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Preconception Hb concentration and risk of preterm birth in over 2·7 million Chinese women aged 20–49 years: a population-based cohort study

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Abstract

Evidence on the association between maternal Hb concentration and preterm birth (PTB) risk is inconclusive. This paper aimed to explore whether women with anaemia or high Hb level before pregnancy would be at higher risk of PTB. We conducted a population-based cohort study with 2 722 274 women aged 20–49 years, who participated in National Free Pre-Pregnancy Checkups Project between 2013 and 2015 and delivered a singleton before 2016 in rural China. Logistic models were used to estimate OR and 95 % CI after adjusting for confounding variables. Restricted cubic spline models were applied to evaluate the dose–response relationships. A total of 192 819 (7·08 %) women had preterm deliveries. Compared with women with Hb of 110–149 g/l, the multivariable-adjusted OR for PTB was 1·19 (95 % CI 0·98, 1·44) for women with Hb < 70 g/l, 1·01 (95 % CI 0·97, 1·03) for 70–99 g/l, 0·96 (95 % CI 0·95, 0·98) for 100–109 g/l, 1·04 (95 % CI 1·01, 1·06) for 150–159 g/l, 1·11 (95 % CI 1·05, 1·17) for 160–169 g/l and 1·19 (95 % CI 1·11, 1·27) for ≥170 g/l, respectively. The multivariable-adjusted OR for very PTB (VPTB) was 1·07 (95 % CI 1·03, 1·12) and 1·06 (95 % CI 1·01, 1·12) for women with Hb <110 and ≥150 g/l, compared with those with Hb of 110–149 g/l, respectively. Our study identified a U-shaped relationship between maternal preconception Hb concentration and PTB risk. Both preconception anaemia and high Hb level can significantly increase VPTB risk. Appropriate intervention for women with abnormal Hb levels before pregnancy is very necessary.

Key words: Preterm birth: Maternal high Hb: Anaemia: Pre-pregnancy: Cohort studies

Preterm birth (PTB), which is defined as a live baby younger than 37 weeks of gestation by the WHO, has become a major global health problem pertaining to perinatal mortality and morbidity[1,2]. Over one-third of the 2·76 million global neonatal deaths each year are ascribed to PTB complications, and PTB is the leading cause of death in children younger than 5 years of age[3,4]. Furthermore, many surviving preterm children have an increased risk of neurodevelopmental dysfunction and chronic disease in adulthood, which can bring huge economic burden to families and society[1]. Therefore, effective prevention and reducing the incidence of PTB are crucial for public health improvement.

Traditional risk factors for PTB include maternal demographic characteristics, nutritional status, pregnancy history, infection, uterine contractions and cervical length in the gestation period[5]. Among these factors, maternal abnormal Hb status, including anaemia and high Hb level, has long been a hot research issue on the aetiology of PTB. However, previous studies have reported conflicting results for the association between maternal anaemia or high Hb level and PTB risk[6–11]. A systematic review published in 2013 reported that anaemia in the first trimester increased the risk of PTB, and that Hb above 140 g/l in the third trimester decreased the risk of PTB[12], whereas another recent review

Abbreviations: MPTB, moderate preterm birth; NFPCP, National Free Pre-Pregnancy Checkups Project; PTB, preterm birth; VPTB, very preterm birth.

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reported a U-shaped relationship of maternal Hb concentration with PTB risk[13].

Assessing haematological indices before pregnancy can detect abnormal Hb status in the preconceptional period, which makes primary prevention and intervention before pregnancy possible. However, little has been done to investigate the relationship between maternal preconception Hb concentration and PTB risk. Therefore, we conducted a large population-based cohort study in over 2·7 million reproductive-aged women in rural China to assess the association between maternal Hb concentration before pregnancy within 6 months and the risk of PTB.

Methods

Population and study design

A large population-based retrospective cohort study was conducted based on National Free Pre-Pregnancy Checkups Project (NFPCP), which is a national free health service for reproductive-aged couples who planned to conceive within 6 months. The project has been administered by the National Health and Family Planning Commission and the Ministry of Finance of the People's Republic of China. The service began with 100 rural counties in 2010 and was further expanded to 2907 counties in mainland of China after 2013. Detailed design, organisation and implementation of NFPCP are described elsewhere[14,15]. The study was approved by the Institutional Research Review Board at the National Health and Family Planning Commission. Written informed consent in Chinese was obtained from all NFPCP participants.

A total of 2 931 199 women aged 20–49 years old completed the NFPCP from January 2013 to December 2015 and pregnancy outcome follow-up before December 2016 in a rural household registration. We then further excluded participants who gave multiple births, did not get pregnant within 6 months and had missing information of preconception Hb concentration and last menstrual period (LMP) date or delivery date. As a result, 2 722 274 women were included in the current analysis. Detailed information on the study population recruitment, and derivation of the population used in the final analysis, is shown in Fig. 1.

