British Journal of Nutrition (2020), 124, 1285–1292 doi:10.1017/S0007114520002354

Association of gestational weight gain rate with infant anaemia in China: a birth cohort study

Shaohua Yin[1,2], Yubo Zhou[1,2]*, Hongtian Li[1,2], Zhihao Cheng[1,2], Yali Zhang[1,2], Le Zhang[1,2], Jufen Liu[1,2] and Jianmeng Liu[1,2]*

[1]*Institute of Reproductive and Child Health/National Health Commission Key Laboratory of Reproductive Health, Peking University Health Science Center, Beijing, 100191, People's Republic of China*

[2]*Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, 100191, People's Republic of China*

(Submitted 28 February 2020 – Final revision received 4 June 2020 – Accepted 20 June 2020 – First published online 29 June 2020)

Abstract

Excessive gestational weight gain (GWG) increases the risk of maternal anaemia during pregnancy, but whether it is associated with offspring anaemia has not been investigated. We aimed to prospectively investigate the association of GWG rate in the second/third trimester with infant Hb concentration and anaemia risk. The present study comprised 13 765 infants born during 2006–2009 to mothers who participated in a trial on prenatal micronutrient supplementation. The GWG was calculated by subtracting the maternal weight at enrolment from that at end-pregnancy. The GWG rate was calculated as dividing the GWG by number of weeks between the two measurements and classified into quintiles within each category of maternal BMI. Infant Hb concentrations were measured at 6 and 12 months of age, and anaemia was defined as an Hb concentration <110 g/l. Of the 13 765 infants, 949 (6·9 %) were anaemic at 6 months and 728 (5·3 %) at 12 months. The GWG rate was inversely and linearly associated with the infant Hb concentrations at both 6 and 12 months ($P < 0{\cdot}001$ for linearity). Compared with the middle quintile of GWG rate, the highest quintile was associated with an increased risk of anaemia at 6 months (adjusted OR 1·30, 95 % CI 1·07, 1·59) and 12 months (adjusted OR 1·74, 95 % CI 1·40, 2·17). The associations were consistently mediated by maternal anaemia during pregnancy ($P < 0{\cdot}001$). In conclusion, excessive GWG rate appears to be associated with an increased risk of infant anaemia, partly independent of maternal anaemia during pregnancy that mediates the association.

Key words: Gestational weight gain: Infants: Anaemia: Hb: Chinese birth cohorts

Anaemia in children remains epidemic worldwide[1], adversely affecting their cognitive, motor and behavioural development[2]. In 2011, 273 million children under 5 years of age were anaemic, with a prevalence as high as 43 %[3]. The underlying reasons are complex. Maternal nutrition during pregnancy, in addition to infection and maternal anaemia, is crucial[1,4]. Gestational weight gain (GWG) is a comprehensive indicator of maternal nutritional status, reflecting maternal fat accumulation, fetal growth, increased maternal blood volume and expansion of uterus and placenta[5,6]. A recent meta-analysis[7] with a sample of over 1·3 million pregnant women showed that the prevalence of excessive GWG was 51 %, and the prevalence did not materially differ among the USA, Europe and Asia including China[8]. Given the universal excessive GWG, its adverse consequences on offspring health are much concerned[9,10].

Excessive GWG has been linked to maternal anaemia during pregnancy[11,12] that probably predisposes offspring to anaemia[13]. Two small studies have explored the association of GWG with Fe indices in cord blood[14,15], but no study has directly investigated the association between GWG and offspring anaemia. In this large Chinese birth cohort analysis, we examined (1) the relationship of GWG rate in the second/third trimester with infant Hb concentrations at 6 and 12 months; (2) the association between GWG rate and the risk of infant anaemia and (3) whether the association is mediated or modified by maternal anaemia during pregnancy.

Methods

Study population

Data were retrieved from a randomised controlled trial conducted in Hebei Province, China from May 2006 through April 2009. The trial investigated the effect of prenatal micronutrient

Abbreviation: GWG, gestational weight gain.

* **Corresponding authors:** Jianmeng Liu, fax +86-10-82805356, email liujm@pku.edu.cn; Yubo Zhou, fax +86-10-82805356, email zhouyubo@bjmu.edu.cn

British Journal of Nutrition

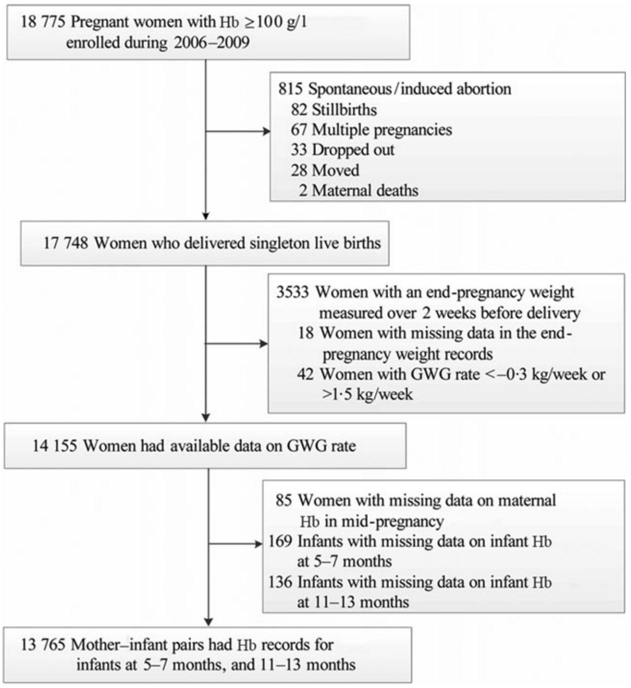

Fig. 1. Flow chart of the mother–infant pairs. GWG, gestational weight gain.

