being collected in the ongoing school-age follow-up of this cohort, which will enable future analyses linking early growth trajectories with later body composition and metabolic outcomes. Finally, while LCMM and other trajectory analysis methods provide valuable insights, they cannot perfectly capture individual trajectories, and misclassification remains a possibility. Alternative trajectory modeling approaches are encouraged to validate our findings. While our study suggests an association between maternal HIP and slower growth trajectories in children, this should not be interpreted as evidence of a causal relationship due to the observational nature of the study design.

Conclusions

Our study showed that maternal HIP was associated with lower *z*-scores for length, weight and weight-for-length during the first 3 years of life, as well as reduced weight and BMI growth velocity. For the first time, we observed that HIP appears to be associated with a high-decreasing growth pattern. These findings underscore the imperative for further investigation into the growth patterns of infants with in utero HIP exposure, specifically to delineate its effects during the critical 0–3 year developmental window.

Abbreviations

95% CI	95% Confidence interval
BMI	Body mass index
DAG	Directed acyclic graphs
FBG	Fasting blood glucose
GDM	Gestational diabetes mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HCZ	Head-circumference-for-age *Z*-score
HD	High-decreasing
HIP	Hyperglycemia in pregnancy
IGF	Insulin-like growth factor
JBC	Jiangsu Birth Cohort

LAZ	Length/height-for-age *Z*-score
LBW	Low birth weight
LCMM	Latent class mixed model
LGA	Large for gestational age
LI	Low-increasing
LMM	Linear mixed model
MS	Moderate-stable
OGTT	Oral glucose tolerance test
pGDM	Pre-gestational diabetes mellitus
RR	Relative risk
SD	Standard deviation
SGA	Small for gestational age
WAZ	Weight-for-age *Z*-score
WFL	Weight-for-length *Z*-score
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04521-0.

Additional file 1: Figures S1–S7. Figure S1. Flow chart for the study participants selection. Figure S2. The directed acyclic graph (DAG) for all potential confounders considered in the statistical analyses.Figure S3. Anthropometric measures in children at each time points.Figure S4. Trajectories of weight-for-age, length/height-for-age, and weight-for-length z-scores from birth to 36 months by maternal hyperglycemia in pregnancy status. Figure S5. Stratified analysis of the association between maternal HIP and offspring anthropometric measures across different age periods. Figure S6. Sensitivity analyses of associations between maternal HIP and offspring anthropometries at different periods. Figure S7. Trajectory groups identified in two to five growth pattern groups for weight-for-length trajectory.

Additional file 2: Table S1-S11. Table S1. Anthropometric data and number of children measured at each point in time. Table S2. Growth velocity of anthropometric indicators at different ages. linear mixed mod. Table S4. Association between maternal HIP and offspring birth size categories. Table S5. Association between maternal HIP and offspring anthropometries at different periods. Table S6. Stratified analysis of the association between maternal HIP and offspring anthropometric measures across different age periods. Table S7. Sensitivity analyses of associations between maternal HIP and offspring anthropometries at different periods. Table S8. Model fit and number of participants for different numbers of infant growth trajectory groups in the study. Table S9. Baseline characteristics of mothers and their children according to WFL trajectory groups identified by latent class mixed modeling. Table S10. Association between HIP subtypes and WFL growth trajectories identified in three groups. Table S11. Sensitivity analyses of associations between maternal HIP and WFL trajectories identified in four groups.

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Authors' contributions
ZH and JD initiated, conceived and supervised the study. YC, SW and XC carried out the initial analyses, and critically reviewed and revised the manuscript and involved in the conduct of the study and the analysis and interpretation of the results. YC, JW, ZY, HL, YD, YL1, YJ were involved in study design, conduct of the cohort study, long-term follow-up with YZ, RQ, XX, XL, XH, BX and KZ. YL2, YJ, KY designed the data collection instruments, collected data and critically reviewed and revised the manuscript. HM, JD, TJ, ZY and YD proofread the manuscript. ZH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability
After publication, the data collected for the study (deidentified participant data) could be accessed on reasonable request to the corresponding author. A proposal with detailed description of study objectives and statistical analyses plan will be needed for evaluation of the reasonability of requests. Additional, relevant documents might also be required during the process of evaluation.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Committee of Nanjing Medical University (NJMUIRB [2014]248).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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