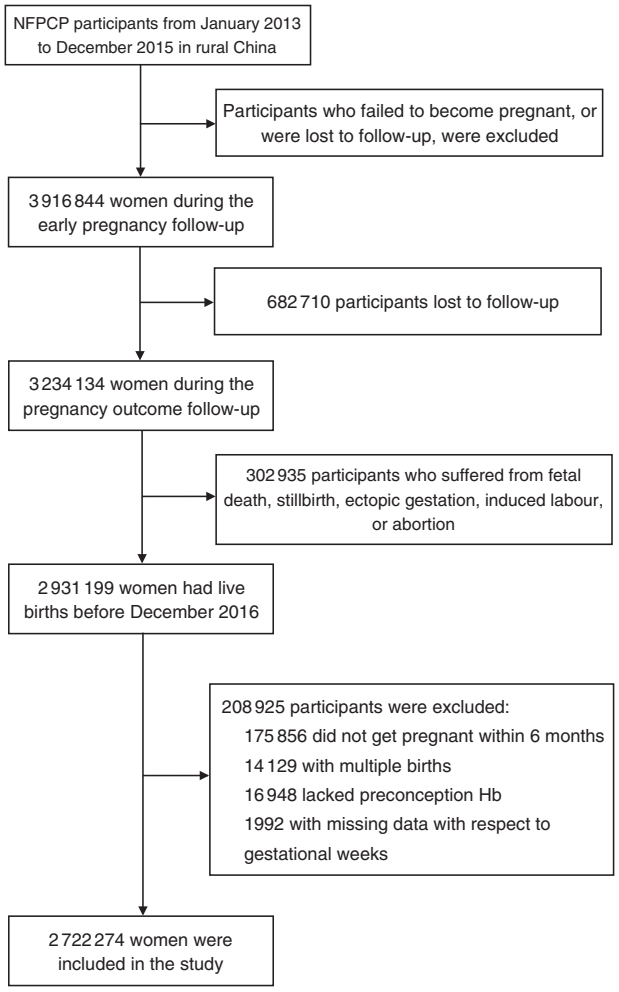

Fig. 1. Flow chart of the study population. NFPCP, National Free Pre-Pregnancy Checkups Project.

Measurements and data collection

All enrolled participants completed a standard questionnaire to collect baseline information about demographic characteristics, history of chronic diseases, family history, reproductive history and other relevant factors such as smoking and alcohol consumption through face-to-face interviews by trained staff in the local family planning service agencies or maternal and child care service centres in each county.

During the pre-pregnancy physical examination, body weight and height of participants wearing light, indoor clothing and no shoes were measured. Next, BMI was calculated. Seated blood pressure (BP) was measured using an automated BP monitor on a single occasion after participants rested for ≥10 min. Blood sample after at least 8 h of fasting was taken from each participant and immediately sent to the local laboratories. Hb concentration was measured with haematology analysers immediately in accordance with National Guide to Clinical Laboratory Procedures. Serum glucose level and thyroid-stimulating hormone (TSH) were also measured. The accuracy and stability of Hb measurements and other laboratory tests were ensured through the establishment of quality assurance system of the NFPCP[16]. Hypertension was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or self-reported hypertension. Diabetes was defined as a fasting blood glucose ≥7·0 mmol/l or a history of diabetes. Thyroid dysfunction was defined as current serum TSH level of <0·44 mIU/ml or >3·45 mIU/ml, or a history of thyroid disease.

Follow-up and outcome

Two follow-up interviews were conducted after baseline examination by trained nurses using telephone. The first follow-up was conducted within three months after baseline examination to track pregnancy status of the participants. If the participants did not get pregnant at the first interview, repeated investigations were conducted subsequently within the next three months until 12 months after baseline examination. Information about the LMP and any lifestyle changes in the first trimester of pregnancy was collected. Within 1 year after the

first follow-up survey was completed, the second interview was carried out to find out the pregnancy outcomes of the subjects who had become pregnant. Information regarding the delivery date and delivery mode was self-reported.

PTB is defined as any birth before 37 completed weeks of gestation. PTB can be further subdivided based on gestational age: moderate PTB (MPTB, 32 to <37 weeks) and very PTB (VPTB, <32 weeks). The gestational age (weeks) was calculated as the number of weeks between the date of delivery and the 1st day of the LMP using relevant information collected in the two follow-up surveys.

Statistical analysis

Baseline characteristics were presented as mean values and standard deviations for continuous variables and numbers and percentages for categorical variables. The χ^2 test or Kruskal–Wallis test was used to compare the distributions of baseline characteristics according to different preconception Hb status.