supplementation on the pregnancy outcomes among 18 775 nulliparous women. The women with an Hb level greater than 100 g/l were enrolled before twenty gestational weeks and randomised to receive daily folic acid, Fe–folic acid (containing 30 mg Fe) or multiple micronutrients (containing 30 mg Fe); they were followed monthly from enrolment to delivery, and their infants were followed until 1 year after birth. The study design and primary findings of the trial have been detailed elsewhere[16].

For this present analysis, we initially excluded 1027 women who had spontaneous/induced abortions (*n* 815), stillbirths (*n* 82) or multiple pregnancies (*n* 67), as well as those who dropped out (*n* 33), moving out of the study area (*n* 28) or died (*n* 2), leaving 17 748 women who delivered singleton live births. We excluded a further 3983 mother–infant pairs with an end-pregnancy weight measured over 2 weeks before delivery (*n* 3533), missing data in the end-pregnancy weight records (*n* 18), an extremely low (–0·3 kg/week) or high (>1·5 kg/week) GWG rate (*n* 42), missing data on maternal Hb in mid-pregnancy (*n* 85) or missing data on infant Hb at 5–7 (*n* 169) or 11–13 (*n* 136) months. Finally, 13 765 (73·3 %) mother–infant pairs were included in our analyses (Fig. 1). Most of maternal and infant characteristics differed between the included (*n* 13 765) and excluded (*n* 5010) mother–infant pairs due to the large sample size, such as farmer (91·7 *v.* 88·7 %), vaginal delivery (49·6 *v.* 45·1 %) and exclusively breast-feeding (31·3 *v.* 42·2 %) (all $P < 0·05$), but the micronutrient supplementations were comparable between the included and excluded ($P = 0·813$) (online Supplementary Table S1).

The sample size (about 2750 per quintile group) would have a statistical power of 80 % or higher to detect a significant OR of 0·74 or lower (if a protective effect existed) or a significant OR of 1·31 or higher (if an adverse effect existed) with an estimated infant anaemia prevalence of 11·6 % in the reference group[17], at a two-sided significance level of $\alpha = 0·0125$ (Bonferroni correction used for multiple comparisons).

The trial was approved by the Institutional Review Boards of the US Centers of Disease Control and Prevention (Atlanta, GA) and Peking University (Beijing, China). Informed consent to participate in the trial was obtained from all women.

Gestational weight gain rate in the second/third trimester

Maternal weight was measured at enrolment and at the end of pregnancy (within 2 weeks before delivery) by trained staff using standard procedures; height was measured at enrolment[16]. Weight was measured to the nearest 50 g using an electronic scale (BW 150; UWE), and height to the nearest 0·1 cm using a collapsible height board.

In the analyses, GWG rate in the second/third trimester was the exposure measure. Compared with total GWG, GWG rate is preferable as it does not rely heavily on the duration of pregnancy and is less likely to be associated with pregnancy outcomes such as preterm, which could increase the risk of anaemia in later life[18]. Considering weight gain is slower in the first trimester, and increases more rapidly and linearly in the second/third trimester[19], the GWG rate in the second/third trimester was calculated separately for women enrolled before 12 gestational weeks and for those enrolled at 12–20 gestational weeks. For women enrolled before 12 gestational weeks, the GWG rate in the second/third trimester was calculated as ((total GWG – estimated first trimester weight gain)/(gestational age at delivery – 12 weeks)). Here, total GWG was calculated by subtracting the weight at enrolment from the end-pregnancy weight; the estimated first trimester weight gain was calculated as follows: (12 weeks – gestational age at enrolment) × 0·11 kg/week (the GWG rate in the first trimester for Asians)[20]. For women enrolled at 12–20 gestational weeks, the GWG rate was calculated directly by dividing the total GWG by the number of weeks between enrolment and measurement of the end-pregnancy weight. As GWG rate differs with maternal BMI[21], the GWG rate was then categorised into highest, higher, middle (reference), lower and lowest quintiles by early pregnancy BMI categories (online Supplementary Table S2).

