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INNOVATION AND TECHNOLOGY FOR GENDER EQUALITY

UN WOMEN

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This week's issue was organized by Guest Editor Linhong Wang.

Preplanned Studies

Optimal Gestational Weight Gain for Women with Gestational Diabetes Mellitus — China, 2011–2021

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Summary

What is already known about this topic?

Joint effects of gestational weight gain (GWG) and hyperglycemia on adverse pregnancy outcomes suggest that lower optimal GWG is optimal for women with gestational diabetes mellitus (GDM). However, there is still a lack of guidelines.

What is added by this report?

Optimal weekly GWG range after diagnosis of GDM for underweight, normal-weight, overweight, and obese women was 0.37–0.56 kg/week, 0.26–0.48 kg/week, 0.19–0.32 kg/week, and 0.12–0.23 kg/week, respectively.

What are the implications for public health practice?

The findings may be used to inform prenatal counseling regarding optimal gestational weight gain for women with gestational diabetes mellitus, and suggest the need for weight gain management.

Excessive gestational weight gain (GWG) and hyperglycemia can have additive effects on adverse pregnancy outcomes, suggesting that optimal GWG might be lower for women with gestational diabetes mellitus (GDM) (*1*). However, there is a lack of guidelines for GWG among women with GDM. This multicenter cohort study aimed to determine the optimal GWG ranges after diagnosis for Chinese women with GDM and evaluate whether the new ranges could effectively reduce adverse outcomes. Data were extracted through electronic medical record systems at seven regional tertiary hospitals in China. Weekly GWG after diagnosis were calculated using the average weight gain each week from diagnosis of GDM to delivery. Optimal weekly GWG ranges were constructed for each pre-pregnancy body mass index (BMI) group by identifying the ranges that had relatively lower incidence of adverse outcomes. The proposed ranges were found to be associated with reduced adverse outcomes. Compared with the ranges of the National Academy of Medicine (NAM, previously called the Institute of Medicine) (*2*), the new ranges reduced the lower limits of GWG without causing additional risks of adverse outcomes and lowered the upper limit as well to avoid higher occurrence of large for gestational age births and macrosomia. These findings may inform prenatal counseling regarding optimal GWG after diagnosis of GDM and suggest the need for weight gain management.

Based on the previous work of Chinese Pregnant Women Cohort Study (CPWCS), a retrospective cohort study was conducted to extract data from electronic medical record systems from 2011 to 2021 in seven tertiary hospitals from Beijing, Zhejiang, Hebei, Shandong, Guizhou, and Shaanxi (*3*). A total of 11,168 women with GDM were included in this study. GDM was diagnosed according to the criteria of the International Association of Diabetes and Pregnancy Study Group (*4*). Previous evidence suggests that GWG is linear during the second and third trimesters of pregnancy (*2*,*5*), so the weekly GWG after diagnosis was calculated using the average weight gain each week from diagnosis of GDM to delivery. Adverse outcomes included full-term low birth weight, macrosomia, small for gestational age (SGA), large for gestational age (LGA), and preterm birth. An infant with a birth weight <2,500 g and delivered at ≥37 weeks was classified as having a full-term low birth weight, and with a birth weight >4,000 g was classified as having macrosomia. SGA and LGA were defined according to Chinese standards, referring to birth weight below the 10th percentile for gestational age or above the 90th percentile for gestational age, respectively (*6*). Preterm birth was defined as birth occurring prior to 37 weeks gestation.

The recommended ranges of weekly GWG for women with GDM were constructed using an outcome-based approach. The main idea of this

approach was to define the GWG ranges with the relatively lower incidence of adverse outcomes as the optimal ones, based on the thresholds of GWG below or above which the adverse outcome increased (*7*–*9*). The usual procedure was to group GWG at certain intervals and then find the intervals with lower incidence of adverse outcomes compared to others. In this study, for each maternal pre-pregnancy BMI group (defined by the standards for Chinese adults), weekly GWG after diagnosis of GDM was first divided into groups by an interval of 0.10 kg/week, and the number and incidence of adverse outcomes were calculated at each interval. The intervals with lower incidence compared with others were further subdivided by an interval of 0.05 kg/week. Similarly, the groups in 0.05 intervals with lower incidence were further subdivided by an interval of 0.02 kg/week and 0.01 kg/week sequentially. Finally, the optimal ranges accurate to 0.01 kg/week with lower risks of adverse outcomes were confirmed through groups divided by an interval of 0.01.

To verify the obtained optimal ranges, logistic regression was used to calculate the odds ratios (*OR*s) for each adverse outcome for the inadequate and excessive GWG groups, with the adequate GWG group as the reference. To compare the performance between the new ranges and NAM ranges, incidences of adverse outcomes across different groups of adequate GWG according to these two recommendations were also compared. Three sensitivity analyses were conducted. First, potential confounders (e.g., maternal age, drug treatment after diagnosis) were adjusted in the model when analyzing the association between GWG status and adverse outcomes. Subgroup analyses were also conducted by region. Additionally, subgroup analyses and the comparison with NAM were reconducted by excluding full-term low birth weight from outcomes of interest, as the great disparity of incidence it caused might affect the robustness of the results. Data analyses were conducted using R software (Version 4.0.3; John Chambers and colleagues, Jersey City, NJ, USA). Statistical significance was set at a two-sided *P*-value <0.05. Further details on the methods can be found in the supplementary file.

A total of 11,168 women were included (see Supplementary Figure S1, available in https://weekly.chinacdc.cn/), with a mean age of 31.0 [standard deviation (SD): 4.4] years and a mean gestational age of 38.7 (SD: 1.4) weeks. The sample was categorized into four weight groups: underweight (*n*=810), normal weight (*n*=6,835), overweight (*n*=2,775), and obesity (*n*=748; see Table 1). The incidence of adverse pregnancy outcomes ranged from 1.1% to 12.0%. Regional distribution is presented in Supplementary Table S1 (available in https://weekly.chinacdc.cn/).

In the underweight group, when the weekly GWG was less than 0.37 kg/week, the incidence of full-term low birth weight and preterm birth both increased. Among groups with GWG ≥0.56 kg/week, the incidence of LGA, macrosomia, and preterm birth increased. Thus, the optimal GWG range was 0.37–0.56 kg/week. Similarly, in the normal weight group, the optimal range was 0.26–0.48 kg/week to keep the incidence of adverse outcomes at a lower level. In the overweight group, when the GWG was less than 0.19 kg/week, the incidences of SGA, full-term low birth weight, and preterm birth all increased substantially. When the weekly weight gain was higher than 0.32 kg/week, the incidence of LGA and preterm birth showed a large increase. Therefore, the optimal

TABLE 1. Maternal characteristics and adverse pregnancy outcomes of all participants and in different pre-pregnancy body mass index (BMI) groups.

Characteristic and outcomes	All Population (*N* =11,168)	Underweight (*N*=810)	Normal weight (*N*=6,835)	Overweight (*N*=2,775)	Obesity (*N*=748)
Maternal age [years (mean±SD)]	31.0±4.4	29.7 ±4.2	31.0±4.3	31.3±4.5	31.1±4.4
Nulliparous, *n* (%)	8,461 (75.8)	691 (85.3)	5,270 (77.1)	1,980 (71.4)	520 (69.5)
Gestational age [weeks(mean±SD)]	38.7±1.4	29.7±4.2	31.0±4.3	38.6±1.5	38.4±1.5
Male neonates, *n* (%)	4,430 (53.4)	360 (57.8)	2,663 (52.8)	1,095 (53.2)	312 (54.9)
Adverse outcomes, *n* (%)					
Preterm birth	574 (5.1)	32 (4.0)	347 (5.1)	144 (5.2)	51 (6.8)
Small size for gestational age	623 (5.6)	70 (8.6)	383 (5.6)	141 (5.1)	29 (3.9)
Large size for gestational age	1,338 (12.0)	44 (5.4)	689 (10.1)	447 (16.1)	158 (21.1)
Full-term low birth weight	121 (1.1)	9(1.1)	68 (1.0)	36 (1.3)	8 (1.1)
Macrosomia	764 (6.8)	26 (3.2)	403 (5.9)	254 (9.2)	81 (10.8)

weekly weight gain for the overweight group was 0.19–0.32 kg/week. The range in the obesity group was 0.12–0.23 kg/week, which was able to avoid macrosomia and LGA (see Supplementary Tables S2–S5, available in https://weekly.chinacdc.cn/).

GWG status after GDM diagnosis was categorized according to the ranges proposed. The odds ratios (*OR*s) of inadequate and excessive GWG for each adverse pregnancy outcome, with the adequate GWG as the reference group, are presented in Table 2. Inadequate GWG defined by the new range was associated with increased risks of preterm birth, while excessive GWG was associated with higher risks of preterm birth, LGA and macrosomia. The associations were not altered after adjusting for potential confounders and were similar among different regions (Supplementary Figure S2, available in https://weekly.chinacdc.cn/). When comparing with the NAM ranges, reduced lower limits of GWG did not increase risks of adverse outcomes in the four groups. In the obesity group, women with adequate GWG according to the new ranges had lower risks of LGA and macrosomia compared to the part of NAM ranges discrepant with the new ranges (Supplementary Tables S6–S9, available in https://weekly.chinacdc.cn/).

TABLE 2. Association between GWG status and adverse outcomes in different pre-pregnancy BMI groups.*

Pre-pregnancy BMI (kg/m^2)	GWG status	SGA			LGA			Full-term low birth weight			Macrosomia			Preterm birth		
		OR	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*
Underweight (<18.5)	Adequate	1.00			1.00			1.00			1.00			1.00		
	Inadequate	1.59	0.90, 2.88	0.116	1.25	0.58, 2.74	0.573	0.46	0.06, 2.36	0.369	0.79	0.27, 2.22	0.650	3.09	1.30, 8.57	0.017†
	Excessive	1.05	0.52, 2.08	0.884	1.75	0.81, 3.88	0.154	0.98	0.19, 4.49	0.979	1.81	0.72, 4.74	0.212	1.28	0.39, 4.14	0.676
Normal weight (18.5–23.9)	Adequate	1.00			1.00			1.00			1.00			1.00		
	Inadequate	1.20	0.92, 1.55	0.175	0.66	0.52, 0.82	<0.001†	1.30	0.69, 2.44	0.406	0.59	0.43, 0.80	<0.001†	1.88	1.42, 2.50	<0.001†
	Excessive	1.14	0.89, 1.47	0.297	1.33	1.12, 1.59	0.001†	1.42	0.80, 2.56	0.232	1.48	1.18, 1.85	<0.001†	1.55	1.18, 2.04	0.002†
Overweight (24.0–27.9)	Adequate	1.00			1.00			1.00			1.00			1.00		
	Inadequate	1.11	0.67, 1.87	0.693	0.53	0.37, 0.75	<0.001†	1.65	0.46, 7.68	0.471	0.44	0.28, 0.70	<0.001†	2.98	1.62, 5.94	<0.001†
	Excessive	0.92	0.58 1.50	0.735	1.16	0.88, 1.52	0.289	2.78	0.97, 11.70	0.095	1.08	0.78, 1.52	0.646	2.20	1.24, 4.27	0.012†
Obesity (≥28.0)	Adequate	1.00			1.00			1.00			1.00			1.00		
	Inadequate	0.52	0.10, 2.44	0.408	0.86	0.39, 1.92	0.711	–	–	0.992	1.20	0.43, 3.66	0.730	1.37	0.50, 4.10	0.553
	Excessive	1.13	0.42, 3.95	0.824	2.04	1.13, 3.96	0.024†	0.57	0.13, 3.95	0.498	2.05	0.93, 5.44	0.105	1.02	0.44, 2.75	0.973

Abbreviation: BMI=body mass index; GWG=gestational weight gain; SGA=small for gestational age; LGA=large for gestational age; *OR*=odds ratio; *CI*=confidence interval.

* GWG status was judged using the new obtained optimal ranges.

† *P*<0.05.

"–" means that Model for full-term low birth weight in this group cannot be well fitted due to sample size.

DISCUSSION

This multicenter study proposed optimal weekly GWG ranges after diagnosis of GDM among Chinese populations using an outcome-based approach. Inadequate GWG, as defined by the new range, was associated with increased preterm birth risks, while excessive GWG was associated with increased risks of preterm birth, LGA, and macrosomia. The new ranges reduced the lower limits of GWG without causing additional risks and modification of the upper limits avoided higher occurrences of LGA and macrosomia. This study provides tailored GWG recommendations to promote optimal pregnancy outcomes for women with GDM, and enables clinicians to give targeted weight control suggestions and counsel patients week to week regarding their performance.

Only a few studies have attempted to propose GWG targets for GDM pregnancies, and most of them provided recommendations on the total GWG during the entire pregnancy without distinguishing before and after GDM diagnosis. As GDM women cannot be identified before diagnosis, GWG ranges should be proposed after diagnosis. Although the previous studies had different methods and results, studies focusing on

exploration of optimal range in China and abroad have supported stricter optimal GWG ranges than the NAM standards to improve pregnancy outcomes (*10*–*11*). Considering the great impact of GWG during the second and third trimesters on adverse outcomes, proposing an optimal GWG after diagnosis of GDM rather than the total GWG allows clinicians to give targeted suggestions and counsel their patients on their weekly GWG regarding their weight control performance. Only one study in China could be compared with this study for similar methods (*9*). However, there were limitations in their study, such as a single-center design and an insufficient number of samples to obtain a statistically significant lower limit. Our analyses indicated that inappropriate GWG under the new ranges was associated with increased adverse outcomes, which were similar to most relevant reports on the associations between GWG and prenatal outcomes.

The new ranges reduced the lower limits of weekly GWG compared with the NAM ranges. The new ranges did not significantly increase the risks of any adverse outcomes and excluded women with a higher occurrence of adverse outcomes, suggesting that weight management stricter than the NAM standard during pregnancy might be more beneficial among Chinese individuals with GDM. Previous research has found that people of Asian descent tend to possess a lower BMI and a higher percentage of body fat than white populations, along with a higher susceptibility of metabolic conditions (*12*). GWG standards constructed by the Chinese Nutrition Society (CNS) for singleton pregnancy without pregnancy complications were also generally lower than the NAM standards (*13*). Evidence supports that GDM itself is an independent risk factor for adverse outcomes and metabolic changes induced by GDM combining with excess gestational weight gain could have joint effects. Thus, the evidence above supports that optimal GWG ranges for women with GDM in China should be different and they would benefit from a more tailored recommendation.

Results of this study showed consistency with the CNS guidelines among women categorized as pre-pregnancy underweight or normal weight, but the upper and lower limits of the recommended ranges for groups of overweight and obesity were lower. To effectively avoid the adverse effects of the three risk factors (pre-pregnancy obesity, excessive GWG and GDM), researchers suggested that stricter weight management might offer additional benefits for women with pre-pregnancy obesity. The co-occurrence of pre-pregnancy obesity and gestational abnormal glucose metabolism was found to further worsen adverse pregnancy outcomes (such as LGA and macrosomia) compared to a single condition alone. One possible explanation is that higher nutritional status may exaggerate insulin resistance and worsen GDM outcomes. Pre-pregnancy obese women with adequate GWG within our ranges had a lower risk of LGA and macrosomia, and women in the overweight group with adequate GWG within our ranges also had a lower risk of preterm birth. These results indicate that the new ranges are more beneficial for GDM women with pre-pregnancy overweight and obesity, as adverse outcomes need to be prevented intensively in this population.

This study has several limitations. First, we did not adjust for glycemic control in the analyses since these data were not collected. However, we attempted to minimize its impact by adjusting the variable of drug treatment in the models. Second, we did not include the adverse outcomes of long-term outcomes such as postpartum complications or offspring diseases, which should be explored in the future. Third, the sample sizes of the underweight or obese groups were limited and the results await further validation. Additionally, conclusions of this study came from observational studies and the ranges need to be further validated by intervention studies in the future.

In conclusion, this multicenter study established lower optimal GWG ranges for women with GDM. Clinics should provide additional targeted advice after GDM diagnosis to help women maintain weekly weight gains within a reasonable range. As management of weight gain after GDM diagnosis is an important component of GDM intervention, further validation of our findings is also needed in the future.

Conflicts of interest: No conflicts of interest.