In this study, Hb concentrations of women who resided in areas with altitude ≥1000 m were adjusted by subtracting the adjustment values from the original Hb concentrations according to the recommendation by the WHO[17,18]. Detailed adjustments are presented in the online Supplementary Table S1. Then we classified women into three groups (anaemia: <110 g/l; normal Hb level: 110–149 g/l; and high Hb level: ≥150 g/l) and seven groups (severe anaemia: <70 g/l; moderate anaemia: 70–99 g/l; mild anaemia: 100–109 g/l; normal Hb level: 110–149 g/l; mild high Hb level: 150–159 g/l; moderate high Hb level: 160–169 g/l; and severe high Hb level: ≥170 g/l). Hb categorisation was based on WHO guidelines for the grading of anaemia[17,18] and one previous study, which indicated that high Hb level can be defined as Hb concentration ≥160 g/l[19]. Because the definition of anaemia in China is 10 g/l lower than the criterion of the WHO[20], all of the cut-off values in our study were reduced by 10 g/l as compared with the recommendations.

We examined associations between the two categories of preconception Hb concentration and the risk of PTB, as well as MPTB and VPTB. The OR and their corresponding 95 % CI were estimated by age-adjusted and multivariate-adjusted logistic regression models separately, using normal Hb level (110–149 g/l) as the reference group. Covariates in the multivariate-adjusted logistic regression model included baseline age, education, ethnicity, occupation, pre-pregnancy BMI, smoking, passive smoking, alcohol consumption, hypertension, diabetes, thyroid dysfunction, parity, region with GDP per capita, history of adverse pregnancy outcomes and sex of the child. In addition, we assessed the dose–response relationships between preconception Hb concentrations and the risk of PTB, MPTB and VPTB using restricted cubic spline models[21], and plotted smooth curves with four knots at the fifth, 35th, 65th and 95th percentiles of preconception Hb concentrations. Subgroup analysis was performed according to the residence altitude of participants. To examine the robustness of our findings, we performed sensitivity analyses by using the original Hb concentration with or without additional adjustment of residence altitude in the models. All analyses were performed using R, version 3.2.2, with the 'speedglm' and 'rms' packages (Development Core Team, 2015). All statistical tests were two-sided, and values of $P < 0{\cdot}05$ were considered statistically significant.

Ethical statements

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving humans were approved by the Institutional Research Review Board at the National Population and Family Planning Commission. Written informed consent in Chinese was obtained from all NFPCP participants.

Results

In the current study, the median age of the participants was 25·0 years (interquartile range (IQR): 23·0–27·4). Only 2·32 % of the participants were older than 35 years, and 69·90 % were primipara. Overall, 387 523 (14·20 %) women had anomalous preconception Hb concentration: 267 372 (9·80 %) were anaemic and 120 151 (4·40 %) had high Hb concentration (Table 1). Those with abnormal Hb concentrations were more likely to be with less educational attainment, have pre-existing diabetes or thyroid dysfunction.

The median length of time from baseline examination to pregnancy was 1·54 months (IQR: 0·64–3·04). A total of 192 819 (7·08 %) PTB events were documented. The incidence of PTB was 6·93, 7·07 and 7·76 % for women who were anaemic, with normal Hb level and high Hb level, respectively (Table 2). Compared with women with Hb level of 110–149 g/l, the multivariable-adjusted OR for PTB was 0·98 (95 % CI 0·96, 0·99) and 1·06 (95 % CI 1·04, 1·09) for women with Hb <110 and ≥150 g/l, respectively. Increased risk of PTB was also observed for women with mild, moderate and severe high Hb levels (OR 1·04; 95 % CI 1·01, 1·06; 1·11; 95 % CI 1·05, 1·17; 1·19; 95 % CI 1·11, 1·27), whereas decreased risk of PTB was observed for women with mild anaemia (OR 0·96; 95 % CI 0·95, 0·98).

Table 2 also summarises the associations between the maternal preconception Hb categories and risk of MPTB, as well as VPTB. Compared with women with Hb level of 110–149 g/l, the multivariable-adjusted OR for MPTB was 0·96 (95 % CI 0·94, 0·98) and 1·06 (95 % CI 1·04, 1·09) for women with Hb <110 and ≥150 g/l, respectively. The corresponding OR for VPTB was 1·07 (95 % CI 1·03, 1·12) and 1·06 (95 % CI 1·01, 1·12), respectively. When anaemia and high Hb concentration were further subdivided into mild, moderate and severe status, increased risk of VPTB was also observed for mild and moderate anaemia (OR 1·06; 95 % CI 1·01, 1·12; 1·09; 95 % CI 1·02, 1·17), and for severe high Hb level (OR 1·21; 95 % CI 1·03, 1·42).

Fig. 2 shows U-shaped dose–response relationships of maternal preconception Hb concentration with PTB and MPTB ($P_{\text{non-linear}} < 0{\cdot}001$), even though the multivariable-adjusted OR were not significant when Hb concentration was below 110 g/l. Although the OR remained stable when Hb concentration was lower than 130 g/l in the dose–response curve of maternal preconception Hb concentration with VPTB, the relationship was also approximately U-shaped ($P_{\text{non-linear}} < 0{\cdot}001$).