For women enrolled before 12 gestational weeks, early pregnancy BMI (kg/m^2) was calculated as the weight at enrolment in kg divided by the height in m^2. For women enrolled at 12–20 gestational weeks, weight in the first trimester was first calculated as: weight at enrolment – (gestational age at enrolment – 12 weeks) × 0·56 kg/week (the GWG rate in the second trimester for Asians)[20]; the early pregnancy BMI was then calculated. Accordingly, women were categorised into four categories: underweight (<18·5 kg/m^2), normal weight (18·5–22·9 kg/m^2), overweight (23·0–27·4 kg/m^2) or obese (≥27·5 kg/m^2), based on the WHO recommended cut-offs for Asians[22].

Infant anaemia and covariates

The outcomes of interest in our study were the infant Hb concentration (g/l) and anaemia at 6 and 12 months. Hb concentrations were measured at 5–7 (mean, 6·3) and 11–13 (mean,

https://doi.org/10.1017/S0007114520002354 Published online by Cambridge University Press

12·3) months of age using a HemoCue photometric instrument (Model 201; HemoCue) by trained staff, and anaemia was defined as an Hb concentration <110 g/l, in accordance with WHO guidelines[23].

Maternal Hb concentration was measured at enrolment and mid-pregnancy (24–28 gestational weeks), and anaemia was defined as an Hb concentration <110 g/l[24]. During the 6-month postnatal visit, mothers were asked by healthcare providers to classify their infant feeding modes as follows: (1) exclusively breast-feeding, representing infants received only breast milk and without other liquids or solids with the exception of drops or syrups consisting of micronutrient, or medicines; (2) mixed feeding, representing infant received a combination of breast milk and formula milk and (3) formula feeding, representing infant received exclusively formula milk. Other covariates included maternal age (<25, 25–29 or ≥30 years), education (high school or above, middle school or primary school or less), ethnicity (Han or other), occupation (farmer or other), gestational age at enrolment (calculated by subtracting the date of last menstrual period from date of enrolment, continuous variable), gestational age at delivery (calculated by subtracting the date of last menstrual period from date of delivery, <37 or ≥37 weeks), mode of delivery (vaginal or Caesarean delivery), infant sex (male or female) and birth weight (<2500, 2500–3999 or ≥4000 g). Above all information on relevant covariates was retrieved from medical records or surveillance system.

Statistical analyses

Categorical variables are presented as frequencies and percentages, and continuous variables as mean values and standard deviations or as medians and interquartile ranges. The χ^2 test was used to compare categorical variables among GWG rate quintiles; ANOVA or the Kruskal–Wallis test was used to analyse continuous variables.

We first examined the relationship between GWG rate and infant Hb concentration using fractional polynomial model with generalised linear regression[25] and estimated respective regression coefficients using linear regression. We then estimated the crude OR of infant anaemia across GWG rate quintiles using univariate logistic regression, with the middle quintile serving as the reference. We then estimated the adjusted OR using multiple logistic regression with covariates of maternal age, education, ethnicity, occupation, micronutrient supplementation, early pregnancy BMI, gestational age at enrolment (as a continuous variable), anaemia during mid-pregnancy (yes or no), gestational age at Hb measurement (as a continuous variable), gestational age at delivery, mode of delivery, infant sex, birth weight, feeding mode and age of infant at Hb measurement (as a continuous variable).

To evaluate the robustness of the results, we performed sensitivity analyses, first excluding women enrolled before 12 weeks of gestation and then those with anaemia at enrolment or during mid-pregnancy; an additional sensitivity analysis was performed by using multiple imputation methods in which missing values on the quintiles of GWG rate were imputed. For comparison with the results from Western countries, we repeated the main analyses using the categories of GWG rate in the second/third trimester (inadequate, appropriate and excessive) recommended in the 2009 Institute of Medicine guidelines[21] with BMI classified using the cut-off values recommended for Western populations[26]: underweight <18·5 kg/m^2; normal weight 18·5–24·9 kg/m^2; overweight 25·0–29·9 kg/m^2 and obese ≥ 30·0 kg/m^2. We performed mediation and stratified analyses to examine whether maternal anaemia during mid-pregnancy, previously linked to offspring anaemia[27], was a mediator or modifier of the association.

All analyses were conducted using SPSS software (version 24.0; IBM Corp.), and a two-sided P value <0·05 indicated statistical significance.

Results

The GWG rate in the second/third trimester was 0·5 (SD 0·2) kg/week for the 13 765 enrolled mothers, of whom 13 598 (98·8 %) were ethnic Han, 12 618 (91·7 %) were farmers and 13 554 (98·5 %) had a middle school education or above. Of the infants, 6887 (50·0 %) were born by Caesarean section and 4301 (31·3 %) were exclusively breast-feeding. Table 1 presents more detailed characteristics of the mothers and infants by GWG rate quintiles.

Gestational weight gain rate and infant Hb concentrations

The mean Hb concentration of the infants was 121·7 (SD 8·7) g/l at 6 months and 122·2 (SD 8·2) g/l at 12 months. Fractional polynomial regression showed inverse and linear relationships between the GWG rate and Hb concentrations at 6 and 12 months (Fig. 2), that is, the Hb concentrations tended to be lower in infants born to mothers who gained weight at a faster rate during the second or third trimester. After adjustment for covariates, linear regression showed that the Hb concentration of a 6-month-old infant decreased by 3·22 g/l when maternal weight increased by 1 kg/week (Table 2).