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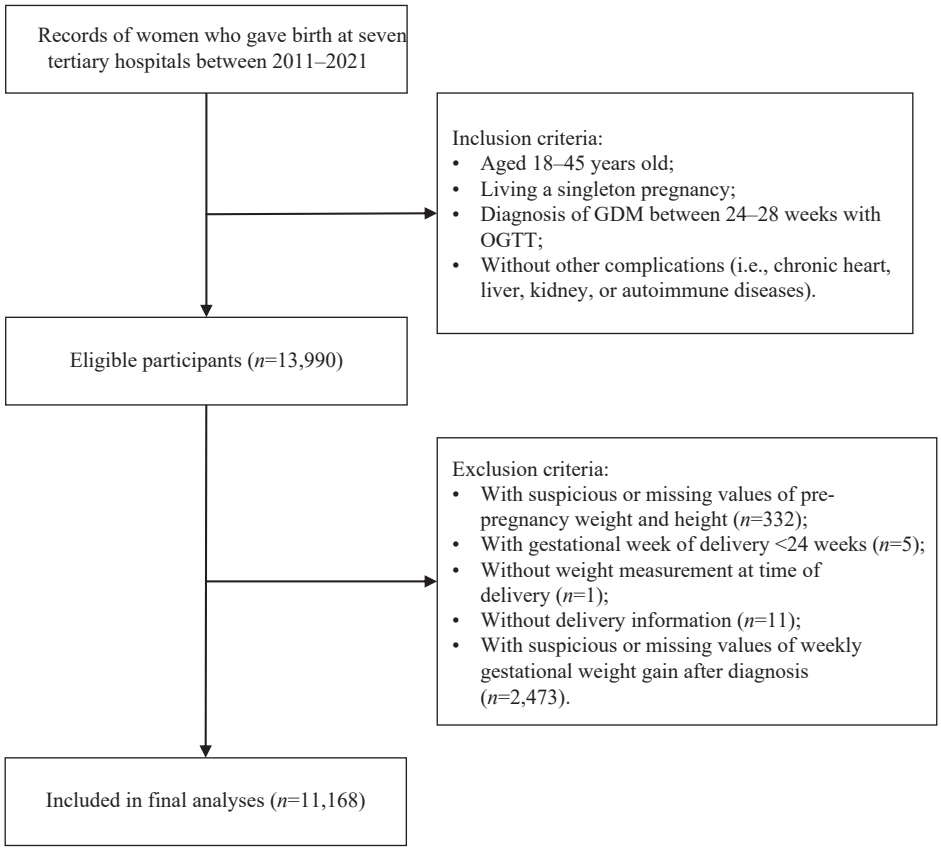
SUPPLEMENTARY MATERIAL

Data Collection and Data Processing

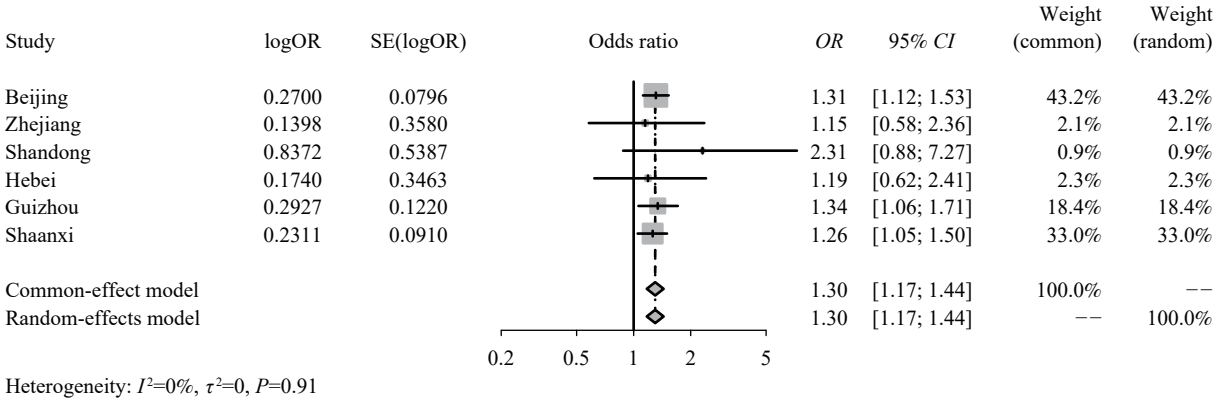
Based on the previous work of Chinese Pregnant Women Cohort Study (CPWCS), this retrospective cohort study selected seven regional tertiary hospitals from China after considering the standard level of clinical treatment, data quality, hospital's willingness to participate, and cooperation between the hospital and the researchers. Information was extracted from electronic medical record systems from 2011 to 2021. Because weight was not routinely measured and recorded at the time of 75 g oral glucose tolerance test (OGTT), we widened the time period to get more cases with complete information. We included 13,990 participants, of whom 2,822 were excluded. Finally, 11,168 (79.8%) women with gestational diabetes mellitus (GDM) were included in this study (See Supplementary Figure S1).

Associations Between GWG Status and Adverse Outcomes

We also conducted subgroup analyses to test whether the associations between adverse outcomes and inappropriate gestational weight gain (GWG) according to the newly obtained ranges were different among regions. Considering the small sample size in some regions, the odds ratios (*OR*s) for any adverse outcome were calculated for the inappropriate group (combining inadequate GWG group and excessive GWG group), with the adequate group as the reference. According to the pooled results of meta-analysis (Supplementary Figure S2), inappropriate GWG according to the newly obtained range was associated with increased risks of adverse perinatal outcomes, indicating no heterogeneity among different regions (I^2=0, P=0.91). After removing participants from Beijing, the results in the remaining regions also showed no heterogeneity (I^2=0, P=0.83). And after excluding full-term low birthweight from outcomes of interest, the result of meta-analysis remained similar as well (I^2=0, P=0.91).



SUPPLEMENTARY FIGURE S1. Flowchart of participants in the study.
Abbreviation: GDM=gestational diabetes mellitus; OGTT=oral glucose tolerance test.



SUPPLEMENTARY FIGURE S2. Associations between adverse outcomes and inappropriate GWG according to the newly obtained ranges by different regions.
Abbreviation: *OR*=odds ratio; *CI*=confidence interval; GWG=gestational weight gain.

Comparisons of Performance Between the New Ranges and NAM Ranges

To assess whether our newly obtained ranges were more feasible for GDM women than the National Academy of Medicine (NAM) recommended range, we compared the incidences of adverse outcomes across groups of adequate GWG according to our ranges and NAM ranges.

For normal weight group and overweight group with relatively large sample sizes, we calculated the odds ratio of different adverse outcomes by logistic regression for the discrepant ranges of the two targets, with the overlapping range (regarded as adequate in both recommendations) as the reference. For underweight and obesity groups with relatively small sample sizes, we calculated the odds ratio of adverse outcomes for the discrepant ranges, with the new ranges or the NAM ranges as the reference. And in these two groups, adverse outcomes were grouped into two types: outcomes positively associated with weekly GWG [large for gestational age (LGA) and macrosomia] and outcomes negatively associated with GWG [small for gestational age (SGA), full-term low birth weight, and preterm birth]. These analyses were aimed to find out whether the changes we made comparing to the NAM recommended ranges would have a lower occurrence of adverse outcomes.

In underweight and the normal weight groups, we found out that GWG range below the lower limits of the NAM did not significantly increase the risk of adverse outcomes. However, in GWG range group below our lower limit, the incidence of preterm birth increased significantly (*OR*: 2.07, 95% *CI*: 1.49, 2.94) in the normal weight group. Similar to the overweight group, the part of the new ranges discrepant with the NAM's did not lead to a significant change, but GWG above 0.33 kg/week (almost close to our upper limit 0.32 kg/week) or below our lower limit will lead to increased risks of preterm birth (*OR*: 2.10, 95% *CI*: 1.10, 4.53; *OR*: 2.88, 95% *CI*: 1.47, 6.35). In obesity group, women with adequate GWG under our new ranges had lower risks of LGA and macrosomia compared to the part of the NAM ranges above our upper limit (*OR*: 2.76, 95% *CI*: 1.20, 6.50). And the reduced lower limit in the obesity group did not cause extra risks as well. After removing full-term low birth weight from the outcomes of interest, the results in the four groups remained the same as the newly defined lower and upper limits did not cause extra risks.

SUPPLEMENTARY TABLE S1. Geographic distribution of 11,168 participants by different pre-pregnancy body mass index (BMI) groups.

Pre-pregnancy BMI group	Beijing *n* (%)	Zhejiang *n* (%)	Shandong *n* (%)	Hebei *n* (%)	Guizhou *n* (%)	Shaanxi *n* (%)
Underweight	316 (7.1)	20 (9.9)	4 (2.7)	26 (7.9)	152 (7.4)	292 (7.3)
Normal Weight	2,775 (62.1)	131 (64.9)	65 (44.2)	156 (47.4)	1,231 (60.1)	2,477 (62.3)
Overweight	1,138 (25.5)	45 (22.3)	48 (32.7)	101 (30.7)	495 (24.2)	948 (23.8)
Obesity	238 (5.3)	6 (3.0)	30 (20.4)	46 (14.0)	170 (8.3)	258 (6.5)
Total	4,467	202	147	329	2,048	3,975

Abbreviation: BMI=body mass index.

SUPPLEMENTARY TABLE S2. Incidence for adverse outcomes in each GWG category (kg/week) in the underweight group.

GWG category (kg/week)	*N*=810	SGA *n* (%)	LGA *n* (%)	Full-term low birth weight *n* (%)	Macrosomia *n* (%)	Preterm birth *n* (%)
<0.32	240	26 (10.8)	13 (5.4)	2 (0.8)	5 (2.1)	18 (7.5)
0.32–0.37	73	8 (11.0)	3 (4.1)	0 (0.0)	2 (2.7)	2 (2.7)
0.37–0.39	25	3 (12.0)	1 (4.0)	0 (0.0)	1 (4.0)	0 (0.0)
0.39–0.41	30	4 (13.3)	1 (3.3)	2 (6.7)	1 (3.3)	0 (0.0)
0.41–0.43	35	5 (14.3)	3 (8.6)	1 (2.9)	1 (2.9)	1 (2.9)
0.43–0.45	32	1 (3.1)	2 (6.2)	0 (0.0)	2 (6.2)	2 (6.2)
0.45–0.47	41	1 (2.4)	1 (2.4)	1 (2.4)	0 (0.0)	0 (0.0)
0.47–0.49	22	2 (9.1)	1 (4.5)	0 (0.0)	1 (4.5)	1 (4.5)
0.49–0.50	11	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
0.50–0.51	20	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.51–0.52	12	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)	0 (0.0)
0.52–0.53	12	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.53–0.54	15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.54–0.55	12	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)	0 (0.0)
0.55–0.56	11	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
0.56–0.57	12	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
0.57–0.58	14	0 (0.0)	1 (7.1)	0 (0.0)	1 (7.1)	0 (0.0)
0.58–0.59	13	1 (7.7)	2 (15.4)	1 (7.7)	1 (7.7)	0 (0.0)
0.59–0.60	0	–	–	–	–	–
≥0.60	180	14 (7.8)	13 (7.2)	2 (1.1)	9 (5.0)	5 (2.8)

Abbreviation: GWG=gestational weight gain; SGA=small for gestational age; LGA=large for gestational age.

SUPPLEMENTARY TABLE S3. Incidence for adverse outcomes in each GWG category (kg/week) in the normal weight group.

GWG category (kg/week)	*N*=6,835	SGA *n* (%)	LGA *n* (%)	Full-term low birth weight *n* (%)	Macrosomia *n* (%)	Preterm birth *n* (%)
<0.23	1,587	102 (6.4)	101 (6.4)	17 (1.1)	49 (3.1)	108 (6.8)
0.23–0.24	103	6 (5.8)	3 (2.9)	1 (1.0)	2 (1.9)	5 (4.9)
0.24–0.26	195	10 (5.1)	22 (11.3)	2 (1.0)	12 (6.2)	10 (5.1)
0.26–0.28	178	13 (7.3)	20 (11.2)	1 (0.6)	14 (7.9)	7 (3.9)
0.28–0.30	215	17 (7.9)	14 (6.5)	2 (0.9)	7 (3.3)	10 (4.7)
0.30–0.31	121	10 (8.3)	9 (7.4)	2 (1.7)	7 (5.8)	0 (0.0)
0.31–0.32	96	2 (2.1)	14 (14.6)	1 (1.0)	8 (8.3)	6 (6.2)
0.32–0.33	88	2 (2.3)	17 (19.3)	2 (2.3)	7 (8.0)	4 (4.5)
0.33–0.34	151	6 (4.0)	14 (9.3)	0 (0.0)	9 (6.0)	7 (4.6)
0.34–0.35	108	6 (5.6)	11 (10.2)	3 (2.8)	7 (6.5)	5 (4.6)
0.35–0.36	124	3 (2.4)	16 (12.9)	1 (0.8)	12 (9.7)	4 (3.2)
0.36–0.37	115	4 (3.5)	10 (8.7)	0 (0.0)	4 (3.5)	0 (0.0)
0.37–0.38	103	4 (3.9)	10 (9.7)	1 (1.0)	7 (6.8)	9 (8.7)
0.38–0.39	107	2 (1.9)	9 (8.4)	1 (0.9)	1 (0.9)	4 (3.7)
0.39–0.40	86	7 (8.1)	11 (12.8)	2 (2.3)	5 (5.8)	2 (2.3)
0.40–0.41	151	9 (6.0)	12 (7.9)	0 (0.0)	3 (2.0)	7 (4.6)
0.41–0.42	131	6 (4.6)	18 (13.7)	0 (0.0)	10 (7.6)	4 (3.1)
0.42–0.43	122	10 (8.2)	14 (11.5)	0 (0.0)	10 (8.2)	2 (1.6)
0.43–0.44	111	6 (5.4)	9 (8.1)	0 (0.0)	4 (3.6)	3 (2.7)
0.44–0.45	103	2 (1.9)	8 (7.8)	0 (0.0)	4 (3.9)	5 (4.9)
0.45–0.46	120	5 (4.2)	12 (10.0)	1 (0.8)	11 (9.2)	3 (2.5)
0.46–0.47	129	9 (7.0)	8 (6.2)	3 (2.3)	6 (4.7)	1 (0.8)
0.47–0.48	72	1 (1.4)	6 (8.3)	0 (0.0)	2 (2.8)	4 (5.6)
0.48–0.49	118	5 (4.2)	12 (10.2)	0 (0.0)	7 (5.9)	7 (5.9)
0.49–0.50	82	7 (8.5)	6 (7.3)	2 (2.4)	2 (2.4)	4 (4.9)
0.50–0.51	217	8 (3.7)	28 (12.9)	1 (0.5)	17 (7.8)	11 (5.1)
0.51–0.52	59	3 (5.1)	5 (8.5)	0 (0.0)	1 (1.7)	1 (1.7)
0.52–0.53	84	8 (9.5)	10 (11.9)	2 (2.4)	3 (3.6)	3 (3.6)
0.53–0.54	132	8 (6.1)	20 (15.2)	1 (0.8)	17 (12.9)	1 (0.8)
0.54–0.55	106	9 (8.5)	12 (11.3)	4 (3.8)	9 (8.5)	3 (2.8)
0.55–0.60	379	23 (6.1)	47 (12.4)	1 (0.3)	25 (6.6)	16 (4.2)
0.60–0.65	312	14 (4.5)	33 (10.6)	6 (1.9)	24 (7.7)	18 (5.8)
0.65–0.70	255	11 (4.3)	44 (17.3)	1 (0.4)	29 (11.4)	14 (5.5)
≥0.70	775	45 (5.8)	104 (13.4)	10 (1.3)	68 (8.8)	59 (7.6)

Abbreviation: GWG=gestational weight gain; SGA=small for gestational age; LGA=large for gestational age.

SUPPLEMENTARY TABLE S4. Incidence for adverse outcomes in each GWG category (kg/week) in the overweight group

GWG category (kg/week)	*N*=2,775	SGA *n* (%)	LGA *n* (%)	Full-term low birth weight *n* (%)	Macrosomia *n* (%)	Preterm birth *n* (%)
<0.10	409	25 (6.1)	33 (8.1)	3 (0.7)	19 (4.6)	35 (8.6)
0.10–0.15	133	6 (4.5)	10 (7.5)	1 (0.8)	5 (3.8)	6 (4.5)
0.15–0.16	47	0 (0.0)	9 (19.1)	0 (0.0)	4 (8.5)	1 (2.1)
0.16–0.17	35	4 (11.4)	3 (8.6)	1 (2.9)	1 (2.9)	2 (5.7)
0.17–0.18	26	3 (11.5)	5 (19.2)	2 (7.7)	1 (3.8)	1 (3.8)
0.18–0.19	36	4 (11.1)	5 (13.9)	0 (0.0)	2 (5.6)	3 (8.3)
0.19–0.20	19	0 (0.0)	3 (15.8)	0 (0.0)	2 (10.5)	0 (0.0)
0.20–0.21	54	2 (3.7)	7 (13.0)	0 (0.0)	5 (9.3)	1 (1.9)
0.21–0.22	25	0 (0.0)	2 (8.0)	0 (0.0)	1 (4.0)	0 (0.0)
0.22–0.23	36	2 (5.6)	8 (22.2)	1 (2.8)	5 (13.9)	2 (5.6)
0.23–0.24	39	2 (5.1)	5 (12.8)	0 (0.0)	2 (5.1)	2 (5.1)
0.24–0.25	13	0 (0.0)	3 (23.1)	0 (0.0)	1 (7.7)	0 (0.0)
0.25–0.26	42	3 (7.1)	9 (21.4)	0 (0.0)	4 (9.5)	0 (0.0)
0.26–0.27	44	1 (2.3)	5 (11.4)	0 (0.0)	1 (2.3)	1 (2.3)
0.27–0.28	45	3 (6.7)	10 (22.2)	0 (0.0)	7 (15.6)	1 (2.2)
0.28–0.29	43	3 (7.0)	6 (14.0)	0 (0.0)	4 (9.3)	3 (7.0)
0.29–0.30	32	2 (6.2)	9 (28.1)	1 (3.1)	7 (21.9)	1 (3.1)
0.30–0.31	65	5 (7.7)	9 (13.8)	1 (1.5)	8 (12.3)	0 (0.0)
0.31–0.32	31	2 (6.5)	5 (16.1)	0 (0.0)	3 (9.7)	1 (3.2)
0.32–0.33	42	0 (0.0)	9 (21.4)	0 (0.0)	2 (4.8)	3 (7.1)
0.33–0.34	63	3 (4.8)	5 (7.9)	1 (1.6)	2 (3.2)	3 (4.8)
0.34–0.35	30	0 (0.0)	4 (13.3)	0 (0.0)	3 (10.0)	2 (6.7)
0.35–0.36	66	2 (3.0)	13 (19.7)	1 (1.5)	8 (12.1)	3 (4.5)
0.36–0.37	39	1 (2.6)	8 (20.5)	1 (2.6)	4 (10.3)	2 (5.1)
0.37–0.38	40	2 (5.0)	6 (15.0)	0 (0.0)	3 (7.5)	4 (10.0)
0.38–0.39	63	4 (6.3)	16 (25.4)	1 (1.6)	10 (15.9)	1 (1.6)
0.39–0.40	46	3 (6.5)	10 (21.7)	0 (0.0)	7 (15.2)	1 (2.2)
0.40–0.45	192	5 (2.6)	28 (14.6)	2 (1.0)	18 (9.4)	8 (4.2)
0.45–0.50	170	8 (4.7)	36 (21.2)	2 (1.2)	19 (11.2)	9 (5.3)
0.50–0.55	198	12 (6.1)	40 (20.2)	2 (1.0)	28 (14.1)	9 (4.5)
0.55–0.60	140	5 (3.6)	22 (15.7)	4 (2.9)	13 (9.3)	6 (4.3)
≥0.60	512	29 (5.7)	104 (20.3)	12 (2.3)	55 (10.7)	33 (6.4)

Abbreviation: GWG=gestational weight gain; SGA=small for gestational age; LGA=large for gestational age.