In the subgroup analysis, the associations between maternal preconception Hb levels and risk of PTB appeared to be modified

Table 1. Maternal characteristics with respect to preconception status of Hb concentrations
(Numbers and percentages; mean values and standard deviations)

			Maternal preconception Hb levels*						
	Total		Anaemia		Normal Hb level		High Hb level		
	Mean/*n*	SD/%	Mean/*n*	SD/%	Mean/*n*	SD/%	Mean/*n*	SD/%	*P*†
n	2 722 274		267 372	9·80	2 334 751	85·80	120 151	4·40	
PTB	192 819	7·08	18 536	6·93	164 954	7·07	9329	7·76	<0·001
Hb concentration (g/l)	126·50	14·22	101·09	7·75	127·77	9·68	158·35	12·01	
Age (years)									<0·001‡
20–24	1 361 126	50·00	136 821	51·17	1 161 702	49·76	62 603	52·10	
25–29	1 054 089	38·72	100 586	37·62	909 515	38·96	43 988	36·61	
30–34	243 903	8·96	23 766	8·89	209 457	8·97	10 680	8·89	
35–39	53 471	1·96	5219	1·95	45 795	1·96	2457	2·04	
40–49	9685	0·36	980	0·37	8282	0·35	423	0·35	
Education (high school or above)	912 296	34·57	86 968	33·80	791 932	34·97	33 396	28·47	<0·001
Ethnic (Han)	2 493 777	92·93	240 197	91·45	2 144 799	93·17	108 781	91·59	<0·001
Occupation (farmers)	2 054 786	78·18	195 418	76·53	1 762 125	78·11	97 243	83·22	<0·001
BMI (kg/m^2)									<0·001‡
<18·5	395 356	14·52	43 539	16·28	337 138	14·44	14 679	12·22	
18·5–23·9	1 950 968	71·67	190 763	71·35	1 675 957	71·78	84 248	70·12	
24·0–27·9	311 137	11·43	28 375	10·61	265 922	11·39	16 840	14·02	
≥28·0	64 813	2·38	4695	1·76	55 734	2·39	4384	3·65	
Smoking	4942	0·18	419	0·16	4237	0·18	286	0·24	<0·001
Second-hand smoking	285 962	10·54	25 367	9·52	249 612	10·73	10 983	9·18	<0·001
Alcohol drinking	57 086	2·11	4289	1·61	50 394	2·17	2403	2·01	<0·001
Diabetes	29 061	1·08	4027	1·52	23 708	1·03	1326	1·12	<0·001
Hypertension	39 601	1·46	2947	1·11	34 124	1·47	2530	2·12	<0·001
Thyroid disease	369 552	13·85	38 594	14·87	314 262	13·72	16 696	14·26	<0·001
History of adverse pregnancy outcomes	414 676	15·28	42 156	15·82	356 175	15·30	16 345	13·64	<0·001
Parity (primipara)	1 897 358	69·90	187 618	70·39	1 625 415	69·82	84 325	70·39	<0·001
Sex of the child (boy)	1 421 611	52·22	138 551	51·82	1 220 684	52·28	62 376	51·91	<0·001
Region with GDP per capita (¥/year)									<0·001‡
≤40 000	66 427	2·44	6527	2·44	53 960	2·31	5940	4·94	
40 001–50 000	108 2482	39·76	83 173	31·11	945 365	40·49	53 944	44·90	
50 001–70 000	691 597	25·41	82 631	30·90	581 034	24·89	27 932	23·25	
≥70 001	881 768	32·39	95 041	35·55	754 392	32·31	32 335	26·91	
Altitude (<1000 m)	2 480 775	91·13	243 595	91·11	2 134 020	91·40	103 160	85·86	<0·001

Anaemia, Hb concentration <110 g/l; normal Hb level, Hb concentration in the range of 110–149 g/l; high Hb level, Hb concentration ≥ 150 g/l; PTB, preterm birth.
* Preconception Hb concentrations of women who lived in areas with altitude ≥1000 m were adjusted by subtracting the adjustment values from the measured Hb concentrations according to the recommendation by the WHO[17,18].
† Multiple comparison with Bonferroni-adjusted *P* value <0·05 (anaemia group *v.* normal Hb group; high Hb group *v.* normal Hb group).
‡ The Kruskal–Wallis *H* test was used to examine the differences of baseline characteristics among Hb groups. Others used the χ^2 test.