Quintiles of gestational weight gain rate and infant anaemia

Of the 13 765 infants, 949 (6·9 %) were anaemic at 6 months and 728 (5·3 %) at 12 months. The results of the crude analyses were similar to those of the multivariate analyses (Table 3). After multivariate adjustment, the highest quintile of GWG rate as compared with the middle quintile was associated with an increased risk of anaemia at both 6 months (adjusted OR 1·30, 95 % CI 1·07, 1·59) and 12 months (adjusted OR 1·74, 95 % CI 1·40, 2·17); the lowest quintile was associated with a lower risk of anaemia at 6 months (adjusted OR 0·76, 95 % CI 0·61, 0·95), but not at 12 months. Moreover, after further adjustment for maternal anaemia during mid-pregnancy, the OR were slightly attenuated but remained significant. In the sensitivity analyses excluding women enrolled before 12 weeks of gestation, and then also excluding women who were anaemic at enrolment or during mid-pregnancy, the association between the lowest quintile and anaemia risk at 6 months became insignificant, while the associations with the highest quintile persisted (Fig. 3). In the sensitivity analysis with multiple imputation methods used, the results were not materially changed (online Supplementary Table S3).

Table 1. Maternal and infant characteristics according to gestational weight gain (GWG) rate quintiles in the second/third trimester
(Unadjusted mean values and standard deviations; median values and interquartile ranges (IQR) for continuous variables; frequencies and percentages for categorical variables)

	Lowest (*n* 2713)		Lower (*n* 2767)		Middle (*n* 2767)		Higher (*n* 2753)		Highest (*n* 2765)		
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*P*
Mother											
Maternal age (years)											
Mean	23·6		23·6		23·6		23·6		23·5		0·907
SD	2·8		2·8		2·8		2·8		2·9		
Early pregnancy BMI (kg/m^2)											
Median	21·8		21·7		21·6		21·5		21·2		<0·001*
IQR	20·3, 23·4		20·2, 23·3		20·1, 23·3		19·9, 23·3		19·7, 23·4		
GWG rate in the second/third trimester (kg/week)											
Mean	0·2		0·4		0·5		0·5		0·7		<0·001*
SD	0·1		0·1		0·1		0·1		0·1		
Gestational age at enrolment ≤ 12 weeks	1702	62·7	1575	56·9	1460	52·8	1414	51·4	1143	41·3	<0·001*
Micronutrient supplementation											
Folic acid	899	33·1	923	33·4	912	33·0	923	33·5	932	33·7	0·928
Fe–folic acid	919	33·9	944	34·1	935	33·8	929	33·8	893	32·3	
Multiple micronutrients	895	33·0	900	32·5	920	33·2	901	32·7	940	34·0	
Education											
High school or above	495	18·3	495	17·9	492	17·8	407	14·8	529	19·1	<0·001*
Middle school	2179	80·3	2243	81·1	2240	81·0	2297	83·4	2177	78·7	
Primary school or less	39	1·4	29	1·0	35	1·2	49	1·8	59	2·2	
Han ethnicity	2684	98·9	2740	99·0	2728	98·6	2717	98·7	2729	98·7	0·550
Farmer occupation	2482	91·5	2527	91·3	2588	93·5	2542	92·3	2479	89·7	<0·001*
Gestational age at delivery (weeks)											
Mean	39·0		38·9		38·9		38·9		38·8		<0·001*
SD	1·6		1·6		1·6		1·5		1·7		
Mode of delivery											
Vaginal delivery	1412	52·0	1449	52·4	1430	51·7	1381	50·2	1154	41·7	<0·001*
Caesarean delivery	1293	47·7	1305	47·2	1332	48·1	1361	49·4	1596	57·7	
Missing	8	0·3	13	0·4	5	0·2	11	0·4	15	0·5	
Infant											
Male sex	1494	55·1	1435	51·9	1403	50·7	1405	51·0	1487	53·8	0·004*
Birth weight (g)											
Mean	3277·1		3289·5		3289·2		3288·7		3328·6		<0·001*
SD	367·9		370·0		366·4		379·2		423·3		
Feeding mode											
Exclusively breast-feeding	867	32·0	904	32·7	838	30·3	849	30·8	843	30·5	<0·001*
Mixed feeding	1674	61·7	1681	60·7	1722	62·2	1695	61·6	1653	59·8	
Formula feeding	132	4·9	144	5·2	166	6·0	163	5·9	239	8·6	
Missing	40	1·4	38	1·4	41	1·5	46	1·7	30	1·1	
Age at Hb measurement (months)											
5–7											
Mean	6·3		6·2		6·2		6·3		6·2		0·009
SD	0·5		0·4		0·4		0·4		0·5		
11–13											
Mean	12·3		12·3		12·3		12·3		12·3		0·051
SD	0·4		0·4		0·4		0·4		0·4		

* $P < 0·01$.

https://doi.org/10.1017/S0007114520002354 Published online by Cambridge University Press