SUPPLEMENTARY TABLE S5. Incidence for adverse outcomes in each GWG category (kg/week) in the obesity group

GWG category (kg/week)	*N*=748	SGA *n* (%)	LGA *n* (%)	Full-term low birth weight *n* (%)	Macrosomia *n* (%)	Preterm birth *n* (%)
<0.00	60	0 (0.0)	7 (11.7)	0 (0.0)	4 (6.7)	5 (8.3)
0.00–0.05	22	2 (9.1)	6 (27.3)	0 (0.0)	4 (18.2)	2 (9.1)
0.05–0.10	32	1 (3.1)	2 (6.2)	0 (0.0)	1 (3.1)	1 (3.1)
0.10–0.11	7	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)	1 (14.3)
0.11–0.12	8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)
0.12–0.13	8	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)
0.13–0.14	8	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.14–0.15	10	0 (0.0)	3 (30.0)	0 (0.0)	1 (10.0)	2 (20.0)
0.15–0.16	9	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
0.16–0.17	9	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	1 (11.1)
0.17–0.18	6	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
0.18–0.19	7	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)	0 (0.0)
0.19–0.20	8	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)
0.20–0.21	12	0 (0.0)	4 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)
0.21–0.22	9	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	1 (11.1)
0.22–0.23	8	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
0.23–0.24	14	0 (0.0)	5 (35.7)	0 (0.0)	2 (14.3)	1 (7.1)
0.24–0.25	10	0 (0.0)	2 (20.0)	0 (0.0)	1 (10.0)	0 (0.0)
0.25–0.26	18	1 (5.6)	6 (33.3)	1 (5.6)	4 (22.2)	2 (11.1)
0.26–0.27	9	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
0.27–0.28	18	2 (11.1)	4 (22.2)	1 (5.6)	1 (5.6)	2 (11.1)
0.28–0.29	7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)
0.29–0.30	14	1 (7.1)	4 (28.6)	0 (0.0)	1 (7.1)	0 (0.0)
0.30–0.35	53	0 (0.0)	11 (20.8)	0 (0.0)	7 (13.2)	5 (9.4)
0.35–0.40	59	1 (1.7)	13 (22.0)	0 (0.0)	8 (13.6)	3 (5.1)
≥ 0.40	323	17 (5.3)	81 (25.1)	4 (1.2)	41 (12.7)	20 (6.2)

Abbreviation: GWG=gestational weight gain; SGA=small for gestational age; LGA=large for gestational age.

SUPPLEMENTARY TABLE S6. Adverse outcomes across groups of adequate GWG under the new range and NAM range in the underweight group.

GWG range (kg/week)	Outcomes positively associated with GWG			Outcomes negatively associated with GWG		
	OR	95% *CI*	*P*	*OR*	95% *CI*	*P*
Range above upper limit						
0.37–0.56*	1.00			1.00		
0.56–0.58†	0.85	0.05, 4.61	0.879	0.84	0.13, 3.07	0.818
Range below lower limit						
0.44–0.58§	1.00			1.00		
0.37–0.44¶	1.35	0.40, 4.18	0.605	2.00	0.89, 4.44	0.091

Abbreviation: GWG=gestational weight gain; *OR*=odds ratio; *CI*=confidence interval; NAM=National Academy of Medicine.
* The new range.
† Part of the NAM range above upper limit of the new range.
§ The NAM range.
¶ Part of the new range below the lower limit of the NAM range.

SUPPLEMENTARY TABLE S7. Adverse outcomes across groups of adequate GWG under the new range and NAM range in the normal weight group.

GWG range (kg/week)*	LGA			Macrosomia			Preterm birth			SGA			Full-term low birth weight		
	OR	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*
<0.26	0.68	0.53, 0.87	0.002§	0.63	0.45, 0.88	0.007§	2.07	1.49, 2.94	<0.001§	1.34	0.99, 1.82	0.065	1.77	0.83, 4.10	0.156
0.26-0.35	1.09	0.83, 1.43	0.532	1.17	0.82, 1.65	0.372	1.26	0.82, 1.94	0.289	1.30	0.90, 1.86	0.162	1.93	0.79, 4.80	0.145
0.35-0.48†	1.00			1.00			1.00			1.00			1.00		
0.48-0.50	0.93	0.54, 1.53	0.799	0.83	0.38, 1.60	0.613	1.73	0.84, 3.27	0.111	1.31	0.66, 2.38	0.403	1.67	0.25, 6.54	0.514
≥0.50	1.42	1.15, 1.76	0.001§	1.64	1.26, 2.16	<0.001§	1.71	1.22, 2.42	0.002§	1.27	0.94, 1.73	0.122	1.96	0.95, 4.43	0.084

Abbreviation: GWG=gestational weight gain; LGA=large for gestational age; SGA=small for gestational age; *OR*=odds ratio; *CI*=confidence interval; NAM=National Academy of Medicine.
* The new range was 0.26–0.48 kg/week and the NAM range was 0.35–0.50 kg/week, groups in the table were parts of the new ranges discrepant with NAM.
† The overlapping range of the two recommended ranges.
§ *P*<0.05.

SUPPLEMENTARY TABLE S8. Adverse outcomes across groups of adequate GWG under the new range and NAM range in the overweight group.

GWG range (kg/week)*	LGA			Macrosomia			Preterm birth			SGA			Full-term low birth weight		
	OR	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*
<0.19	0.50	0.32, 0.73	<0.001§	0.433	0.26, 0.71	<0.001§	2.88	1.47, 6.35	<0.001§	0.94	0.55, 1.64	0.822	1.79	0.43, 12.05	0.470
0.19–0.23	0.81	0.46, 1.39	0.455	0.915	0.45, 1.74	0.794	0.88	0.19, 2.99	0.847	0.47	0.14, 1.27	0.177	1.31	0.01, 13.78	0.827
0.23–0.32†	1.00			1.00			1.00			1.00			1.00		
0.32–0.33	1.22	0.52, 2.58	0.626	0.430	0.07, 1.48	0.257	2.95	0.63, 10.36	0.116	–	–	0.973	–	–	0.985
≥0.33	1.09	0.81, 1.49	0.575	1.074	0.74, 1.58	0.701	2.10	1.10, 4.53	0.037§	0.80	0.49, 1.36	0.393	3.10	0.92, 19.32	0.124

Abbreviation: GWG=gestational weight gain; LGA=large for gestational age; SGA=small for gestational age; *OR*=odds ratio; *CI*=confidence interval; NAM=National Academy of Medicine.
* The new range was 0.19–0.32 kg/week and the NAM range was 0.23–0.33 kg/week, groups in the table were parts of the new ranges discrepant with NAM.
† The overlapping range of the two recommended ranges.
§ *P*<0.05.
"–" means that models for SGA and full-term low birth weight in this group can't be well fitted due to sample size.

SUPPLEMENTARY TABLE S9. Adverse outcomes across groups of adequate GWG under the new range and NAM range in the obesity group.

GWG range (kg/week)	Outcomes positively associated with GWG			Outcomes negatively associated with GWG		
	OR	*95% CI*	*P*	*OR*	*95% CI*	*P*
Range above upper limit						
0.12–0.23*	1.00			1.00		
0.23–0.27†	2.76	1.20, 6.50	0.018**	0.92	0.24, 2.97	0.889
Range below lower limit						
0.17–0.27§	1.00			1.00		
0.12–0.17¶	0.34	0.10, 0.97	0.064	2.92	0.94, 9.53	0.065

Abbreviation: GWG=gestational weight gain; *OR*=odds ratio; *CI*=confidence interval; NAM=National Academy of Medicine.
* The new range.
† Part of the NAM range above upper limit of the new range.
§ The NAM range.
¶ Part of the new range below the lower limit of the NAM range.
** *P*<0.05.

Preplanned Studies

Hematological Parameters in the First Trimester and the Risk of Gestational Diabetes Mellitus — Beijing, China, 2017–2020

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Summary

What is already known about this topic?

Hematological parameters may indicate the presence of chronic low-grade inflammation and increasing viscosity, which are involved in the pathological processes of gestational diabetes mellitus (GDM). However, the association between several hematological parameters in early pregnancy and GDM has yet to be elucidated.

What is added by this report?

Hematological parameters in the first trimester, particularly red blood cell (RBC) count and systematic immune index, have a significant impact on GDM incidence. The neutrophils (NEU) count in the first trimester was particularly pronounced for GDM. The upward trend of RBC, white blood cell (WBC), and NEU counts was consistent across all GDM subtypes.

What are the implications for public health practice?

Early pregnancy hematological parameters are associated with the risk of GDM.

Gestational diabetes mellitus (GDM) is a prevalent high-risk disorder during pregnancy, increasing the risk of adverse pregnancy outcomes (*1*). Previous studies have documented that abnormalities in hematological cells reflect the increasing level of maternal immune dysregulation and viscosity, which may play a role in the pathophysiology of GDM (*2*–*3*). However, reports of the association between several hematological parameters in early pregnancy and GDM are equivocal. Although some epidemiological studies have demonstrated a positive association between red blood cell (RBC) (*4*), white blood cell (WBC) (*5*), or hemoglobin (Hb) (*6*) in early pregnancy and GDM, inconsistent results were observed in other studies (*7*). To our knowledge, previous studies have not included certain novel immune blood parameters, such as the neutrophil-lymphocyte ratio (NLR). We conducted a retrospective study and used adjusted logistic regression models to assess the association between increased hematological parameters in early pregnancy and incident GDM, collecting data from the Haidian District Maternal and Child Health Care Hospital on pregnant women between 2017 and 2020. All analyses were performed using the R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). The results showed that a quartile increment in Hb, RBC, WBC, platelet (PLT), neutrophils (NEU), NLR, and systemic immune-inflammation index (SII) was positively associated with GDM incident (P_{trend}<0.05) after multivariable adjustment.

This retrospective cohort study was conducted among 29,570 reproductive-aged women with singleton pregnancies who were registered in the obstetric archives between January 2017 and April 2020 and completed their routine prenatal visits in the Maternal and Child Health Care Hospital of Haidian District, Beijing. After excluding participants with chronic diseases (e.g., hypertension, diabetes, or chronic nephritis), infectious diseases [e.g., syphilis, clap, or acquired immune deficiency syndrome (AIDS)], missing values of hematological parameters before 13 gestational weeks, or women who did not undergo a standard oral glucose tolerance test (OGTT) at 24 to 28 gestational weeks, a total of 5,529 participants were finally included (Supplementary Figure S1, available in https://weekly.chinacdc.cn/).

Hematological parameters included blood cell counts [RBC, PLT, and WBC, including neutrophil (NEU) and lymphocyte (LYM)] and hemoglobin concentration, which were tested from fasting blood samples collected in the first trimester and immediately stored at 4–8 °C for 24 h. We further calculated NLR and SII [(neutrophil × platelet)/lymphocyte], indicating the degree of individual inflammatory burden (*8*). Both NLR and SII reflect the balance of adaptive immune and inflammatory factors in the human body. Physical examinations, previous obstetric history, laboratory parameters, and diagnoses were extracted from the electronic medical record system.

Information on physical examinations contained height and weight.

GDM was diagnosed if at least one value of plasma glucose concentration was equal to or exceeded the thresholds of 5.1, 10.0, and 8.5 mmol/L for fasting, 1 h, and 2 h post-glucose load values, respectively, after performing a 75 g OGTT at gestational 24–28 weeks according to the Guidelines for Diagnosis and Treatment of Diabetes in Pregnancy (2014) in China (*9*). We further distinguished the impact of three subtypes of GDM: isolated fasting hyperglycemia (GDM-IFH), isolated post-load hyperglycemia (GDM-IPH), and combined hyperglycemia (GDM-CH) (*10*). This study used age-adjusted and multivariable-adjusted logistic regression models to examine the associations between hematological parameters and GDM. The odds ratio (*OR*) and 95% confidence interval (*CI*) of having GDM were used to quantify the association. We categorized participants into four groups based on quartile cutoff values of hematological parameters. A linear trend was tested by recoding individual hematological parameters as a continuous variable into the regression model. To provide clinical recommendation (*11*), the normal ranges of RBC, Hb, WBC, PLT, NEU, and LYM in the first trimester were defined as 3.42–4.55 ($\times10^{12}$/L), 116–139 (g/L), 5.7–13.6 ($\times10^{9}$/L), 174–391 ($\times10^{9}$/L), 3.61–10.19 ($\times10^{12}$/L), and 1.1–3.6 ($\times10^{12}$/L), respectively. All the regression models were adjusted for the following covariates: age (categorical, <30, ≥30), gestational week (categorical, <9, ≥9), parity (categorical, 0, ≥1), body mass index (BMI) before 20 gestational weeks (categorical, <18.5, 18.5–23.9, 24.0–27.9, ≥28.0), history of adverse pregnancy outcomes (categorical, have, not have), and fasting blood glucose (categorical, <6.1, ≥6.1). All analyses were conducted using R software 4.1.2, and two-sided P<0.05 values were considered statistically significant.

Among the 5,529 participants, 1,017 incident GDM cases (18.4%, including 503 GDM-IPH, 339 GDM-IFH, and 175 GDM-CH) were identified. Table 1 shows the baseline characteristics of the pregnant women. The median age of participants was 31 (29 to 34) years, and the median gestational week at enrollment was 12.01. Participants with GDM were more likely to be older, parous, have an abnormal pregnancy history, and have higher levels of fasting plasma glucose and BMI in the first trimester (P<0.05). The hematological parameters in the first trimester, including RBC, Hb, WBC, PLT, LYM, NEU, NLR, and SII, were higher in GDM than in non-GDM women (P<0.05). Results from multivariable-adjusted logistic regressions revealed that, compared with the first quartile, the odds ratios (95% *CI*) of GDM across the highest quartile of NEU, WBC, RBC, Hb, SII, NLR, and PLT were 1.87 (1.53, 2.29), 1.81 (1.48, 2.21), 1.56 (1.28, 1.91), 1.52 (1.26, 1.84), 1.51 (1.24, 1.84), 1.42 (1.17, 1.74), and 1.36 (1.12, 1.67), respectively (all P_{trend}<0.01, Table 2). For GDM subtypes, increased risks of GDM-IFH, GDM-IPH, and GDM-CH were associated with an increase in RBC, WBC, and NEU count. Elevated LYM, rather than SII or NLR, was only significantly associated with GDM-CH. In addition, Hb and PLT were only significantly associated with GDM-IPH (Table 3). In summary, the results verified that a high level of each hematological parameter was a significant predictor of GDM. According to clinical classification, the risk for GDM was significantly increased with higher WBC [*OR*=2.03 (1.21, 3.31) for WBC ≥13.7×10^{12}/L], NEU [*OR*=2.01 (1.33, 2.98) for NEU ≥10.2×10^{12}/L], RBC [*OR*=1.55 (1.28, 1.87) for RBC ≥4.56×10^{12}/L], and Hb [*OR*=1.7 (1.34, 2.14) for Hb ≥140 g/L] levels in the first trimester (Supplementary Table S1, available in https://weekly.chinacdc.cn/).

DISCUSSION

This study found that several high-level hematological parameters (Hb concentration, RBC, PLT, and WBC, including NEU count, NLR, and SII) in the first trimester were significantly associated with an increased risk of gestational diabetes mellitus (GDM). Notably, elevated Hb concentration and PLT count, as well as elevated LYM count, could be used as potential biomarkers to identify isolated post-load hyperglycemia and GDM with fasting hyperglycemia, respectively. Our results also provide clinical evidence that elevated RBC and NEU counts in early pregnancy could be novel risk factors and biomarkers of GDM in addition to Hb concentration. To our knowledge, this is the first study to assess the impact of SII, RBC, and other hematological indices in early pregnancy on GDM and to discuss their impact on different GDM subtypes with a moderate sample size. Given that the discovery of symptoms or signs at the early stage of GDM is difficult, combining elevated hematological parameters in the first trimester with clinical risk factors or laboratory indicators may be able to identify women at higher risk as early as possible.