Table 2. Associations between maternal preconception Hb concentrations and risk of preterm birth (Odds ratios and 95 % confidence intervals)

		PTB		Age adjusted		Multivariable adjusted*	
Hb category (g/l)†	No. of participants	*n*	%	OR	95 % CI	OR	95 % CI
PTB							
Class I							
<110	267 372	18 536	6·93	0·98‡	0·96, 0·99	0·98‡	0·96, 0·99
110–149	2 334 751	164 954	7·07	1		1	
≥150	120 151	9329	7·76	1·11‡	1·08, 1·13	1·06‡	1·04, 1·09
Class II							
<70	1453	127	8·74	1·26‡	1·05, 1·51	1·19	0·98, 1·44
70–99	80 929	5791	7·16	1·01	0·99, 1·04	1·01	0·97, 1·03
100–109	184 990	12 618	6·82	0·96‡	0·94, 0·98	0·96‡	0·95, 0·98
110–149	2 334 751	164 954	7·07	1		1	
150–159	88 503	6682	7·55	1·07‡	1·05, 1·10	1·04‡	1·01, 1·06
160–169	19 565	1591	8·13	1·16‡	1·10, 1·22	1·11‡	1·05, 1·17
≥170	12 083	1056	8·74	1·26‡	1·18, 1·34	1·19‡	1·11, 1·27
MPTB							
Class I							
<110	264 379	15 543	5·88	0·96‡	0·95, 0·98	0·96‡	0·94, 0·98
110–149	2 310 198	140 401	6·08	1		1	
≥150	118 731	7909	6·66	1·10‡	1·08, 1·13	1·06‡	1·04, 1·09
Class II							
<70	1435	109	7·60	1·27‡	1·04, 1·54‡	1·22	0·99, 1·50
70–99	80 001	4863	6·08	0·99	0·97, 1·03	0·98	0·95, 1·02
100–109	182 943	10 571	5·78	0·95‡	0·93, 0·97	0·95‡	0·93, 0·97
110–149	2 310 198	140 401	6·08	1		1	
150–159	87 502	5681	6·49	1·07‡	1·04, 1·10	1·04‡	1·01, 1·07
160–169	19 314	1340	6·94	1·15‡	1·09, 1·22	1·11‡	1·04, 1·17
≥170	11 915	888	7·45	1·24‡	1·16, 1·33	1·18‡	1·10, 1·27
VPTB							
Class I							
<110	251 829	2993	1·19	1·06‡	1·02, 1·10	1·07‡	1·03, 1·12
110–149	2 194 350	24 553	1·12	1		1	
≥150	112 242	1420	1·27	1·13‡	1·07, 1·19	1·06‡	1·01, 1·12
Class II							
<70	1344	18	1·34	1·21	0·76, 1·92	1·01	0·62, 1·65
70–99	76 066	928	1·22	1·09‡	1·02, 1·17	1·09‡	1·02, 1·17
100–109	174 419	2047	1·17	1·05‡	1·01, 1·10	1·06‡	1·01, 1·12
110–149	2 194 350	24 553	1·12	1		1	
150–159	82 822	1001	1·21	1·08‡	1·01, 1·15	1·04	0·97, 1·11
160–169	18 225	251	1·38	1·23‡	1·09, 1·40	1·09	0·96, 1·25
≥170	11 195	168	1·50	1·34‡	1·15, 1·57	1·21‡	1·03, 1·42

PTB, preterm birth (<37 weeks of gestation); MPTB, moderate preterm birth (32 to <37 weeks of gestation); VPTB, very preterm birth (<32 weeks of gestation).
* Multivariable-adjusted OR (95 % CI) were adjusted for characteristics of women (age, education, ethnic, occupation, region with GDP per capita), smoking, passive smoking and alcohol drinking status at baseline, history of diseases (diabetes, hypertension and thyroid dysfunction), pre-pregnancy BMI, parity, history of adverse pregnancy outcomes and sex of the child.
† Class I refers that women were classified into three groups (anaemia: <110 g/l; normal Hb level: 110–149 g/l; and high Hb level: ≥150 g/l); class II refers that women were classified into seven groups (severe anaemia: <70 g/l; moderate anaemia: 70–99 g/l; mild anaemia: 100–109 g/l; normal Hb level: 110–149 g/l; mild high Hb level: 150–159 g/l; moderate high Hb level: 160–169 g/l; and severe high Hb level: ≥170 g/l).
‡ Statistical significance ($P < 0·05$).

by altitude (Table 3). For women living in areas ≥1000 m, anaemia was associated with an increased risk of PTB (OR 1·15; 95 % CI 1·10, 1·21), but high Hb level was observed to be associated with a decreased risk of PTB (OR 0·92; 95 % CI 0·87, 0·98). Mild, moderate and severe anaemia had 13, 19 and 30 % higher risks of PTB, respectively, whereas no significant association was found between different grades of high Hb level and PTB risk. In the sensitivity analyses, the associations between preconception Hb categories and risk of PTB, as well as MPTB and VPTB, did not change appreciably by using original Hb concentrations (online Supplementary Tables S2 and S3).