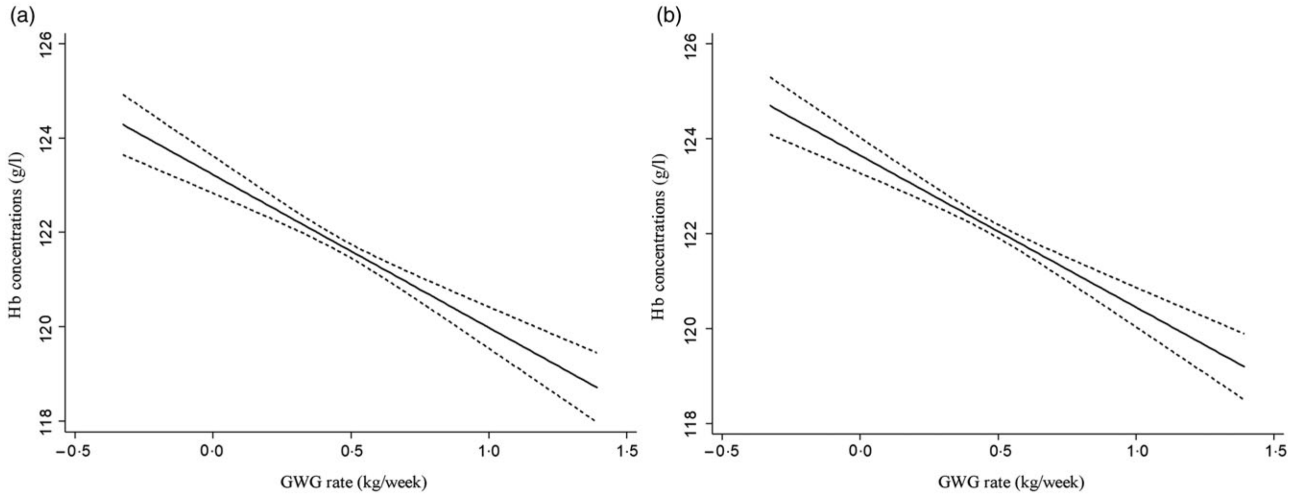

Fig. 2. Relationship of gestational weight gain (GWG) rate in the second/third trimester with infant Hb concentration at (a) 6 and (b) 12 months. Hb concentrations, solid lines; 95 % confidence intervals, broken lines.

Table 2. Adjusted regression coefficients estimated by linear regression (*B* coefficients with their standard errors)

	*B**	SE	*P*
Infants at 6 months			
GWG rate (kg/week)	−3·22	0·42	<0·001
Infants at 12 months			
GWG rate (kg/week)	−3·43	0·39	<0·001

GWG, gestational weight gain.
* Adjusted covariates included maternal age, ethnicity, education, occupation, micronutrient supplementation, early pregnancy BMI, gestational age at enrolment, gestational age at delivery, mode of delivery, and infant sex, birth weight, feeding mode and age of infant at Hb measurement.

Mediation analyses showed that maternal anaemia during mid-pregnancy mediated the association between the highest quintile and anaemia at 6 months ($Z = 3{\cdot}861$, $P < 0{\cdot}001$) and 12 months ($Z = 3{\cdot}536$, $P < 0{\cdot}001$).

In repeated analyses of GWG rate in the second/third trimester classified according to the 2009 Institute of Medicine guidelines, a positive association between excessive GWG rate and anaemia at 6 and 12 months was consistently observed (online Supplementary Table S4).

Discussion

In this large Chinese birth cohort, we found negative linear relations between GWG rate in the second/third trimester and infant Hb concentrations at both 6 and 12 months of age. When the Hb concentrations were dichotomised, the highest quintile of GWG rate as compared with the middle quintile was associated with a 30 and 74 % increased risk of infant anaemia at 6 and 12 months, respectively. The results persisted in infants born to mothers who were enrolled at 12–20 gestational weeks and born to mothers who were not anaemic at enrolment or during mid-pregnancy. The results were robust, when GWG rate was categorised according to the 2009 Institute of Medicine guidelines. That excessive GWG increased offspring anaemia risk appeared, to some extent, partly independent of maternal anaemia during pregnancy, though maternal anaemia probably mediated the associations.

To date, there has been no study to investigate the association between GWG and offspring anaemia. Two studies investigated the relationship of GWG with Hb concentration or Fe indices in umbilical cord blood[14,15]. One cross-sectional study with a sample size of 230 American women reported negative relationships of GWG with Hb concentration and Fe indices in cord blood, but not statistically significant, possibly due to small sample size[14]. Another cohort study with a sample size of 316 American women showed that GWG >18 kg *v.* <18 kg was associated with poor Fe indices in cord blood[15]. Our study with a large sample size consistently found that excessive GWG rate increased infant anaemia risk, and that the adverse effect persisted up to 12 months after birth. Underlying mechanisms remained unclear. Excessive GWG could expand blood volume or stimulate secretion of hepcidin[5,28], a biomarker of inflammation and a regulator of Fe metabolism; both blood volume expansion and higher hepcidin level are probably leading to maternal anaemia[11] that was linked to offspring anaemia[27], as indicated by our mediation analyses. On the other hand, excessive GWG was likely to play an independent role. Pregnant women with excessive GWG rates were more likely to undergo a Caesarean delivery that was associated with an increased risk of offspring anaemia[29,30]. Excessive GWG was also associated with higher birth weight that was linked to higher hepcidin levels in newborns, consequently leading to offspring anaemia[31,32].