Research evidence suggests that subclinical inflammation may lead to insulin resistance by

TABLE 1. Characteristics among participants in the cohort according to GDM status (*n*=5,529).

Variable	Overall (*N*=5,529)	non-GDM (*n*=4,512)	GDM (*n*=1,017)	*P* value*
Age, years [median (IQR)]	31.00 (29.00, 34.00)	31.00 (29.00, 33.00)	32.00 (29.00, 35.00)	<0.001
Parity (%)				
≥1	1,966 (35.6)	1,565 (34.7)	401 (39.4)	0.005
BMI, kg/m^2, *n* (%)				<0.001
<18.5	190 (3.4)	154 (3.4)	36 (3.5)	
18.5–23.9	3,548 (64.2)	2,998 (66.4)	550 (54.1)	
24.0–27.9	1,450 (26.2)	1,129 (25.0)	321 (31.6)	
≥28.0	341 (6.2)	231 (5.1)	110 (10.8)	
Gestational weeks (mean±SD)	12.01±0.98	12.01±0.98	12.02±0.96	0.868
Adverse pregnancy history, *n* (%)	456 (8.2)	330 (7.3)	126 (12.4)	<0.001
Fasting plasma glucose, mmol/L (mean±SD)	4.91±0.34	4.88±0.33	5.02±0.33	<0.001
OGTT fasting, mmol/L (mean±SD)	4.63±0.38	4.54±0.30	5.01±0.46	<0.001
OGTT 1 hour, mmol/L (mean±SD)	7.69±1.61	7.29±1.32	9.45±1.59	<0.001
OGTT 2 hour, mmol/L (mean±SD)	6.63±1.24	6.32±0.95	7.99±1.43	<0.001
Hematological parameters				
RBC, 10^{12}/L (mean±SD)	4.20±0.31	4.19±0.31	4.25±0.31	<0.001
HB, g/L (mean±SD)	127.78±8.27	127.47±8.22	129.20±8.38	<0.001
WBC, 10^9/L [median (IQR)]	8.60 (7.40, 9.90)	8.50 (7.30, 9.80)	9.00 (7.70, 10.40)	<0.001
PLT, 10^9/L (mean±SD)	237.77±49.62	236.32±49.49	244.20±49.71	<0.001
LYM, 10^9/L [median (IQR)]	1.70 (1.40, 2.00)	1.70 (1.40, 2.00)	1.70 (1.50, 2.00)	0.001
NEU, 10^9/L [median (IQR)]	6.30 (5.20, 7.40)	6.20 (5.20, 7.30)	6.60 (5.50, 7.90)	<0.001
NLR [median (IQR)]	3.72 (3.00, 4.58)	3.71 (3.00, 4.56)	3.80 (3.13, 4.69)	0.005
SII [median (IQR)]	872.14 (678.57, 1113.60)	860.50 (672.19, 1099.820)	914.52 (709.71, 1186.67)	<0.001

Abbreviation: GDM=gestational diabetes mellitus; BMI=body mass index; OGTT=oral glucose tolerance test; RBC=red blood cell count; Hb=hemoglobin concentration; WBC=white blood cell count; PLT=platelet; LYM=lymphocytes; Neu=neutrophil; NLR=Neutrophil-to-lymphocyte ratio; SII=systemic immune-inflammation index, IQR=interquartile range; SD=standard deviation.

* Data are presented as mean±SD, and *P* values were from 2-sample independent *t*-tests; or presented as median (interquartile range), and *P* values were from Mann–Whitney U test; or presented as number (percent), and *P* values were from Chi-squared tests.

† OGTT was tested at 24–28 gestational weeks, and other variables were collected or measured in early pregnancy.

impairing β cell function and affecting insulin signaling directly (*12*). This may explain why classical inflammatory markers, such as WBC count and NLR, as well as the novel inflammation marker, SII, are correspondingly increased in early pregnancy among women with GDM. Additionally, platelet aggregation and glycated platelets have been reported in diabetes, which is correlated to a setting of acute and chronic inflammation with a similar cytokine milieu as that implicated in increased WBC count (*13*). In terms of surrogacy for nutritional improvement, higher RBC and Hb levels are often accompanied by higher blood viscosity, which has been demonstrated to be associated with insulin resistance (*14*). Furthermore, GDM-IFH and GDM-CH reveal impaired β-cell function and a high risk of maternal and neonatal outcomes, rather than GDM-IPH. However, the mechanisms underlying the link between elevated lymphocytes, rather than NLR or SII, and GDM-CH still need to be established in the future.

This study had several limitations. The participants were recruited from one hospital in China, which may have introduced selection bias and limited the generalizability of our findings. Additionally, this observational study cannot explain the causal relationship between parameters in the early trimester and the risk of GDM, nor can it explain the mechanisms between hematological parameters and the risk of GDM. Further experiments or research are needed to explore these mechanisms. Overall, our results provide evidence that abnormally high routine first-trimester complete blood test results are positively associated with the risk of GDM.

Conflicts of interest: No conflicts of interest.

TABLE 2. Odds ratio and 95% confidence intervals for GDM according to quartiles of hematological markers in early pregnancy.

Variable	*ORs* (95% *CIs*) for GDM				P_{trend}*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
SII	<680	680–872	873–1,110	≥1,111	
Cases/total (%)	211/1,383 (15.26)	229/1,382 (16.57)	277/1,382 (20.04)	300/1,382 (21.71)	
Model 1†	1 (ref.)	1.11 (0.90, 1.36)	1.4 (1.15, 1.70)***	1.55 (1.27, 1.88)***	<0.001
Model 2§	1 (ref.)	1.11 (0.90, 1.36)	1.35 (1.10, 1.64)***	1.48 (1.22, 1.81)***	<0.001
Model 3¶	1 (ref.)	1.12 (0.91, 1.38)	1.35 (1.11, 1.65)***	1.51 (1.24, 1.84)***	<0.001
NLR	<3.01	3.01–3.72	3.73–4.58	≥4.59	
Cases/total (%)	218/1,390 (15.68)	268/1,383 (19.38)	253/1,376 (18.39)	278/1,380 (20.14)	
Model 1	1 (ref.)	1.29 (1.06, 1.58)*	1.22 (1.00, 1.50)*	1.37 (1.12, 1.66)***	0.002
Model 2	1 (ref.)	1.29 (1.06, 1.57)*	1.21 (0.99, 1.48)	1.39 (1.14, 1.69)***	0.001
Model 3	1 (ref.)	1.31 (1.07, 1.60)**	1.24 (1.01, 1.52)*	1.42 (1.17, 1.74)***	0.001
RBC	<4.00	4.00–4.19	4.20–4.39	≥4.40	
Cases/total (%)	203/1,397 (14.53)	253/1,427 (17.73)	253/1,340 (18.88)	308/1,365 (22.56)	
Model 1	1 (ref.)	1.27 (1.04, 1.56)*	1.39 (1.13, 1.70)**	1.73 (1.43, 2.11)***	<0.001
Model 2	1 (ref.)	1.24 (1.01, 1.52)*	1.31 (1.07, 1.61)**	1.56 (1.28, 1.91)***	<0.001
Model 3	1 (ref.)	1.25 (1.02, 1.54)*	1.32 (1.07, 1.62)**	1.56 (1.28, 1.91)***	<0.001
HB	<124	124–128	129–133	≥134	
Cases/total (%)	252/1,600 (15.75)	219/1,346 (16.27)	234/1,255 (18.65)	312/1,328 (23.49)	
Model 1	1 (ref.)	1.04 (0.86, 1.27)	1.24 (1.02, 1.51)*	1.67 (1.38, 2.01)***	<0.001
Model 2	1 (ref.)	1.01 (0.83, 1.23)	1.16 (0.95, 1.41)	1.52 (1.26, 1.84)***	<0.001
Model 3	1 (ref.)	1.02 (0.83, 1.24)	1.16 (0.95, 1.41)	1.52 (1.26, 1.84)***	<0.001
WBC	<7.5	7.5–8.6	8.7–9.9	≥10.0	
Cases/total (%)	205/1,448 (14.16)	237/1,436 (16.5)	252/1,307 (19.28)	323/1,338 (24.14)	
Model 1	1 (ref.)	1.20 (0.98, 1.47)	1.46 (1.19, 1.78)***	1.96 (1.61, 2.38)***	<0.001
Model 2	1 (ref.)	1.18 (0.97, 1.45)	1.39 (1.14, 1.71)***	1.79 (1.47, 2.19)***	<0.001
Model 3	1 (ref.)	1.20 (0.98, 1.47)	1.41 (1.16, 1.71)***	1.81 (1.48, 2.21)***	<0.001
PLT	<205	205–234	235–269	≥270	
Cases/total (%)	213/1,416 (15.04)	247/1,367 (18.07)	266/1,393 (19.10)	291/1,353 (21.51)	
Model 1	1 (ref.)	1.25 (1.02, 1.53)*	1.33 (1.09, 1.62)**	1.53 (1.26, 1.86)***	<0.001
Model 2	1 (ref.)	1.23 (1.01, 1.51)*	1.25 (1.03, 1.53)*	1.37 (1.12, 1.67)**	0.001
Model 3	1 (ref.)	1.23 (1.01, 1.51)*	1.25 (1.02, 1.53)*	1.36 (1.12, 1.67)**	0.001
LYM	<1.41	1.41–1.70	1.80–2.00	≥2.01	
Cases/total (%)	243/1,498 (16.22)	298/1,664 (17.91)	249/1,295 (19.23)	227/1,072 (21.18)	
Model 1	1 (ref.)	1.14 (0.94, 1.37)	1.23 (1.01, 1.50)	1.39 (1.13, 1.70)***	0.002
Model 2	1 (ref.)	1.12 (0.93, 1.35)	1.17 (0.96, 1.43)	1.25 (1.01, 1.53)*	0.074
Model 3	1 (ref.)	1.12 (0.93, 1.35)	1.16 (0.96, 1.42)	1.23 (1.00, 1.51)*	0.102
NEU	<5.21	5.21–6.30	6.40–7.40	≥7.41	
Cases/total (%)	196/1,399 (14.01)	252/1,472 (17.12)	248/1,323 (18.75)	321/1,335 (24.04)	
Model 1	1 (ref.)	1.28 (1.04, 1.56)*	1.43 (1.17, 1.76)***	1.99 (1.63, 2.42)***	<0.001
Model 2	1 (ref.)	1.26 (1.02, 1.54)*	1.37 (1.12, 1.69)**	1.85 (1.51, 2.26)***	<0.001
Model 3	1 (ref.)	1.27 (1.03, 1.56)*	1.39 (1.13, 1.71)**	1.87 (1.53, 2.29)***	<0.001

Abbreviation: GDM=gestational diabetes mellitus; RBC=red blood cell count; Hb=hemoglobin concentration; WBC=white blood cell count; PLT=platelet; LYM=lymphocyte; Neu=neutrophils; NLR=Neutrophil-to-lymphocyte ratio; SII=systemic immune-inflammation index; *CIs*=confidence intervals; *ORs*=odds ratios; ref.=reference.

* *P* value <0.05.

† Model 1: adjusted for age.

§ Model 2: adjusted for age and body mass index.

¶ Model 3: adjusted for age, body mass index, gestational week, parity, adverse pregnancy history, and fasting plasma glucose.

** *P* value <0.01.

†† *P* trend values were obtained from the logistic regression models by using individual hematological parameters treated as continuous variables, where standard deviation (SD) was used as a unit to quantify the elevation of each parameter.

*** *P* value <0.001.

TABLE 3. Associations of hematological markers with different gestational diabetes mellitus status.

Variable	GDM-IPH *vs.* NGT			GDM-IFH *vs.* NGT			GDM-CH *vs.* NGT		
	Model 1[†]	Model 2[§]	Model 3[¶]	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	OR (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)
SII									
Quartile 1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Quartile 2	1.26 (0.95, 1.67)	1.27 (0.96, 1.69)	1.29 (0.97, 1.71)	1.03 (0.74, 1.44)	1.02 (0.73, 1.43)	1.02 (0.73, 1.44)	0.88 (0.55, 1.38)	0.88 (0.55, 1.39)	0.89 (0.56, 1.40)
Quartile 3	1.47 (1.12, 1.93)**	1.46 (1.11, 1.93)**	1.47 (1.12, 1.94)**	1.43 (1.04, 1.97)*	1.35 (0.99, 1.87)	1.36 (0.99, 1.87)	1.17 (0.76, 1.80)	1.06 (0.69, 1.64)	1.06 (0.68, 1.64)
Quartile 4	1.71 (1.31, 2.24)***	1.71 (1.31, 2.25)***	1.75 (1.34, 2.30)***	1.46 (1.07, 2.01)*	1.37 (1.00, 1.89)	1.38 (1.00, 1.90)*	1.32 (0.87, 2.02)	1.17 (0.77, 1.79)	1.20 (0.78, 1.84)
P_{trend}	<0.001	<0.001	<0.001	0.002	0.007	0.008	0.026	0.126	0.125
NLR									
Quartile 1	ref.	ref.	ref.	ref.	ref.	1 ref.	ref.	ref.	ref.)
Quartile 2	1.30 (0.99, 1.71)	1.31 (1.00, 1.72)	1.32 (1.01, 1.74)*	1.18 (0.85, 1.63)	1.18 (0.85, 1.63)	1.19 (0.86, 1.64)	1.48 (0.98, 2.26)	1.53 (1.00, 2.35)	1.54 (1.01, 2.37)*
Quartile 3	1.33 (1.02, 1.75)*	1.32 (1.01, 1.74)*	1.35 (1.03, 1.78)*	1.17 (0.85, 1.62)	1.16 (0.84, 1.6)	1.18 (0.85, 1.63)	1.03 (0.65, 1.62)	1.05 (0.66, 1.67)	1.07 (0.67, 1.71)
Quartile 4	1.43 (1.10, 1.88)**	1.43 (1.10, 1.88)**	1.47 (1.12, 1.92)**	1.36 (1.00, 1.87)	1.39 (1.01, 1.90)*	1.42 (1.04, 1.95)*	1.18 (0.76, 1.84)	1.25 (0.80, 1.96)	1.28 (0.81, 2.01)
P_{trend}	0.006	0.006	0.005	0.039	0.024	0.026	0.586	0.389	0.405
RBC									
Quartile 1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Quartile 2	1.16 (0.88, 1.52)	1.15 (0.88, 1.51)	1.17 (0.89, 1.53)	1.23 (0.88, 1.72)	1.19 (0.86, 1.67)	1.21 (0.87, 1.69)	1.83 (1.15, 2.97)*	1.72 (1.08, 2.80)*	1.74 (1.09, 2.84)*
Quartile 3	1.28 (0.98, 1.69)	1.28 (0.98, 1.69)	1.30 (0.99, 1.71)	1.41 (1.02, 1.96)*	1.31 (0.94, 1.83)	1.31 (0.94, 1.83)	1.72 (1.07, 2.82)*	1.44 (0.89, 2.37)	1.46 (0.89, 2.40)
Quartile 4	1.62 (1.25, 2.11)***	1.61 (1.24, 2.11)***	1.62 (1.24, 2.11)***	1.70 (1.24, 2.35)***	1.48 (1.07, 2.05)*	1.49 (1.08, 2.06)*	2.22 (1.41, 3.58)***	1.62 (1.02, 2.64)*	1.64 (1.02, 2.67)*
P_{trend}	<0.001	<0.001	<0.001	0.001	0.024	0.027	<0.001	0.059	0.063
HB									
Quartile 1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Quartile 2	0.98 (0.75, 1.29)	0.99 (0.75, 1.30)	1.00 (0.76, 1.31)	1.10 (0.80, 1.51)	1.05 (0.76, 1.44)	1.05 (0.76, 1.44)	1.11 (0.70, 1.75)	0.99 (0.63, 1.58)	1.00 (0.63, 1.59)
Quartile 3	1.12 (0.85, 1.46)	1.11 (0.85, 1.46)	1.12 (0.85, 1.46)	1.39 (1.02, 1.89)*	1.25 (0.92, 1.72)	1.25 (0.91, 1.71)	1.31 (0.84, 2.06)	1.05 (0.66, 1.66)	1.06 (0.67, 1.69)
Quartile 4	1.71 (1.34, 2.19)***	1.72 (1.34, 2.21)***	1.73 (1.35, 2.23)***	1.43 (1.05, 1.94)*	1.26 (0.92, 1.72)	1.25 (0.91, 1.71)	2.00 (1.33, 3.03)**	1.49 (0.98, 2.28)	1.52 (1.00, 2.34)
P_{trend}	<0.001	<0.001	<0.001	0.007	0.074	0.086	0.004	0.197	0.161

TABLE 3. (Continued)