Discussion

In this large cohort study of over 2·7 million women in rural China, we found that high Hb level was associated with an increased risk of PTB, including MPTB and VPTB, and anaemia was associated with an increased risk of VPTB, independent of other vital risk factors. Furthermore, U-shaped curves for the risk of PTB, as well as MPTB and VPTB, with preconception Hb concentrations were identified. In areas with altitude ≥1000 m, the OR of anaemia with PTB were larger than those of high Hb level with PTB.

In the current study, the incidence of PTB in the anaemia group, especially in the mild anaemia group, was lowest when compared with Hb of 110–149 g/l. In addition, we found that an increased risk of PTB, as well as MPTB, was only significantly associated with severe anaemia (<70 g/l) in age-adjusted models. The possible reason is that women with known anaemia before pregnancy would pay more attention to their Hb concentrations during pregnancy, and it is easier for women with mild anaemia than those with moderate or severe anaemia to improve their anaemia status through medical treatment,

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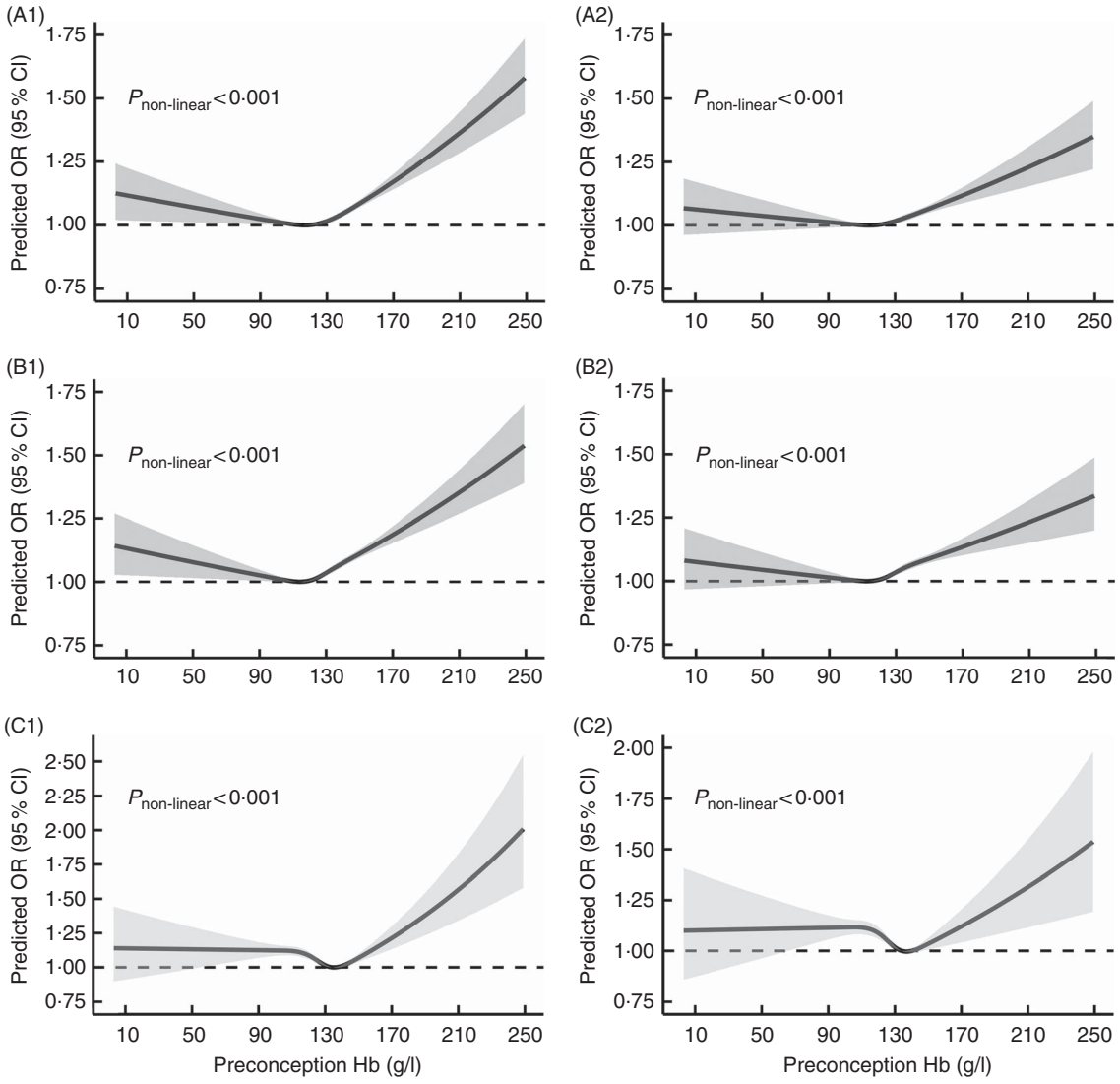