Unexpectedly, a protective effect of the lowest quintile of GWG rate on the infant anaemia at 6 months was observed in the overall analysis. Previous studies reported that women with normal weight were more likely to have a low GWG, probably because of balanced diet and appropriate physical activity[33,34], benefiting to their offspring. In addition, we cannot completely rule out the possibility of residual bias in the protective effect. For example, women in the lowest quintile group were more likely

https://doi.org/10.1017/S0007114520002354 Published online by Cambridge University Press

British Journal of Nutrition

Table 3. Infant anaemia across gestational weight gain (GWG) rate quintiles in the second/third trimester
(Crude and adjusted odds ratios and 95 % confidence intervals; numbers and percentages)

			Univariate		Multivariate‡		Multivariate§	
GWG rate quintiles	*n*	%†	Crude OR	95 % CI	Adjusted OR	95 % CI	Adjusted OR	95 % CI
Anaemia at 6 months								
Lowest	2713	5·4	0·76*	0·61, 0·95	0·76*	0·61, 0·95	0·76*	0·60, 0·94
Lower	2767	6·4	0·92	0·75, 1·14	0·92	0·74, 1·14	0·93	0·75, 1·15
Middle	2767	6·9	1·00	–	1·00	–	1·00	–
Higher	2753	6·5	0·94	0·76, 1·16	0·93	0·75, 1·15	0·92	0·75, 1·14
Highest	2765	9·2	1·35*	1·11, 1·64	1·30*	1·07, 1·59	1·25*	1·02, 1·53
Anaemia at 12 months								
Lowest	2713	4·5	0·89	0·69, 1·14	0·88	0·68, 1·13	0·88	0·68, 1·13
Lower	2767	4·1	0·82	0·64, 1·06	0·82	0·64, 1·06	0·83	0·65, 1·07
Middle	2767	5·0	1·00	–	1·00	–	1·00	–
Higher	2753	4·3	0·85	0·66, 1·09	0·84	0·65, 1·08	0·83	0·65, 1·07
Highest	2765	8·6	1·79*	1·45, 2·23	1·74*	1·40, 2·17	1·71*	1·37, 2·13

* $P < 0·05$.
† Rate of infant anaemia.
‡ Adjusted covariates included maternal age, ethnicity, education, occupation, micronutrient supplementation, early pregnancy BMI, gestational age at enrolment, gestational age at delivery, mode of delivery, and infant sex, birth weight, feeding mode and age of infant at Hb measurement.
§ Additionally adjusted for maternal anaemia during mid-pregnancy.

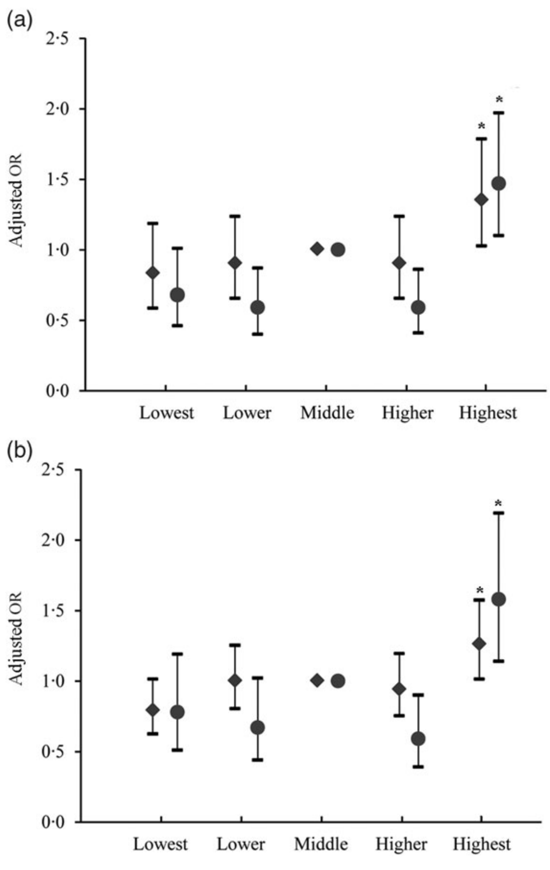

Fig. 3. Adjusted odd ratios (95 % confidence intervals) of infant anaemia by gestational weight gain rate quintiles in the sensitivity analyses. * $P < 0·05$. (a) Excluding women enrolled at ≤12 weeks of gestation (6471 mother–infant pairs remained); (b) further excluding women with anaemia at enrolment or during mid-pregnancy (5698 mother–infant pairs remained). ◆, Infants at 6 months; ●, infants at 12 months.

to be enrolled before 12 gestational weeks (62·7 %), which indicated that they began supplements consumption at an earlier gestational age and thus a lower risk of offspring anaemia. Consistently, in sensitivity analyses by excluding women enrolled before 12 weeks of gestation, the protective effect turned to be insignificant (as shown in Fig. 3(a)).