Variable	GDM-IPH *vs.* NGT			GDM-IFH *vs.* NGT			GDM-CH *vs.* NGT		
	Model 1[†]	Model 2[§]	Model 3[¶]	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	OR (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)
WBC									
Quartile 1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Quartile 2	1.28 (0.98, 1.68)	1.28 (0.98, 1.68)	1.30 (0.99, 1.70)	1.01 (0.72, 1.41)	0.98 (0.71, 1.37)	0.98 (0.70, 1.37)	1.46 (0.87, 2.49)	1.40 (0.83, 2.39)	1.42 (0.84, 2.42)
Quartile 3	1.39 (1.06, 1.83)*	1.39 (1.06, 1.83)*	1.41 (1.07, 1.86)*	1.27 (0.92, 1.77)	1.20 (0.87, 1.67)	1.21 (0.87, 1.68)	2.29 (1.42, 3.79)***	2.01 (1.24, 3.36)**	2.03 (1.24, 3.39)**
Quartile 4	1.72 (1.32, 2.25)***	1.72 (1.31, 2.25)***	1.73 (1.32, 2.27)***	1.80 (1.33, 2.45)***	1.60 (1.17, 2.19)**	1.59 (1.17, 2.18)**	3.37 (2.14, 5.47)***	2.62 (1.65, 4.28)***	2.68 (1.68, 4.39)***
P_{trend}	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PLT									
Quartile 1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Quartile 2	1.38 (1.05, 1.82)*	1.40 (1.07, 1.86)*	1.41 (1.07, 1.86)*	1.17 (0.85, 1.61)	1.14 (0.83, 1.57)	1.14 (0.83, 1.57)	1.09 (0.68, 1.74)	1.03 (0.64, 1.65)	1.03 (0.64, 1.66)
Quartile 3	1.45 (1.10, 1.90)**	1.45 (1.11, 1.91)**	1.46 (1.11, 1.92)**	1.12 (0.81, 1.55)	1.03 (0.75, 1.43)	1.03 (0.74, 1.43)	1.44 (0.93, 2.25)	1.21 (0.78, 1.90)	1.21 (0.77, 1.90)
Quartile 4	1.62 (1.24, 2.12)***	1.62 (1.23, 2.13)***	1.62 (1.23, 2.13)***	1.36 (1.00, 1.86)	1.17 (0.85, 1.61)	1.15 (0.84, 1.59)	1.66 (1.09, 2.58)*	1.21 (0.78, 1.90)	1.22 (0.78, 1.91)
P_{trend}	<0.001	<0.001	<0.001	0.044	0.369	0.362	0.001	0.140	0.106
LYM									
Quartile 1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Quartile 2	1.08 (0.84, 1.38)	1.09 (0.85, 1.39)	1.09 (0.85, 1.40)	1.16 (0.86, 1.58)	1.13 (0.84, 1.54)	1.13 (0.84, 1.54)	1.32 (0.84, 2.11)	1.26 (0.79, 2.02)	1.25 (0.79, 2.01)
Quartile 3	1.09 (0.84, 1.42)	1.09 (0.84, 1.42)	1.09 (0.83, 1.41)	1.26 (0.92, 1.73)	1.19 (0.87, 1.64)	1.17 (0.85, 1.62)	1.74 (1.10, 2.77)*	1.52 (0.96, 2.43)	1.51 (0.95, 2.42)
Quartile 4	1.14 (0.87, 1.50)	1.13 (0.85, 1.49)	1.11 (0.84, 1.46)	1.37 (0.99, 1.91)	1.20 (0.86, 1.68)	1.19 (0.85, 1.67)	2.42 (1.55, 3.83)***	1.82 (1.16, 2.91)*	1.83 (1.16, 2.92)**
P_{trend}	0.513	0.598	0.678	0.074	0.400	0.458	<0.001	0.009	0.010
NEU									
Quartile 1	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Quartile 2	1.16 (0.88, 1.52)	1.15 (0.88, 1.52)	1.16 (0.88, 1.53)	1.13 (0.81, 1.59)	1.11 (0.79, 1.56)	1.11 (0.79, 1.56)	2.33 (1.42, 3.94)***	2.25 (1.37, 3.82)**	2.29 (1.39, 3.89)**
Quartile 3	1.4 (1.07, 1.83)*	1.39 (1.06, 1.83)*	1.41 (1.07, 1.85)*	1.32 (0.95, 1.85)	1.25 (0.90, 1.76)	1.26 (0.90, 1.77)	1.91 (1.13, 3.32)*	1.73 (1.02, 3.01)*	1.75 (1.03, 3.06)*
Quartile 4	1.64 (1.26, 2.14)***	1.62 (1.25, 2.13)***	1.65 (1.26, 2.16)***	1.99 (1.46, 2.72)***	1.81 (1.32, 2.49)***	1.81 (1.32, 2.5)***	3.64 (2.26, 6.08)***	2.99 (1.84, 5.02)***	3.07 (1.89, 5.18)***
P_{trend}	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviation: OGTT=oral glucose tolerance test; RBC=red blood cell count; Hb=hemoglobin concentration; WBC=white blood cell count; PLT=platelet; LYM=lymphocytes; Neu=neutrophils; NLR=Neutrophil-to-lymphocyte ratio; SII=systemic immune-inflammation index; NGT=normoglycaemia; GDM-IFH, fasting glucose values ≥5.1 mmol/L with normal post-load glucose values, GDM-IPH, post-load glucose values ≥10.0 mmol/L at 1 h and/or ≥8.5 mmol/L at 2 h with normal fasting glucose values; GDM-CH, fasting blood glucose values ≥5.1 mmol/L and post-load glucose values ≥10.0 mmol/L at 1 h and/or ≥8.5 mmol/L at 2 h.

* *P* value <0.05.

[†] Model 1: adjusted for age.

[§] Model 2: adjusted for age and body mass index.

[¶] Model 3: adjusted for age, body mass index, gestational week, parity, adverse pregnancy history, and fasting plasma glucose.

** *P* value <0.01.

*** *P* value <0.001.

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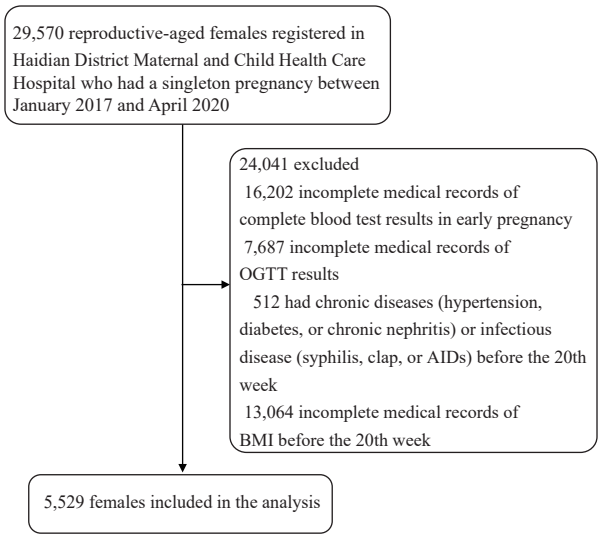
SUPPLEMENTARY MATERIAL



SUPPLEMENTARY FIGURE S1. Participant enrollment flowchart.
Abbreviation: OGTT=oral glucose tolerance test; AIDS=acquired immune deficiency syndrome; BMI=body mass index.

SUPPLEMENTARY TABLE S1. Associations of hematological parameters with GDM according to clinical classification.

Variable	Model 1		Model 2		Model 3	
	OR (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value
RBC <3.42×10^{12}/L	0.49 (0.08, 1.70)	0.338	0.53 (0.08, 1.84)	0.390	0.49 (0.08, 1.70)	0.338
RBC ≥4.56×10^{12}/L	1.55 (1.28, 1.87)	<0.001	1.40 (1.15, 1.70)	0.001	1.55 (1.28, 1.87)	<0.001
Hb <116 g/L	0.75 (0.55, 1.01)	0.068	0.81 (0.59, 1.09)	0.176	0.75 (0.55, 1.01)	0.068
Hb ≥140 g/L	1.70 (1.34, 2.14)	<0.001	1.57 (1.24, 1.99)	<0.001	1.70 (1.34, 2.14)	<0.001
WBC <5.7×10^{9}/L	0.89 (0.59, 1.31)	0.577	0.96 (0.63, 1.42)	0.853	0.89 (0.59, 1.31)	0.577
WBC ≥13.7×10^{9}/L	2.03 (1.21, 3.31)	0.006	1.81 (1.07, 2.98)	0.022	2.03 (1.21, 3.31)	0.006
PLT <174×10^{9}/L	0.64 (0.48, 0.85)	0.002	0.68 (0.51, 0.90)	0.008	0.64 (0.48, 0.85)	0.002
PLT ≥392×10^{9}/L	1.00 (0.29, 2.71)	0.996	0.76 (0.22, 2.11)	0.634	1.00 (0.29, 2.71)	0.996
LYM <1.1×10^{9}/L	1.07 (0.74, 1.51)	0.706	1.14 (0.79, 1.61)	0.475	1.14 (0.78, 1.60)	0.486
LYM ≥3.61×10^{9}/L	5.34 (0.64, 44.89)	0.095	5.24 (0.62, 44.06)	0.099	5.98 (0.71, 50.35)	0.075
NEU <3.60×10^{9}/L	0.70 (0.38, 1.20)	0.226	0.73 (0.39, 1.24)	0.272	0.70 (0.38, 1.20)	0.226
NEU ≥10.2×10^{9}/L	2.01 (1.33, 2.98)	0.001	1.90 (1.25, 2.83)	0.002	2.01 (1.33, 2.98)	0.001

Abbreviation: OGTT=oral glucose tolerance test; RBC=red blood cell count; Hb=hemoglobin concentration; WBC=white blood cell count; PLT=platelet; LYM=lymphocyte; GDM=gestational diabetes mellitus.

Preplanned Studies

Knowledge of Cervical Cancer and HPV, and Willingness to Receive HPV Vaccination Among 20–45-Year-Old Women — Six Provinces, China, 2018

Di Gao[1]; Gengli Zhao[1]; Jiangli Di[2]; Xiaosong Zhang[1,#]; Linhong Wang[3,#]

Summary

What is already known about this topic?

Cervical cancer is a significant public health problem with approximately 570,000 cases and 311,000 deaths occurring in 2018 globally. It is imperative to raise awareness of cervical cancer and human papillomavirus (HPV).

What is added by this report?

Compared to previous studies, this is one of the largest cross-sectional studies of cervical cancer and HPV in Chinese adult females in recent years. We found that knowledge level of cervical cancer and HPV vaccine was still inadequate among women aged 20–45 years old, and the willingness to receive HPV vaccination was highly associated with knowledge level.

What are the implications for public health practice?

Intervention programs should aim to improve awareness and knowledge about cervical cancer and HPV vaccines, primarily focusing on women of lower socio-economic status.

Cervical cancer, the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women (*1*), is a significant public health issue that seriously threatens women's health worldwide (*2*). This cross-sectional study aims to explore the knowledge level of cervical cancer, and willingness to receive human papillomavirus (HPV) vaccination among women aged 20–45 years old. The cross-sectional, community-based study was conducted from June to September 2018 in 6 provinces of China, and a total of 7,240 women aged 20–45 years were surveyed. Overall, 55.3% of women demonstrated low knowledge levels about cervical cancer and HPV vaccination, and only 5.0% correctly answered all 7 questions. High knowledge level was significantly associated with the region, age group, occupation, education level, monthly family income and gravidity. Women with high knowledge levels were significantly more likely to accept HPV vaccination than those with low knowledge levels. With each point increase in the knowledge score, the likelihood of willingness to vaccinate increased significantly (P_{trend}<0.001). Our study indicated that the knowledge level of cervical cancer and HPV vaccine was still inadequate among women aged 20–45 years old, especially those of lower socio-economic status. The willingness to receive HPV vaccination was highly associated with knowledge level.

An analysis of 185 countries from the Global Cancer Observatory database shows that approximately 570,000 cases of cervical cancer and 311,000 deaths from the disease occurred in 2018 globally. Meanwhile, China contributed 106,000 cases and 48,000 deaths (*3*). Increasing the rate of HPV vaccination is an essential strategy for cervical cancer prevention (*4*). The China Food and Drug Administration approved the HPV vaccine in 2016, but the coverage rate remained low in China. Therefore, it is crucial to improve the target population's knowledge about cervical cancer and HPV vaccination. This cross-sectional study aims to explore the knowledge of cervical cancer and willingness to receive HPV vaccination among women aged 20–45 years old in six provinces, and thus to provide evidence for the future intervention of HPV vaccination in China.

The cross-sectional, community-based study was conducted from June to September 2018 in 6 provinces of 3 socio-economic regions of China: eastern (Jiangsu and Shandong provinces), central (Hunan and Anhui provinces), and western (Shaanxi and Sichuan provinces). The capital of each province was regarded as the representative city, including Nanjing, Jinan, Changsha, Hefei, Xi'an, and Chengdu. In each city, one urban and one rural area were selected randomly as the survey sites. We recruited 490 women of different age groups (10–19 years; 20–39 years; 40–49 years; ≥50 years) by a multi-stage stratified random cluster sampling at each investigation site. Face-to-face interviews were conducted by community health service workers to collect information on

demographic characteristics, knowledge of cervical cancer and HPV vaccine, and also willingness to receive HPV vaccination. A total of 7,240 women aged 20–45 years were involved in the analysis, with an average age of 35.1±7.6 years. According to the number of correct answers among the 7 knowledge-related questions about cervical cancer and HPV vaccine, a knowledge score (range: 0–7) was assigned to every participant. And then, a score above or below five of seven items was used to define levels of knowledge (low level: score <5; high level: score ≥5). In addition, participants were further required to answer their willingness to receive the HPV vaccination. The categorical variables were presented by numbers (*n*) and percentages (%). Univariate and multivariate logistic regression models were used to analyze the related factors of knowledge level, and the association between knowledge score and willingness to receive HPV vaccination. Odds ratios (*OR*s) and 95% confidence intervals (*CI*s) were calculated. Statistical analyses were performed with STATA 14.0 (Stata Corporation, College Station, TX, USA). Statistical significance was assessed by two-tailed tests with a level of 0.05. This study has been approved by the Ethical Review Committee of the Chinese Center for Disease Control and Prevention.

A total of 7,240 women (age range: 20–45 years) completed the questionnaires. As shown in Table 1, of the women who responded to concerning questions, 91.1% had heard of cervical cancer (Q1), 75.5% knew cervical cancer could be prevented (Q3), 69.1% knew the benefits of regular cervical cancer screening (Q7), 60.3% had heard of HPV vaccines (Q5), and 54.1% knew HPV vaccines could prevent cervical cancer (Q6). However, only 10.9% knew more than half (4/7) of the risk factors for cervical cancer (Q2), and 10.8% knew more than half (4/7) of the prevention measures for cervical cancer (Q4). Overall, 44.7% of all women demonstrated high knowledge levels of cervical cancer and HPV vaccination (5/7), among whom only 5.0% correctly answered all 7 questions. In addition, 59.3% of women were willing to be vaccinated.

Associations of knowledge level with other factors are presented in Table 2. In the multivariate regression models, region, age group, occupation, education level, monthly family income and gravidity were significantly associated with knowledge level. Women from Central and Eastern China were more likely to have a higher knowledge level than those from Western China (Central: *OR*=1.39, 95% *CI*: 1.23–1.57; Eastern: *OR*=1.27, 95% *CI*: 1.12–1.44). Women aged 30–39 years, working as managerial and technical staff, and having been pregnant one or two times had a higher knowledge level. Women with a higher education level and family income showed a higher knowledge level (P_{trend}<0.001).

A multivariate logistic regression to evaluate the association of cervical cancer and HPV vaccine-related knowledge score with the willingness to receive HPV vaccination is presented in Table 3. After adjustment for socio-demographic factors, women with high knowledge levels were significantly more likely to accept HPV vaccination than those with low knowledge levels (*OR*=9.98, 95% *CI*: 8.80–11.32). Furthermore, with each point increase in the knowledge score, the likelihood of willingness to vaccinate increased significantly (P_{trend}<0.001).

DISCUSSION

The major finding was that more than half of the women had a low level of knowledge, mainly related to the region, age, occupation, education level, family income and gravidity. Furthermore, the willingness to vaccinate increased significantly with the improvement of knowledge level. Thus, improving cervical cancer and HPV vaccine-related knowledge among women, especially those of lower socioeconomic status, will be essential for HPV vaccination programs in China in future.

In this study, 60.3% of women heard of the HPV vaccine, which is much higher than the proportion in a meta-analysis of 58 observational studies in China (15.95%) in 2016 and Shenzhen local residents (35.3%) in 2015. This may be because the survey was conducted after the HPV vaccine entered the market in China and the respondents came from urban and rural areas belonging to the capitals of these provinces (*5*–*6*). When compared with data from college students, women aged 20–45 years old had lower awareness of the HPV vaccine, since the proportion was 74.0% in Zhengzhou (*7*) and 78.6% in Beijing (*8*), indicating that women at higher education levels may have more about the HPV vaccine.

Despite the high awareness rate of the HPV vaccine, the knowledge level of cervical cancer and the HPV vaccine was still inadequate among women. Only 5.0% of women correctly answered all seven questions, and most women (55.3%) knew answers to fewer than five questions. Lack of knowledge has been identified as one of the main barriers to the implementation of HPV vaccination. As the measurement of cervical cancer and HPV knowledge varied in different studies, it is difficult to compare the knowledge level directly.

TABLE 1. Knowledge of cervical cancer and HPV vaccine and willingness to be vaccinated Among 20–45-Year-Old Women, — 6 Provinces, China, 2018.