Fig. 2. Dose–response relationship between maternal preconception Hb concentrations and the risk of preterm birth (PTB, <37 weeks of gestation), moderate preterm birth (MPTB, 32 to <37 weeks of gestation) and very preterm birth (VPTB, <32 weeks of gestation). Graphs show the age-adjusted and multivariable-adjusted OR of associations between maternal preconception altitude-adjusted Hb concentrations and the risk of PTB (A1, A2), MPTB (B1, B2) and VPTB (C1, C2), respectively. In the graph, black lines and shaded grey areas represent predicted OR and 95 % CI, respectively. Multivariable-adjusted OR and 95 % CI were adjusted for characteristics of women (age, education, ethnic, occupation, region with GDP per capita), smoking, passive smoking and alcohol drinking status at baseline, history of diseases (diabetes, hypertension and thyroid dysfunction), pre-pregnancy BMI, parity, history of adverse pregnancy outcomes and sex of the child.

such as Fe supplements. Until now, there were only two studies that have assessed the association between preconception maternal anaemia and the risk of PTB[22,23]. Owing to the different anaemia definitions and reference-level cut-off value adopted, our results were partly consistent with a previous retrospective cohort study conducted in Korean women, which found that moderate-to-severe anaemia (<100 g/l) before pregnancy was associated with PTB risk (OR 1·53; 95 % CI 1·05, 2·23) when compared with Hb of 120–149 g/l[22]. However, another small-size cohort study (which included only 405 women) conducted in China found a null association between anaemia (<95 g/l) and PTB[23]. Our study also found that maternal preconception anaemia was associated with an increased risk of VPTB. However, the evidence on the relationship between maternal Hb concentration and VPTB risk was limited, possibly owing to the lower incidence of VPTB. The rate of self-reported VPTB events in the current study is 1·06 %, whereas that for overall PTB was 7·08 %. Our findings indicated that anaemia in the periconceptional period may have an adverse effect on PTB, especially on VPTB, which suggested that pre-pregnancy intervention for anaemia is very necessary.

Maternal high Hb level during pregnancy was suggested to have a more severe effect on birth outcomes than anaemia[24–26]. Previous studies have documented that high Hb concentration in the first[27] or second trimester[10,24] was significantly associated with an increased risk of PTB, because high Hb concentration may increase blood viscosity and harm placental blood flow[28]. The current study demonstrated that women with preconception Hb ≥150 g/l had an increased risk of PTB, as well as MPTB and VPTB, when compared with those with preconception Hb of 110–149 g/l, and the associations

Table 3. Subgroup analysis by altitude of the association between maternal preconception Hb concentrations and preterm birth (PTB) risk (Odds ratios and 95 % confidence intervals)

	<1000 m				≥1000 m			
	PTB		Multivariable adjusted*		PTB		Multivariable adjusted*	
Hb category (g/l)†	*n*	%	OR	95 % CI	*n*	%	OR	95 % CI
Class I								
<110	16 048	6·59	0·96‡	0·94,0·98	2488	10·46	1·15‡	1·10,1·21
110–149	147 365	6·91	1		17 589	8·76	1	
≥150	7828	7·59	1·08‡	1·05,1·10	1501	8·83	0·92‡	0·87,0·98
Class II								
<70	77	7·80	1·11	0·87,1·42	50	10·73	1·30	0·96,1·77
70–99	4909	6·75	0·97	0·95,1·01	882	10·79	1·19‡	1·10,1·29
100–109	11 062	6·51	0·95‡	0·93,0·97	1556	10·28	1·13‡	1·06,1·20
110–149	147 365	6·91	1		17 589	8·76	1	
150–159	5690	7·38	1·05‡	1·02,1·08	992	8·66	0·92‡	0·86,0·99
160–169	1316	8·04	1·14‡	1·08,1·21	275	8·61	0·87‡	0·76,0·99
≥170	822	8·44	1·21‡	1·12,1·30	234	9·96	1·01	0·87,1·17

* Multivariable-adjusted OR and 95 % CI were adjusted for characteristics of women (age, education, ethnic, occupation, region with GDP per capita), smoking, passive smoking and alcohol drinking status at baseline, history of diseases (diabetes, hypertension and thyroid dysfunction), pre-pregnancy BMI, parity, history of adverse pregnancy outcomes and sex of the child.

† Class I refers that women were classified into three groups (anaemia: <110 g/l; normal Hb level: 110–149 g/l; and high Hb level: ≥150 g/l); class II refers that women were classified into seven groups (severe anaemia: <70 g/l; moderate anaemia: 70–99 g/l; mild anaemia: 100–109 g/l; normal Hb level: 110–149 g/l; mild high Hb level: 150–159 g/l; moderate high Hb level: 160–169 g/l; and severe high Hb level: ≥170 g/l).