To the best of our knowledge, this is the first large-scale prospective study to investigate the relationships of GWG rate in the second/third trimester with infant Hb concentrations and anaemia risk at 6 and 12 months of age after birth. Key variables including maternal weight, infant Hb and major covariates were measured or collected by trained healthcare providers using standard procedures. The GWG rate rather than the total GWG was assessed as the exposure measure, assuredly minimising potential biases related to pregnancy duration. Our study had several limitations. First, the data were retrieved from a randomised controlled trial of prenatal Fe-containing micronutrient supplementation on well-nourished women whose Hb concentrations were greater than 100 g/l at enrolment, probably reducing the generalisability of the findings to other populations. For example, our analysis might have been biased by the start time of micronutrient supplementation because pregnant women were enrolled at different gestational age, such that our findings could not necessarily apply to populations where extensive supplementation was routine[35]. Second, though we could not exclude a possibility of biases related to Fe-containing supplementation, if any it ought to have the estimated risk towards null. Besides, we did not observe a significant interaction between GWG rate and supplementation type (all $P_{interaction} > 0·05$, online Supplementary Table S5). Third, we did not collect data on maternal and infant health status, duration of breast-feeding and complementary foods after 6 months[36,37] which might bias our results on infant anaemia at 12 months. Fourth, data on biomarkers of Fe and inflammation were not recorded. Given the above limitations, further studies in China are needed to confirm the findings.

In conclusion, this prospective cohort analysis showed negative linear relationships between GWG rate in the second/third trimester and infant Hb concentrations. The excessive GWG rate, partly independent of maternal anaemia during pregnancy, appeared to be associated with an increased risk of anaemia in infants. Maternal anaemia probably mediated the associations. These findings indicate a need to optimise GWG and control maternal anaemia during pregnancy to improve offspring health. Although optimum GWG needs to be further studied, balanced diet and appropriate physical activity during pregnancy are warranted to be advocated. Further studies are needed on whether these findings are applied to other populations, and on appropriate GWG in different populations.

Acknowledgements

We thank study participants, healthcare workers from five counties in northern China and all staff who participated in the project at the Peking University Health Science Center and Centers for Disease Control and Prevention, Atlanta.

The present study was supported by the National Key Research and Development Program of China (J. L., grant numbers 2016YFC1000401 and H. L., 2016YFC1000406-1) and the National Natural Science Foundation of China (J. L., grant number 81571517, and Y. Z., grant number 81801542).

J. L. conceived the study; S. Y., J. L. and Y. Z. wrote the manuscript; S. Y. and Z. C. performed the statistical analyses; H. L. Y. Z., L. Z., J. L. and J. L. contributed to the critical review of the manuscript; H. L., Z. C., Y. Z., L. Z. and J. L. participated in the acquisition of the data; J. L. 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 and all authors read and approved the final manuscript.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary materials referred to in this article, please visit https://doi.org/10.1017/S0007114520002354