Knowledge-related questions	Yes [*n* (%)]	No [*n* (%)]
Q1: Have heard of cervical cancer	6,595 (91.1)	645 (8.9)
Q2: Knowledge of risk factors for cervical cancer (≥4)	790 (10.9)	6,450 (89.1)
Q2_1: Having multiple sexual partners	2,862 (39.5)	4,378 (60.5)
Q2_2: Had sexual intercourse and children at a young age	1,452 (20.1)	5,788 (79.9)
Q2_3: History of sexually transmitted diseases	2,150 (29.7)	5,090 (70.3)
Q2_4: Smoking	702 (9.7)	6,538 (90.3)
Q2_5: History of HPV infection	1,298 (17.9)	5,942 (82.1)
Q2_6: Aged 30–65 years old	948 (13.1)	6,292 (86.9)
Q2_7: Long-term use of oral contraceptives pills	785 (10.8)	6,455 (89.2)
Q3: Cervical cancer can be prevented	5,468 (75.5)	1,772 (24.5)
Q4: Knowledge of how to prevent cervical cancer (≥4)	781 (10.8)	6,459 (89.2)
Q4_1: Getting vaccinated	3,019 (41.7)	4,221 (58.3)
Q4_2: Having fewer sexual partners	1,567 (21.6)	5,673 (78.4)
Q4_3: Regular cervical cancer screening	2,583 (35.7)	4,657 (64.3)
Q4_4: Using condoms	823 (11.4)	6,417 (88.6)
Q4_5: Late marriage and late childbearing	412 (5.7)	6,828 (94.3)
Q4_6: Avoid smoking	577 (8.0)	6,663 (92.0)
Q4_7: Timely treatment of genital tract infections	1,359 (18.8)	5,881 (81.2)
Q5: Have heard of HPV vaccines	4,365 (60.3)	2,875 (39.7)
Q6: Know HPV vaccines can prevent cervical cancer	3,913 (54.1)	3,327 (46.0)
Q7: Know the benefits of regular cervical cancer screening	5,004 (69.1)	2,236 (30.9)
High Knowledge level (≥5)	3,237 (44.7)	4,003 (55.3)
Willing to be vaccinated	4,296 (59.3)	2,944 (40.7)

Abbreviation: HPV=human papillomavirus.

Nevertheless, most have found that women still lack knowledge. Moreover, it is worrying that women know little about risk factors and prevention measures for cervical cancer, with only 10% of women able to identify more than half of them. Consequently, further health education should highlight the risk factors and prevention measures for cervical cancer.

Several factors were associated with the knowledge level of cervical cancer and the HPV vaccine. Women with older age, low education level, underemployment, low family income and living in the western region are less likely to have a high knowledge level, resulting in a lower willingness to receive the HPV vaccination. These results were similar to previous studies that socio-economic status might play an essential part in the knowledge score of HPV vaccine and cervical cancer (*9*). These findings highlighted the need for health education for women in the reproductive age group to better understand the significance of HPV vaccination, especially those of low socio-economic status.

Although the knowledge level was low, women had a more positive attitude towards HPV vaccination (59.3%), similar to previous studies. In other studies, more than half of the respondents were willing to take the HPV vaccine against HPV infection (*5*,*10*). In addition, it is very likely that the willingness for HPV vaccination strongly increased with the knowledge score, and the proportion of willingness reached more than 80% when at high knowledge levels (knowledge scores ≥5). In order to enhance the HPV vaccination and decrease the rate of cervical cancer, it is critical to encourage health education for different groups of women, not only for these women in the reproductive age group but also for their children.

Several limitations should be noted. First, the study data were collected from counties/districts in every provincial capital, which might overestimate the awareness and willingness rates of these provinces. However, it did not influence the association analysis.

TABLE 2. Logistic regression analysis on knowledge of cervical cancer and HPV vaccine among 20–45-year-old women, — 6 provinces, China, 2018.

Variable	*N*	High knowledge level (≥5)			P_{trend}
		n (%)	Crude *OR* (95% *CI*)	AOR (95% *CI*)	
Region					
Western	2,364	944 (38.5)	ref.	ref.	<0.001
Central	2,424	1,198 (49.4)	1.56 (1.39, 1.75)†	1.39 (1.23, 1.57)†	
Eastern	2,452	1,095 (46.3)	1.38 (1.23, 1.55)†	1.27 (1.12, 1.44)†	
Area type					0.305
Urban	3,619	1,907 (52.7)	ref.	ref.	
Rural	3,621	1,330 (36.7)	0.52 (0.47, 0.57)†	0.94 (0.83, 1.06)	
Age group (years)					0.185
20–29	2,140	976 (45.6)	ref.	ref.	
30–39	2,483	1,204 (48.5)	1.12 (1.00, 1.26)*	1.25 (1.08, 1.44)†	
40–45	2,617	1,057 (40.4)	0.81 (0.72, 0.91)†	1.15 (0.99, 1.34)	
Occupation					<0.001
Managerial and technical staff	1,412	946 (67.0)	ref.	ref.	
Commercial/service personnel	1,299	634 (48.8)	0.47 (0.40, 0.55)†	0.65 (0.54, 0.77)†	
Workers or farmers	3,039	1,098 (36.1)	0.28 (0.24, 0.32)†	0.62 (0.52, 0.74)†	
Students	287	116 (40.4)	0.33 (0.26, 0.43)†	0.53 (0.40, 0.71)†	
Unemployed	953	324 (34.0)	0.25 (0.21, 0.30)†	0.46 (0.38, 0.56)†	
Others	250	119 (47.6)	0.45 (0.34, 0.59)†	0.59 (0.44, 0.78)†	
Education level					<0.001
Primary school and below	1,000	215 (21.5)	ref.	ref.	
Middle school	2,379	870 (36.6)	2.11 (1.77, 2.50)†	2.11 (1.77, 2.52)†	
Senior high school or equivalent	1,551	760 (49.0)	3.51 (2.93, 4.20)†	3.19 (2.61, 3.90)†	
College and above	2,310	1,392 (60.3)	5.54 (4.66, 6.58)†	4.49 (3.59, 5.63)†	
Monthly family income (CNY)					<0.001
<3,000	1,824	624 (34.2)	ref.	ref.	
3,000–4,999	2,255	930 (41.2)	1.35 (1.19, 1.53)†	1.11 (0.97, 1.28)	
5,000–7,999	1,801	867 (48.1)	1.79 (1.56, 2.04)†	1.22 (1.05, 1.41)†	
≥8,000	1,360	816 (60.0)	2.88 (2.49, 3.34)†	1.61 (1.37, 1.90)†	
Marital status					0.827
Unmarried	1,007	467 (46.4)	ref.	ref.	
Married	6,021	2,680 (44.5)	0.93 (0.81, 1.06)	1.04 (0.79, 1.36)	
Divorced/widowed/others	212	90 (42.5)	0.85 (0.63, 1.15)	0.95 (0.65, 1.39)	
Gravidity					0.153
0	1,257	583 (46.4)	ref.	ref.	
1	2,255	1,158 (51.4)	1.22 (1.06, 1.40)†	1.45 (1.13, 1.87)†	
2	2,190	930 (42.5)	0.85 (0.74, 0.98)*	1.38 (1.07, 1.80)*	
≥3	1,538	566 (36.8)	0.67 (0.58, 0.78)†	1.17 (0.89, 1.54)	
Smoke					0.811
Never	7,013	3,134 (44.7)	ref.	ref.	
Ever	227	103 (45.4)	1.03 (0.79, 1.34)	1.04 (0.78, 1.37)	

Note: All variables in univariate logistic regression models eventually entered the multivariable logistic regression model.
Abbreviation: HPV=human papillomavirus; *CI*=confidence interval; *OR*=odds ratio; AOR=adjusted odds ratio; CNY=China Yuan.
* $P<0.05$.
† $P<0.01$.

TABLE 3. Association between cervical cancer related knowledge score and willingness to receive HPV vaccination among 20–45-year-old women, — 6 provinces, China, 2018.

Knowledge	*n* (%)	Crude *OR* (95% *CI*)	AOR (95% *CI*)*	P_{trend}
Knowledge level				<0.001
Low (<5)	1,556 (38.9)	ref.	ref.	
High (≥5)	2,740 (84.6)	8.67 (7.73, 9.72)†	9.98 (8.80, 11.32)†	
Knowledge score				<0.001
≤1	198 (19.8)	ref.	ref.	
2	279 (25.8)	1.41 (1.15, 1.73)†	1.68 (1.35, 2.09)†	
3	416 (40.1)	2.71 (2.22, 3.30)†	3.37 (2.72, 4.16)†	
4	663 (74.8)	12.03 (9.68, 14.95)†	16.35 (12.91, 20.70)†	
5	2,010 (84.0)	21.23 (17.56, 25.68)†	33.25 (26.81, 41.22)†	
≥6	730 (86.5)	25.91 (20.15, 33.31)†	43.75 (33.12, 57.79)†	

Abbreviation: HPV=human papillomavirus; *CI*=confidence interval; *OR*=odds ratio; AOR=adjusted odds ratio.
* Adjusted for region, area, age group, occupation, education level, monthly family income, marital status, gravidity and smoking.
† *P*<0.01.

Secondly, considering the cross-sectional study design, the causal relationships between knowledge and willingness cannot be inferred. Thirdly, this study only focused on willingness to receive HPV vaccination, not behavior. Therefore, future studies are encouraged to explore how to improve HPV vaccination behavior and the barriers to prevention.

In summary, our study indicated that the knowledge level of cervical cancer and HPV vaccine was still inadequate among women aged 20–45 years old, and was associated with the region, age group, occupation, education level, monthly family income and gravidity. The willingness to receive HPV vaccination was highly associated with knowledge level. Intervention programs and strategies should aim to improve knowledge levels about cervical cancer and HPV vaccines, primarily focusing on those of lower socio-economic status.

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Methods and Applications

An Improved Training Algorithm Based on Ensemble Penalized Cox Regression for Predicting Absolute Cancer Risk

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ABSTRACT

Introduction: Biases in cancer incidence characteristics have led to significant imbalances in databases constructed by prospective cohort studies. Since they use imbalanced databases, many traditional algorithms for training cancer risk prediction models perform poorly.

Methods: To improve prediction performance, we introduced a Bagging ensemble framework to an absolute risk model based on ensemble penalized Cox regression (EPCR). We then tested whether the EPCR model outperformed other traditional regression models by varying the censoring rate of the simulated data.

Results: Six different simulation studies were performed with 100 replicates. To assess model performance, we calculated mean false discovery rate, false omission rate, true positive rate, true negative rate, and the areas under the receiver operating characteristic curve (AUC) values. We found that the EPCR procedure could reduce the false discovery rate (FDR) for important variables at the same true positive rate (TPR), thereby achieving more accurate variable screening. In addition, we used the EPCR procedure to build a breast cancer risk prediction model based on the Breast Cancer Cohort Study in Chinese Women database. AUCs for 3- and 5-year predictions were 0.691 and 0.642, representing improvements of 0.189 and 0.117 over the classical Gail model, respectively.

Discussion: We conclude that the EPCR procedure can overcome challenges posed by imbalanced data and improve the performance of cancer risk assessment tools.

Most cancer predictions involve imbalanced binary classification datasets, i.e., the number of instances of cases is far smaller than the number of instances of controls. We are more concerned about predicting cases because misclassification of cases can be more costly (*1*). However, traditional supervised learning algorithms do not possess high predictive accuracy for minority classes. The "ensemble learning" approach for statistical modeling is a powerful method for generating highly accurate predictive models, in which Bagging (*2–3*), a simple yet effective ensemble method, has been employed in many practical applications (*4*). This paper proposes building an ensemble penalized Cox regression (EPCR) model for disease risk prediction and validates the accuracy of the method through numerical simulations and an empirical study on a Breast Cancer Chinese Women database.

METHODS

Ensemble Penalized Cox Regression Model

We propose an ensemble penalized Cox regression (EPCR) model based on penalized Cox regression (PCR) models (*5–8*) (Supplementary Figure S1, available in https://weekly.chinacdc.cn/). For the original dataset $D = \{\widetilde{T}_i, \Delta_i, Z_i\}\,(i = 1, \cdots, n)$, we first use a repeated sampling technique to generate B bootstrap data sets from the original data set by $D^{(k)} = \left\{\widetilde{T}_i^{(k)}, \Delta_i^{(k)}, Z_i^{(k)}\right\}_{i=1}^{n}\,(k = 1, \cdots, B)$. Next, a set of base learners $\widehat{P}^{(k)}\,(a, \tau, Z)\,(k = 1, \cdots, B)$ are trained by the PCR algorithm independently on $\widehat{D}^{(k)}\,(k = 1, \cdots, B)$. More details about PCR algorithm are provided in Supplementary Materials. For each sample in the test set, EPCR achieves prediction by averaging the probability prediction values given by each of these B base learners.

Simulation Study

To assess the predictive accuracy of the proposed EPCR procedure and to compare its performance to alternative methods — i.e., Cox regression based on a stepwise procedure [using Akaike Information Criterion (AIC) or Bayesian Information Criterion

(BIC)] or single PCR — we conducted simulation studies across a range of conditions by varying the censoring rate or dimensionality of predictors. We were particularly interested in assessing the ability of the proposed EPCR procedure to correctly identify important predictors associated with cancer as well as the accuracy of the EPCR procedure in predicting cancer risk.

Each p-dimensional predictor is assumed to be a continuous variable generated from a multivariate normal distribution with a mean (μ) of zero and a covariance matrix $\Sigma = \left(0.8^{|j-i|}\right), i, j = 1, \ldots p$. The first 15 of the p-dimensional predictors were assumed to be genuinely associated with the onset of cancer. For simplicity, we specified the regression coefficients of the Cox model as 1.5 for the first five predictors, 1 for predictors 6–10, 0.5 for predictors 11–15, and 0 for the rest.

By specifying different baseline hazard functions $h_0(t)$, we can generate different survival times T that obey different distributions (*6*). To obtain this value, the survival function $S(t)$ was first generated through a uniform distribution $U(0,1)$, and T is then generated using the following equation:

$$T = H_0^{-1}\left[-log\left(S\left(t\right)\right) exp\left(-\beta^{'} Z\right)\right] \quad (1)$$

Here, H_0^{-1} denotes the inverse function of the cumulative hazard function $H_0(t) = \int_0^t h_0(u)\,\mathrm{d}u$. For simplicity, we specify $h_0(t)$ as 1, at which point the survival time T follows an exponential distribution. Furthermore, we generated the censoring metric Δ from a Bernoulli $b(0, 1-r)$ distribution, where r is the censoring rate.

Varying the dimensionality of predictors p and censoring rate r, our simulation study considered the following six main settings:

Setting 1: $n = 1{,}000, p = 100, r = 30\%$;
Setting 2: $n = 1{,}000, p = 100, r = 50\%$;
Setting 3: $n = 1{,}000, p = 100, r = 70\%$;
Setting 4: $n = 1{,}000, p = 50, r = 30\%$;
Setting 5: $n = 1{,}000, p = 50, r = 50\%$;
Setting 6: $n = 1{,}000, p = 50, r = 70\%$.

For each setting, bootstrap times B is specified as 200 and simulated data are split into two parts: 70% to train the models and 30% as a test dataset for comparing model performance. The simulation study was repeated 100 times for each setting. Mean values of the four evaluation metrics ["false discovery rate (FDR)," "false omission rate (FOR)," "true positive rate (TPR)," and "true negative rate (TNR)" for variable screening] were calculated to test whether the important predictors could be correctly identified by the models. Finally, the area under the receiver operating characteristic curve (AUC) was calculated for each model to test how well each model could be used for prediction of the onset of cancer.

Empirical Study: Application to a Real-World Cancer Cohort

To validate the disease risk prediction validity of the proposed EPCR model, we applied it to the Shandong sub-database from Breast Cancer Cohort Study in Chinese Women (BCCS-CW) (*9*) to develop a candidate breast cancer incidence risk predictor. The workflow of this part of the study is presented in Supplementary Figure S2 (available in https://weekly.chinacdc.cn/).

The onset of breast cancer was treated as the outcome event and individuals who had not yet developed breast cancer were censoring data. We considered the age of individuals with breast cancer to be the age at which the patient received the first cancer diagnosis, and the age of individuals who had not yet developed breast cancer as the age registered at baseline. We randomly selected 70% individuals from the case and control groups respectively to form a training set for model development; the remaining 30% of the control group was used as a test dataset. The EPCR procedure was performed on the training set to generate an absolute risk prediction model for breast cancer, and this was then used to estimate the probability of onset in the test group over the next three or five years. Similarly, the bootstrap times B is specified as 200. Based on actual three- and five-year follow-up results, receiver operating characteristic (ROC) curves were plotted to assess model performance, where a single PCR model and a classical Gail model (*10*) were used for comparison.

All the analyses were performed in the R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). Packages "glmnet" and "gbm" were used to construct the EPCR model, "pROC" was used to plot the ROC curve, and "Table 1" was used to create a demographic characteristics table. $P<0.05$ was considered statistically significant ($\alpha = 0.05$).

RESULTS

Table 1 summarizes the mean values of the 5 evaluation metrics for 100 replications of each simulation setting. These results clearly show that the

TABLE 1. The mean values of 5 metrics for the 6 models over 100 replicate experiments for each simulation setting.