‡ Statistical significance ($P < 0·05$)

remained significant when high Hb concentration was divided into different grades, except for the associations between mild and moderate high Hb concentration and VPTB. Our findings indicated that monitoring the risk of PTB for women with preconception high Hb concentration should not be ignored. However, another study conducted in Korean women found a null association between preconception high Hb level (≥150 g/l) and risk of PTB[22].The inconsistent results can be explained by the small sample size (2868 women) in the high Hb level group in their study, which limited the statistical power to detect a significant association[22].

The current study indicated that PTB rate was related to maternal preconception Hb concentrations in a U-shaped manner. There is substantial evidence for a U-shaped curve for the risk of adverse birth outcomes with maternal Hb concentration[24,28–30], but some studies reported controversial results[22,31]. The inconsistent results among previous studies might be related to the different criteria or cut-off thresholds for defining low and high Hb concentrations or caused by the various characteristics within the study population, such as different prevalence of abnormal Hb status and PTB. Hb concentration is highly correlated with the Fe stores in the body. Fe deficiency is a common cause of anaemia, and daily Fe supplementation may result in an increase in Hb values in 11 % of pregnant women[32]. A recent meta-analysis indicated that both Fe deficiency and Fe excess would increase the risk of gestational disease and pregnancy outcomes[33]. In China, free prenatal Fe supplements were not provided by the government. Some pregnant women may have Fe supplements during pregnancy by taking multi-vitamin products, such as Elevit. However, detailed information about Fe supplements of pregnant women was not collected in the current study. Therefore, the association between preconception Hb levels and PTB risk, taking Fe supplements or ferritin level during pregnancy into consideration, needs to be further explored in the future. Besides, our results showed that women with less educational attainment, pre-existing diabetes or thyroid dysfunction were more likely to be with abnormal Hb concentrations, which highlights that clinicians pay more attention to those with these risk factors to effectively reduce the risk of PTB.

As is well known, most populations living at high altitude characteristically have an increased Hb concentration as a compensatory mechanism to the effect of hypoxia[34]. This Hb increase can ultimately misclassify anaemia or high Hb if it is not taken into consideration. Therefore, Hb concentration of residents living in areas ≥1000 m should be adjusted according to the adjustment values recommended by the WHO[17,18]. However, no study had used adjusted Hb concentrations to explore its association with adverse pregnancy outcomes, except one study conducted in Bolivia[35]. Our study observed a higher risk of PTB associated with anaemia than that with high Hb level among 241 499 women, 8·87 % of the total participants, who lived in areas ≥1000 m, which is consistent with the results of another cohort study conducted at high altitudes[29]. These findings indicated that anaemia is more harmful than high Hb level in high-altitude areas with respect to PTB.

In the study, over 2·7 million participants were recruited, and were followed up on pregnancy outcomes using strict quality controls. This large sample size enables us to divide Hb into different levels and ensure enough statistical power to detect the associations. Furthermore, Hb concentrations before pregnancy within 6 months were used in our study, which minimises the possibility of differential misclassification of the Hb level and confounding by haemodilution with gestational age.

However, several limitations should be addressed. First, changes in Hb concentrations were not monitored during pregnancy,

which limited the estimation of Hb concentration during pregnancy or the effect of Hb changes on PTB rate. Second, other factors associated with Hb concentration, such as ferritin level or Fe supplements intake, were not collected, so we cannot distinguish which specific type of anaemia or high Hb level is associated with PTB. Third, owing to the lack of detailed information regarding specific types of PTB, such as spontaneous PTB or iatrogenic PTB, the association between maternal Hb concentration and various types of PTB cannot well be examined. Fourth, self-reported information on the LMP and delivery date was used in the current study, which may result in an inaccurate gestational age calculation and the misclassification of PTB. Finally, data on important maternal conditions during pregnancy that have significant effects on PTB, such as gestational hypertension or preeclampsia, were not collected, so we could not adjust for these factors in the multivariable analysis.

In summary, our study identified a U-shaped relationship between maternal preconception Hb concentration and the risk of PTB in Chinese, rural, reproductive-aged women. Both maternal anaemia and high Hb level before pregnancy can significantly increase the risk of VPTB. Early detection of Hb concentration and providing appropriate intervention for women with anaemia or high Hb concentration, before pregnancy, should be considered an important approach for primary prevention of PTB, and would be helpful in reducing perinatal mortality and morbidity.

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The corresponding author has full access to data in the study and takes responsibility for data integrity and the accuracy of data analysis. X. Z. and Q. X. searched the literature, analysed the data, interpreted the results and drafted the manuscript. L. W., Q. L., M. J., Y. H., Y. W., Y. Z., H. Z. and Z. P. collected the data. F. L. revised the manuscript. Y. Y., X. M. and Z. Y. conceived of the study, provided overall guidance and revised the manuscript. All authors revised the article for important intellectual content, and each approved the final manuscript as submitted.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114518001721

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