References

1. Balarajan Y, Ramakrishnan U, Ozaltin E, *et al.* (2011) Anaemia in low-income and middle-income countries. *Lancet* **378**, 2123–2135.
2. McCann JC & Ames BN (2007) An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. *Am J Clin Nutr* **85**, 931–945.
3. Stevens GA, Finucane MM, Deregil LM, *et al.* (2013) Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. *Lancet Glob Health* **1**, e16–e25.
4. Rahman MM, Abe SK, Rahman MS, *et al.* (2016) Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. *Am J Clin Nutr* **103**, 495–504.
5. Pritchar JA (1965) Changes in blood volume during pregnancy and delivery. *Anesthesiology* **26**, 393–399.
6. Widen EM, Whyatt RM, Hoepner LA, *et al.* (2015) Excessive gestational weight gain is associated with long-term body fat and weight retention at 7 y postpartum in African American and Dominican mothers with underweight, normal, and overweight prepregnancy BMI. *Am J Clin Nutr* **102**, 1460–1467.
7. Goldstein RF, Abell SK, Ranasinha S, *et al.* (2018) Gestational weight gain across continents and ethnicity: systematic review and meta-analysis of maternal and infant outcomes in more than one million women. *BMC Med* **16**, 153–166.
8. Ye B, Yifan D, Jie W, *et al.* (2018) Status and related factors for gestational weight gain of Chinese pregnant women during 2010–2012. *Chin J Prev Med* **52**, 26–30.
9. Goldstein RF, Abell SK, Ranasinha S, *et al.* (2017) Association of gestational weight gain with maternal and infant outcomes a systematic review and meta-analysis. *JAMA* **317**, 2207–2225.
10. Bodnar LM, Siega-Riz AM, Simhan HN, *et al.* (2010) Severe obesity, gestational weight gain, and adverse birth outcomes. *Am J Clin Nutr* **91**, 1642–1648.
11. Tan J, Qi YN, He GL, *et al.* (2018) Association between maternal weight indicators and iron deficiency anemia during pregnancy: a cohort study. *Chin Med J* **131**, 2566–2574.
12. Yanoff LB, Menzie CM, Denkinger B, *et al.* (2007) Inflammation and iron deficiency in the hypoferremia of obesity. *Int J Obes* **31**, 1412–1419.
13. Meinzen-Derr JK, Guerrero ML, Altaye M, *et al.* (2006) Risk of infant anemia is associated with exclusive breast-feeding and maternal anemia in a Mexican cohort. *J Nutr* **136**, 452–458.
14. Cao C, Pressman EK, Cooper EM, *et al.* (2016) Prepregnancy body mass index and gestational weight gain have no negative impact on maternal or neonatal iron status. *Reprod Sci* **23**, 613–622.
15. Phillips AK, Roy SC, Lundberg R, *et al.* (2014) Neonatal iron status is impaired by maternal obesity and excessive weight gain during pregnancy. *J Perinatol* **34**, 513–518.
16. Liu JM, Mei ZG, Ye RW, *et al.* (2013) Micronutrient supplementation and pregnancy outcomes: double-blind randomized controlled trial in China. *JAMA Intern Med* **173**, 276–282.
17. Fang HY, Yu DM, Guo YQ, *et al.* (2018) Anemia prevalence of among 0–5 years old children in China, 2013. *Chin J Public Health* **34**, 1654–1657.
18. Stockman JA, Garcia JF & Oski FA (1977) Anemia of prematurity – factors governing erythropoietin response. *N Engl J Med* **296**, 647–650.
19. Siega-Riz AM, Adair LS & Hobel CJ (1994) Institute of Medicine maternal weight gain recommendations and pregnancy outcome in a predominantly Hispanic population. *Obstet Gynecol* **84**, 565–573.
20. Abrams B, Carmichael S & Selvin S (1995) Factors associated with the pattern of maternal weight gain during pregnancy. *Obstet Gynecol* **86**, 170–176.
21. Institute of Medicine (2009) *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC: National Academies Press.
22. WHO Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* **363**, 157–163.
23. World Health Organization (2011) Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. https://www.who.int/vmnis/indicators/haemoglobin/en/
24. World Health Organization (2001) *Iron Deficiency Anaemia: Assessment, Prevention and Control. A Guide for Programme Managers*. Geneva: WHO.
25. Royston P, Ambler G & Sauerbrei W (1999) The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* **28**, 964–974.

British Journal of Nutrition

26. World Health Organization (1998) *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation*. Geneva: World Health Organization.
27. Zhang YT, Jin L, Liu JM, *et al.* (2016) Maternal hemoglobin concentration during gestation and risk of anemia in infancy: secondary analysis of a randomized controlled trial. *J Pediatr* **175**, 106–110.
28. Bekri S, Gual P, Anty R, *et al.* (2006) Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH. *Gastroenterology* **131**, 788–796.
29. Zhou YB, Li HT, Ye RW, *et al.* (2017) Gestational weight gain, Cesarean delivery, and Cesarean delivery on maternal request: a cohort analysis of Chinese nulliparous women. *Ann Epidemiol* **27**, 96–102.
30. Li HT, Trasande L, Zhu LP, *et al.* (2015) Association of cesarean delivery with anemia in infants and children in 2 large longitudinal Chinese birth cohorts. *Am J Clin Nutr* **101**, 523–529.
31. Subhan FB, Colman I, McCargar L, *et al.* (2017) Higher pre-pregnancy BMI and excessive gestational weight gain are risk factors for rapid weight gain in infants. *Matern Child Health J* **21**, 1396–1407.
32. Sanad M, Osman M & Gharib A (2011) Obesity modulate serum hepcidin and treatment outcome of iron deficiency anemia in children: a case control study. *Ital J Pediatr* **37**, 34–39.
33. Warren L (2013) *Keeping the Balance: Promoting Physical Activity and Healthy Dietary Behaviour in Pregnancy*. Swansea: Swansea University.
34. Mamun AA, Kinarivala M, O'Callaghan MJ, *et al.* (2010) Associations of excess weight gain during pregnancy with long-term maternal overweight and obesity: evidence from 21 y postpartum follow-up. *Am J Clin Nutr* **91**, 1336–1341.
35. Vaivada T, Gaffey MF & Bhutta ZA (2017) Promoting early child development with interventions in health and nutrition: a systematic review. *Pediatrics* **140**, e20164306.
36. Pham VP, Nguyen VH, Salvignol B, *et al.* (2010) Complementary foods fortified with micronutrients prevent iron deficiency and anemia in Vietnamese infants. *J Nutr* **140**, 2241–2247.
37. Wang FL, Liu HJ, Wan Y, *et al.* (2016) Prolonged exclusive breastfeeding duration is positively associated with risk of anemia in infants aged 12 months. *J Nutr* **146**, 1707–1713.

British Journal of Nutrition