Method	FDR	FOR	TPR	TNR	AUC
Setting 1: 30% censoring					
Traditional approach					
Stepwise-AIC*	0.766	0.127	0.344	0.795	0.721
Stepwise-BIC	0.173	0.125	0.201	0.99	0.733
PCR-LASSO†	0.275	0.009	0.952	0.922	0.863
PCR-EN ($\alpha = 0.5$)	0.375	0.005	0.973	0.878	0.873
Ensemble approach					
EPCR-LASSO§	0.111	0.011	0.936	0.977	0.878
EPCR-EN ($\alpha = 0.5$)	0.202	0.007	0.963	0.952	0.878
Setting 2: 50% censoring					
Traditional approach					
Stepwise-AIC	0.795	0.134	0.317	0.779	0.704
Stepwise-BIC	0.239	0.130	0.168	0.986	0.704
PCR-LASSO	0.321	0.011	0.939	0.907	0.858
PCR-EN ($\alpha = 0.5$)	0.407	0.007	0.965	0.864	0.869
Ensemble approach					
EPCR-LASSO	0.169	0.017	0.903	0.964	0.865
EPCR-EN ($\alpha = 0.5$)	0.255	0.012	0.937	0.936	0.874
Setting 3: 70% censoring					
Traditional approach					
Stepwise-AIC	0.809	0.140	0.299	0.76	0.690
Stepwise-BIC	0.301	0.136	0.124	0.984	0.678
PCR-LASSO	0.368	0.018	0.905	0.892	0.842
PCR-EN ($\alpha = 0.5$)	0.46	0.011	0.945	0.842	0.855
Ensemble approach					
EPCR-LASSO	0.242	0.028	0.843	0.945	0.864
EPCR-EN ($\alpha = 0.5$)	0.348	0.018	0.903	0.904	0.872
Setting 4: 30% censoring					
Traditional approach					
Stepwise-AIC	0.555	0.260	0.337	0.809	0.733
Stepwise-BIC	0.098	0.258	0.199	0.987	0.732
PCR-LASSO	0.191	0.020	0.955	0.888	0.858
PCR-EN ($\alpha = 0.5$)	0.257	0.010	0.979	0.834	0.882
Ensemble approach					
EPCR-LASSO	0.093	0.028	0.935	0.954	0.883
EPCR-EN ($\alpha = 0.5$)	0.163	0.017	0.963	0.909	0.894
Setting 5: 50% censoring					
Traditional approach					
Stepwise-AIC	0.609	0.272	0.315	0.784	0.713
Stepwise-BIC	0.121	0.267	0.161	0.985	0.705
PCR-LASSO	0.207	0.027	0.941	0.878	0.853
PCR-EN ($\alpha = 0.5$)	0.277	0.016	0.969	0.818	0.867

TABLE 1. (Continued)

Method	FDR	FOR	TPR	TNR	AUC
Ensemble approach					
EPCR-LASSO	0.115	0.040	0.905	0.943	0.877
EPCR-EN (α = 0.5)	0.179	0.026	0.941	0.901	0.877
Setting 6: 70% censoring					
Traditional approach					
Stepwise-AIC	0.617	0.281	0.281	0.793	0.716
Stepwise-BIC	0.127	0.275	0.128	0.987	0.696
PCR-LASSO	0.271	0.047	0.903	0.835	0.836
PCR-EN (α = 0.5)	0.322	0.032	0.940	0.783	0.851
Ensemble approach					
EPCR-LASSO	0.149	0.066	0.845	0.927	0.862
EPCR-EN (α = 0.5)	0.217	0.047	0.898	0.875	0.870

Abbreviation: EPCR=Ensemble penalized Cox regression; PCR=Penalized Cox regression; AUC=Areas under the receiver operating characteristic curve; EN=Elastic net; FDR=False discovery rate; FOR=False omission rate; TPR=True positive rate; TNR=True negative rate; AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; LASSO=Least absolute shrinkage and selection operator.
* The method "Stepwise-AIC (BIC)" refers to fitting a Cox model using stepwise procedures based on AIC (BIC) criterion.
† The method "PCR-LASSO [EN (α = 0.5)]" refers to a Cox model with a LASSO-Type [EN-Type (α = 0.5)] penalty.
§ The method "EPCR-LASSO [EN (α = 0.5)]" refers to an Ensemble Penalized Cox Regression model whose base models were trained by Cox Regression algorithm with a LASSO-Type [EN-Type (α = 0.5)] penalty.

EPCR-least absolute shrinkage and selection operator (LASSO) model has the lowest FDR, which indicates that the model has the lowest probability of incorrectly screening out unimportant variables, while its TPR is also at a high level among all models. So EPCR-LASSO model is better able to correctly screen out important models compared to other models. Furthermore, a comparison of the EPCR-elastic net (EN) and PCR-EN models showed that the introduction of the ensemble framework was able to reduce the FDR of variable screening while maintaining a similar FOR. As shown in Figure 1, the AUCs based on the risk scores estimated by the EPCR procedure were higher than those from the other models at all six settings.

The censoring rate reflects the level of imbalance in the database. The higher the censoring rate, the more imbalanced the database is and the lower the percentage of cases in the database. As seen in Table 1, we observed increases in mean FDR, decreases in mean TPR and AUC for all models as the censoring rate increased; however, the EPCR-LASSO and EPCR-EN models (i.e., those that used the ensemble framework) consistently performed better than their competitors. For example, at $n = 1,000$ and $p = 100$, the PCR-LASSO model's FDR increased to 0.368 when the censoring rate was increased to 70%, meaning that more than a third of the important variables identified by the model were incorrect. In contrast, the EPCR-LASSO model was able to reduce this error by 0.146. Finally, it is worth noting that among the ensemble methods, the EPCR model with the LASSO penalty performed better overall during variable screening than the model with the elastic net (α = 0.5) penalty. Both were used for prediction with comparable accuracy, and here the elastic net penalty model performed slightly better.

For the empirical study, Supplementary Table S1 (available in https://weekly.chinacdc.cn/) shows the baseline population characteristics of risk factors in the Shandong sub-dataset across overall, cases and controls. The proportion of cases present in this dataset was only 0.3%, which is a serious imbalance. For the EPCR model, the AUC for 3- and 5-year predictions were 0.691 and 0.642, respectively, while those are 0.502 and 0.525, respectively, for the Gail model (see Figure 2). Supplementary Figure S3 (available in https://weekly.chinacdc.cn/) shows factor importance scores based on the EPCR model. See Supplementary Materials (available in https://weekly.chinacdc.cn/) for details of the factor importance measures for the EPCR model. Here the red line indicates the importance score threshold that distinguished important from unimportant variables. This analysis revealed that life satisfaction, dysmenorrhea, number of miscarriages, and breastfeeding were all predicted to be influential variables, a finding that is consistent with empirical data.

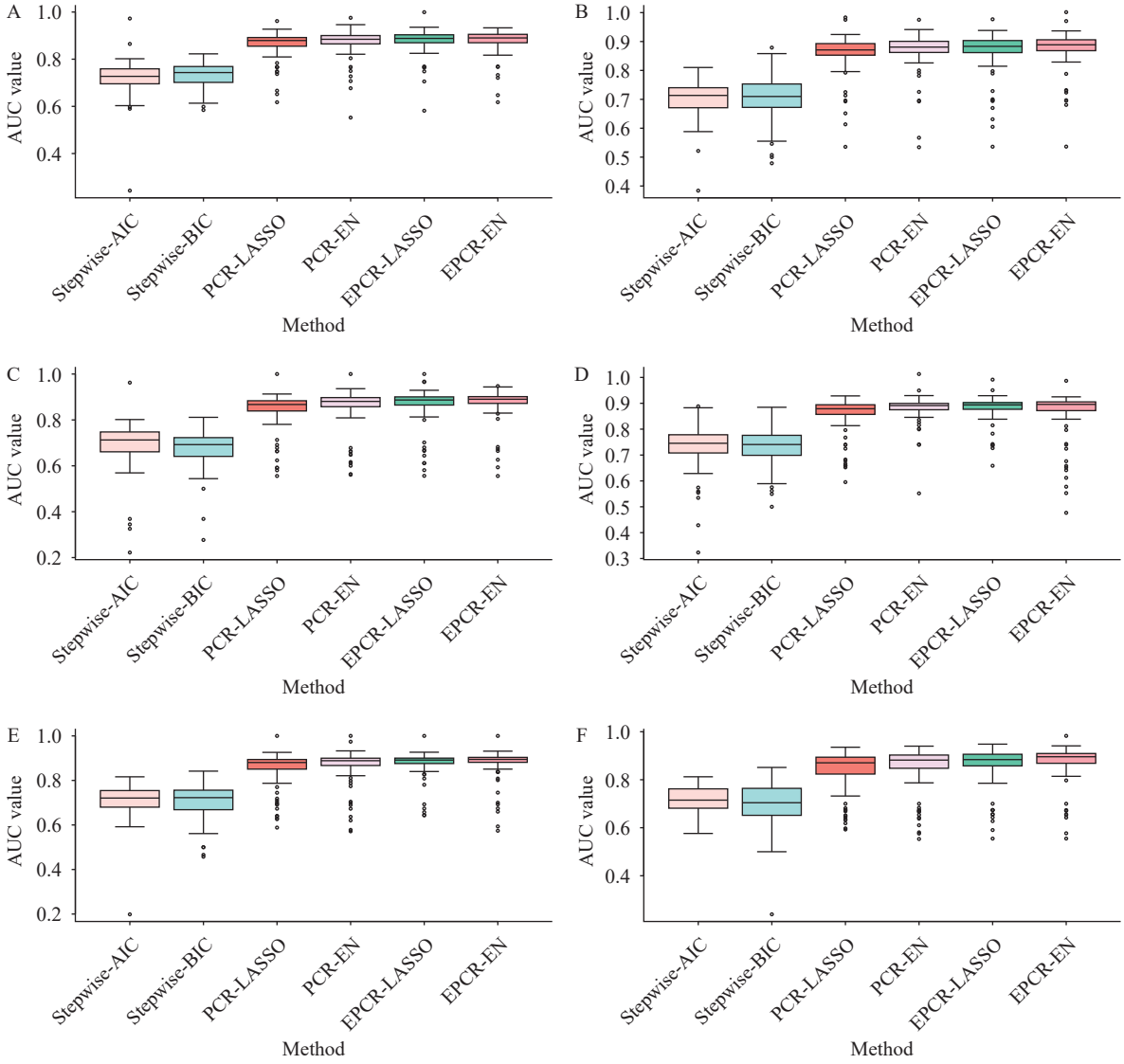

FIGURE 1. Box plots of AUC values for each modeling method. Data show boxplots of 100 replicates of settings 1–6. (A) *n*=1,000, *p*=100, 30% censoring; (B) *n*=1,000, *p*=100, 50% censoring; (C) *n*=1,000, *p*=100, 70% censoring; (D) *n*=1,000, *p*=50, 30% censoring; (E) *n*=1,000, *p*=50, 50% censoring; (F) *n*=1,000, *p*=50, 70% censoring.
Abbreviation: EPCR=Ensemble penalized Cox regression; PCR=Penalized Cox regression; AUC=Areas under the receiver operating characteristic curve; EN=Elastic net; AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; LASSO=Least absolute shrinkage and selection operator.

DISCUSSION

Most existing cancer prediction models can be divided into absolute risk models and relative risk models. The latter, however, is actually a single classifier that can only predict whether an individual is at high risk or not, but not an individual's risk of developing cancer over time in the future. The widely-used Gail model (*10*), a breast cancer risk assessment tool, is an absolute risk model based on five breast cancer risk factors and their interactions.

In recent years, ML has been used to improve the predictive performance of cancer prediction models. Most current studies have focused on ML methods using classifiers such as k-nearest neighbor (KNN) (*11*), random forest (*12*) (i.e., for the identification of high-risk individuals), or Support Vector Machine (SVM) (*13*) or logistic regression models (i.e., for the prediction of relative risk). Moreover, most of these models only utilize the label of cancer or not in the sample, and the follow-up information of the data is not fully utilized.

At the same time, given that the databases used to develop tumorigenesis risk prediction models are

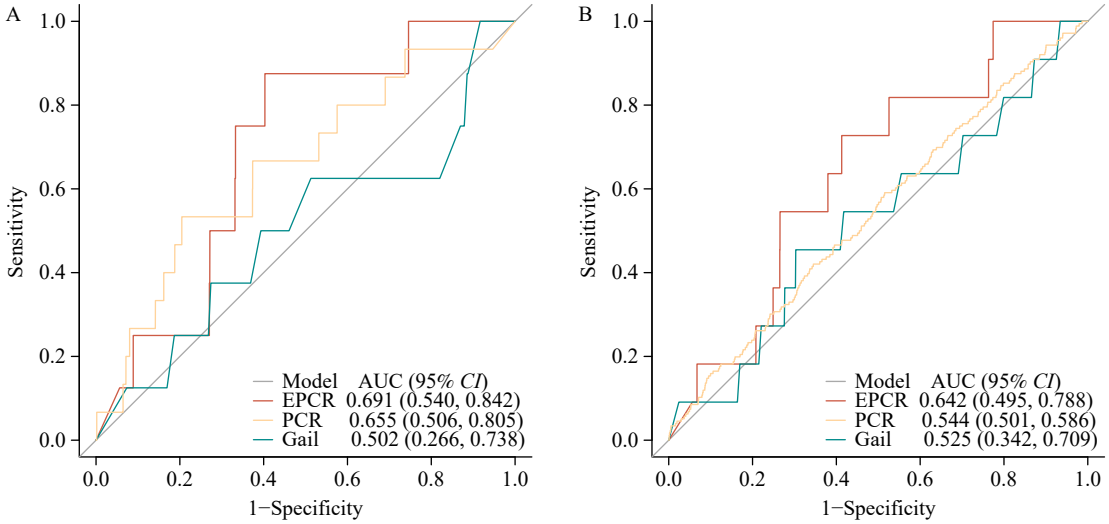

FIGURE 2. The ROC curve for 3- and 5-year model predictions of disease onset. (A) 3-year ROC; (B) 5-year ROC.
Note: Red indicates the ROC curve of the EPCR model, orange indicates the ROC curve of the PCR model, and lime green indicates the ROC curve of the Gail model.
Abbreviation: ROC=receiver operating characteristic; EPCR=ensemble penalized Cox regression; PCR=penalized Cox regression; AUC=the areas under the receiver operating characteristic curve.

mostly imbalanced, we propose applying ensemble learning methods to improve prediction performance. Specifically, the Bagging ensemble framework can be used to be able to better handle imbalanced data. Here, a PCR model was used as the base predictor, since it can make full use of follow-up information while also being able to adapt to high-dimensional data. Several simulation studies were carried out to verify the effectiveness of this method under different censoring rates settings. As shown in Table 1, the AUC based on the risk scores estimated by the EPCR model was consistently higher than that of a single PCR model or a traditional stepwise regression model under all settings. This suggests that the introduction of the Bagging ensemble framework can improve the predictive performance of PCR models, and this advantage becomes more apparent as the censoring rate increases. For example, compared to penalized logistics regression (PLR)-LASSO, the AUC of ensemble penalized logistics regression (EPLR)-LASSO increased by 1.5% and 2.2% for 30% and 70% deletion rates when $n = 1,000, p = 100$, respectively.

In addition, the EPCR model allows for a more robust data-driven identification of risk factors. Under all simulation settings, we calculated FDR, FOR, TPR, and TNR values for variable screening. These results showed that EPCR-LASSO had the lowest FDR while maintaining a very high TPR. For example, for Setting 1, EPCR-LASSO had the lowest FDR (0.164 lower than PCR-LASSO) as well as a TPR greater than 0.93. This means that the variables identified by the EPCR-LASSO approach contain the fewest insignificant variables and the most significant variables compared to the other five models; that is, EPCR-LASSO is a more accurate approach for the identification of significant variables. Moreover, EPCR-LASSO continued to perform the best as the censoring rate increased. In addition, we also found that EPCR-EN can also significantly reduce FDR while maintaining the same level of TPR as PCR-EN. Taken together, these results suggest that the EPCR procedure is the best choice to use to identify important risk factors. For cancers whose etiology is unknown, the number of cases that can be used to train a prediction model is extremely small. Therefore, the exclusion or inclusion of a case can have a significant impact on the selection of risk factors. The EPCR model benefits from the Bagging ensemble framework to more robustly identify risk factors (*14*), which in turn can provide a more meaningful reference for studies of disease etiology.

Next, we developed and validated a breast cancer risk prediction model by analyzing the large BCCS-CW database using the EPCR procedure. Compared to the classical Gail model, our model achieved a higher degree of discrimination with higher accuracy (Figure 2). The AUC for 3- and 5-year predictions of the EPCR model were 0.691 and 0.642, which represented improvements of 0.189 and 0.117 over the classic Gail model, respectively. The other published absolute risk prediction model for the Chinese

population showed a maximum AUC of only 0.634 (*15*). The difference between our results and this model further demonstrates that cancer prediction models developed by the EPCR procedure are more accurate in identifying high-risk populations and may be more useful for rationally allocating healthcare resources under medical constraints.

However, it is also important to be aware that the EPCR model developed here has limitations. The application of the EPCR procedure to develop disease prediction models is only applicable where the corresponding risk factors satisfy the proportional hazards assumption. This is because the EPCR model is actually an average of multiple COX regression models. However, in most cases, especially those containing high-dimensional data, the proportional hazards assumption does not hold. Therefore, the EPCR model is more suitable for short-term disease risk prediction. As shown in Figure 2, the 5-year AUC based on the risk score estimated by the EPCR model is lower than the 3-year AUC. Therefore, the actual effectiveness of the EPCR model in predicting risk may be lower when applied to a longer (e.g., 10-year) timeframes.

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SUPPLEMENTARY MATERIAL

Penalized Cox Regression Model

In this study, the outcome event of interest is the onset of cancer, and the initial event is the birth of the individual, so survival time is defined as the time span from birth to diagnosis of cancer — i.e., the age of the individual when cancer is first diagnosed. Similarly, we defined the censoring time as the age of the individual at the cutoff of the cancer time observation process. We first give a concise description of the EPCR model. Denote the data set as $D = \{T_i, \Delta_i, Z_i\}(i = 1, \cdots, n)$, where $T_i = \min(T_i, C_i)$, T_i is the survival time of the ith individual, C_i is the censoring time of the ith individual, $\Delta_i = I(T_i \le C_i)$ indicates that the ith individual was diagnosed with cancer $(\Delta_i = 1)$ or was censored $(\Delta_i = 0)$, $I(\cdot)$ is the indicator function, and Z_i is the p-dimensional predictor associated with the onset of cancer.

Given a p-dimensional predictor vector Z, the Cox (*1*) proportional hazard model specifies that an individual's hazard function for the onset of cancer at age t takes the form

$$\lambda(tZ) = \lambda_0(t)\, e^{\beta^T Z} \tag{1}$$

Here, $\beta = (\beta_1, \cdots, \beta_p)$ represents a p-dimensional vector of unknown regression parameters, and $\lambda_0(\mathbf{t})$ is an arbitrary baseline hazard function. Let $R_i = \{j : T_j \ge T_i\}$ be the set of individuals who are still at risk at age T_i, Cox (*1–2*) proposed that the maximum partial likelihood estimator β is the maximizer of partial likelihood:

$$\hat{\beta} = \underset{\beta}{argmax} Pl(\beta) = \underset{\beta}{argmax} \prod_{i=1}^{n} \left\{ \frac{e^{\beta^T Z_i}}{\sum_{j \in R_i} e^{\beta^T Z_j}} \right\}^{\Delta_i} \tag{2}$$

or equivalently the maximizer of log partial likelihood:

$$\hat{\beta} = \underset{\beta}{arg\,max}\, Pl(\beta) = \underset{\beta}{arg\,max} \sum_{i=1}^{n} \Delta_i \left\{ \beta^T Z_i - ln \sum_{j \in R_i} e^{\beta^T Z_j} \right\} \tag{3}$$

Due to the numerous predictive indicators of the onset of cancer and the low incidence of cancer, cancer-related datasets often have high dimensionality, strong correlational structure, and a small sample size. It is particularly important to efficiently screen out those predictors related to the onset of cancer from a large number of predictors. This paper screens out these predictors by imposing a penalty on the regression parameter β in the traditional Cox model. The PCR model estimates β as

$$\hat{\beta} = \underset{\beta}{arg\,min} - Pl(\beta) + P(\beta) \tag{4}$$

where $P(\beta)$ is an elastic net (*3*) penalty function forβ:

$$P(\beta) = \lambda \left[\alpha \beta_1 + (1 - \alpha) \beta_2^2 \right] \tag{5}$$

The baseline hazard function $\lambda_0(t)$ from in formula (*1*) is also unknown. After estimating regression parameter β, we can estimate the cumulative baseline hazard function using a Breslow estimator (*4*):

$$\widehat{\Lambda_0}(t) = \sum\nolimits_{i=1}^{n} \frac{I\left(\widetilde{T_i} \le t\right) \Delta_i}{\sum_{j \in R_i} e^{\widehat{\beta^T} Z_j(\widetilde{T_i})}} \tag{6}$$

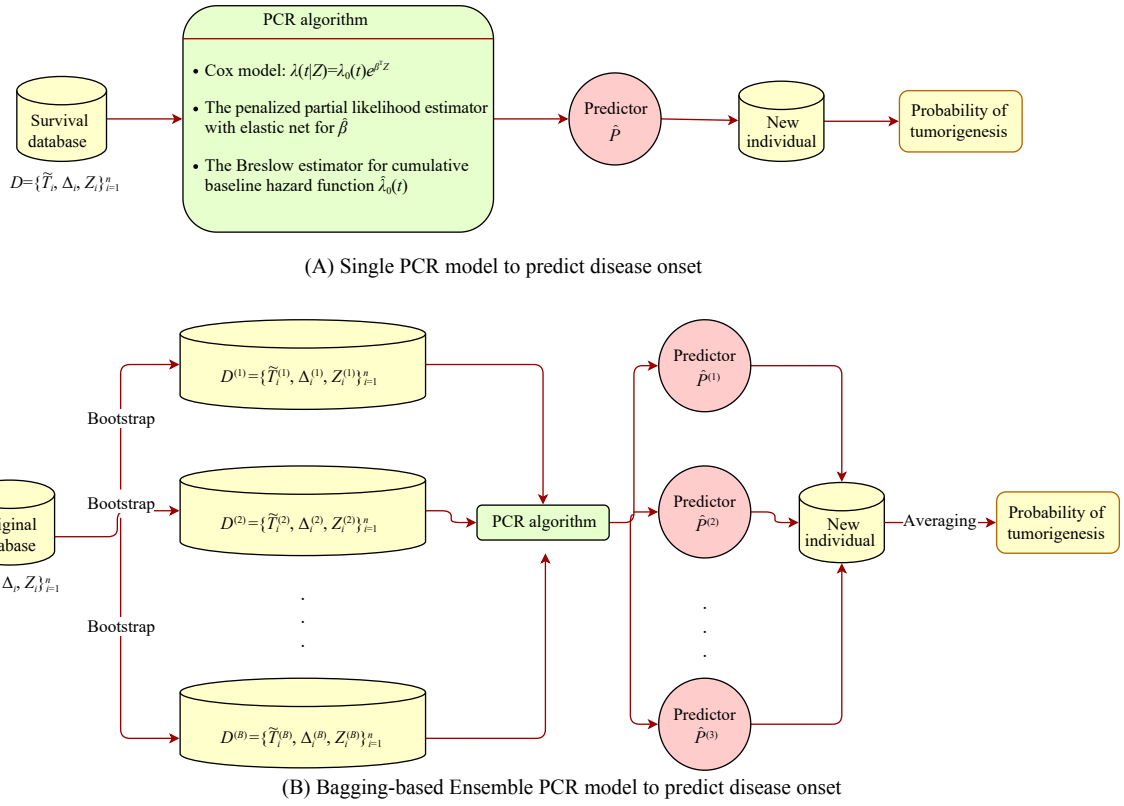
Therefore, if it is known that an individual whose predictor Z is Z^* does not have cancer at age a, then the PCR model (as shown in Supplementary Figure S1A) predicts the probability of developing cancer within τ years as

$$\widehat{P}(a, \tau, Z^*) = \int_a^{a+\tau} - \hat{\lambda}_0(t)\, exp\left(\hat{\beta}^T Z^*\right) \frac{\hat{S}(t)}{\hat{S}(a)} dt \tag{7}$$

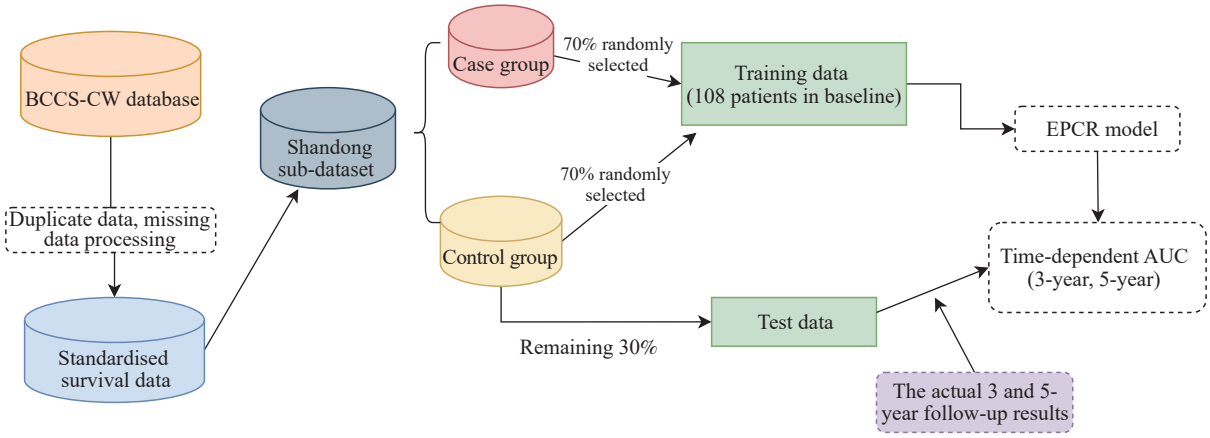
where $\hat{S}(t) = \int_0^t - \hat{\lambda}_0(u)\, exp\left(\hat{\beta}^T Z^*\right) du$ is the estimator of the survival function.

Predictor Importance Measures

As shown in Supplementary Figure S1B, the EPCR model establishes B different and mutually independent penalized COX models. Thus, the EPCR model creates a $B \times p$ importance assessment matrix for the p-dimensional predictors, denoted E. Let $E(b, j)$ denote the(b, j)th entry of $ \mathit{E} $. We then have



SUPPLEMENTARY FIGURE S1. Flowcharts for the single PCR model and the Bagging-based ensemble PCR model.
Abbreviation: PCR=Penalized Cox regression.

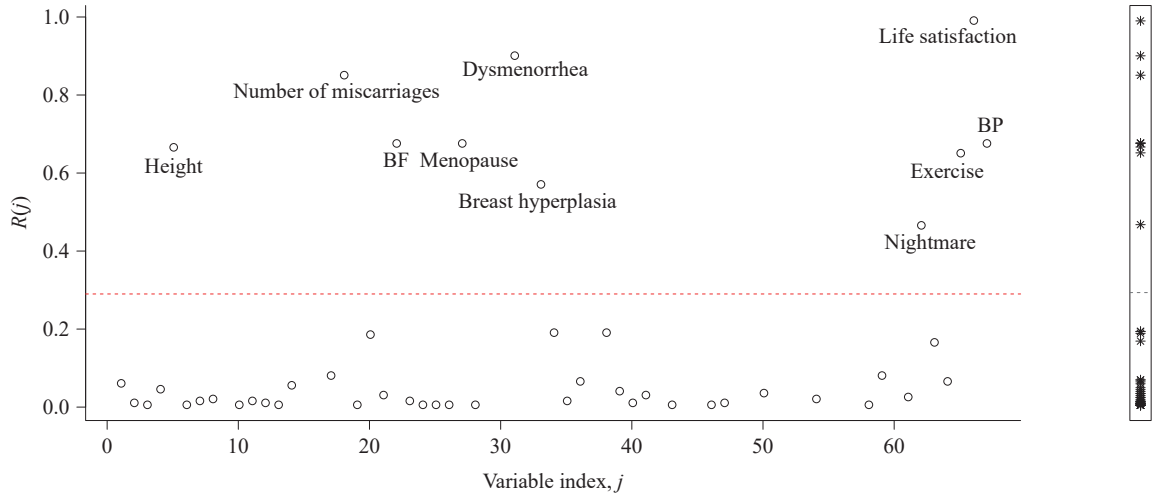


SUPPLEMENTARY FIGURE S2. Workflow of the empirical study.
Abbreviation: BCCS-CW=Breast Cancer Cohort Study in Chinese Women; EPCR=Ensemble penalized Cox regression; AUC=Areas under the receiver operating characteristic curve.

$$E(b,j) = \begin{cases} 1, \textit{If the coefficient of the jth predictor in the bth PCR model is nonzero} \\ 0, \textit{otherwise} \end{cases} \quad (8)$$

Using a majority-vote summary (5), the EPCR model quantifies the importance of the jth predictor for disease occurrence as $R(j) = \frac{1}{B}\sum_{b=1}^{B} E(b,j), j = 1, \ldots, p$.

Based on the definition of the importance assessment matrix E, it is easy to see that the importance assessment indicator $R(j)$ for the jth predictor is actually the frequency by which the jth predictor is selected by all EPCR base models. Thus, the larger $R(j)$ is, the more important predictor j is. Some studies (5) have sorted predictors



SUPPLEMENTARY FIGURE S3. Factors influencing the development of breast cancer identified by the EPCR-based assessment.
Note: Left (wide) panel shows R(j) against j. Right (narrow) panel shows R(j) sorted in order to identify the largest gap; for more details please see Methods. Variable j with an R(j) value above the red line indicates a significant variable identified by the EPCR model. Supplementary Table S1 lists the meaning of the variable indices for explanation.
Abbreviation: EPCR=Ensemble penalized Cox regression; BP=Bean product; BF=Breast feeding.

according to the values $R(1), R(2), \ldots, R(p)$, then searched for the maximum gap between any consecutive entries, ultimately choosing predictor j if $R(j)$ is above this gap.

In our study, we simply specify a certain cutoff and select predictors where $R(j)$ is greater than the cutoff. The cutoff can be $\frac{1}{p}\sum_{j=1}^{p} R(j)$, or 0.5 (indicating that half of the base models of EPCR have selected this variable).

Four Evaluation Metrics in Simulation Study

Denote the set of variables that are truly associated with the response variable as M, and the set of important variables comprising the model screening is $\widehat{M}$. In simulation studies, the following indicators are mainly used to measure the ability of the model to correctly screen variables:

1) False Discovery Rate (FDR)= $\frac{\left|\widehat{M} \bigcap M^{C}\right|}{\left|\widehat{M}\right|}$;

2) False Omission Rate (FOR)= $\frac{\left|\widehat{M}^{C} \bigcap M\right|}{\left|\widehat{M}^{C}\right|}$;

3) True Positive Rate (TPR)= $\frac{\left|\widehat{M} \bigcap M\right|}{|M|}$;

4) True Negative Rate (TNR)= $\frac{\left|\widehat{M}^{C} \bigcap M^{C}\right|}{\left|M^{C}\right|}$.

SUPPLEMENTARY TABLE S1. Population characteristics for Shandong subset of the BCCS-CW database, overall and by diagnosis of BC in the baseline.

Risk factor	Overall (*N*=60,397)	Case (*N*=154)	Control (*N*=60,243)	*P* value*
Age†, mean (SD)	43.56 (11.58)	46.82 (8.55)	43.55 (11.58)	<0.001
Location, *n* (%)				
Rural	7,903 (13.1)	27 (17.5)	7,876 (13.1)	0.129
Urban	52,494 (86.9)	127 (82.5)	52,367 (86.9)	
Occupation, *n* (%)				
Farmer	43,158 (71.5)	102 (66.2)	43,056 (71.5)	0.272
Worker	8,838 (14.6)	19 (12.3)	8,819 (14.6)	

Continued

Risk factor	Overall (*N*=60,397)	Case (*N*=154)	Control (*N*=60,243)	*P* value*
Teacher	336 (0.6)	1 (0.6)	335 (0.6)	
Civil service	164 (0.3)	1 (0.6)	163 (0.3)	
Individual traders	989 (1.6)	4 (2.6)	985 (1.6)	
Driver	32 (0.1)	0 (0.0)	32 (0.1)	
Services	469 (0.8)	0 (0.0)	469 (0.8)	
Staff	853 (1.4)	2 (1.3)	851 (1.4)	
Housewife	4,527 (7.5)	19 (12.3)	4,508 (7.5)	
Health care	858 (1.4)	5 (3.2)	853 (1.4)	
Student	2 (0.0)	0 (0.0)	2 (0.0)	
Others	171 (0.3)	1 (0.6)	170 (0.3)	
Education year, mean (SD)	6.14 (3.99)	5.74 (4.08)	6.14 (3.98)	0.211
Education, *n* (%)				
Primary or below	29,772 (49.3)	81 (52.6)	29,691 (49.3)	0.133
Junior high school	22,177 (36.7)	49 (31.8)	22,128 (36.7)	
Senior middle or vocational high school	6,814 (11.3)	23 (14.9)	6,791 (11.3)	
University	1,634 (2.7)	1 (0.6)	1,633 (2.7)	
Height, mean (SD)	1.59 (0.05)	1.59 (0.05)	1.59 (0.05)	0.201
Weight, mean (SD)	59.65 (9.10)	63.85 (10.48)	59.64 (9.09)	<0.001
BMI, mean (SD)	23.66 (3.40)	25.12 (3.60)	23.66 (3.40)	<0.001
Waistline (Chi[§]), mean (SD)	2.39 (0.25)	2.52 (0.28)	2.39 (0.25)	<0.001
Hip circumference (Chi[§]), mean (SD)	3.00 (0.24)	3.10 (0.25)	3.00 (0.24)	<0.001
WHR, mean (SD)	0.80 (0.05)	0.81 (0.06)	0.80 (0.05)	0.001
Number of family members, mean (SD)	3.47 (1.12)	3.37 (1.31)	3.47 (1.12)	0.29
Family annual income, mean (SD)	14,928.10 (15,807.75)	15,853.40 (13,636.80)	14,925.74 (15,812.94)	0.467
Economic status, *n* (%)				
Very good	337 (0.6)	1 (0.6)	336 (0.6)	<0.001
Good	8,172 (13.5)	19 (12.3)	8,153 (13.5)	
Common	50,459 (83.5)	125 (81.2)	50,334 (83.6)	
Poor	1,368 (2.3)	7 (4.5)	1,361 (2.3)	
Very poor	61 (0.1)	2 (1.3)	59 (0.1)	
Social status, *n* (%)				
Very good	339 (0.6)	1 (0.6)	338 (0.6)	0.007
Good	7,880 (13.0)	20 (13.0)	7,860 (13.0)	
Common	51,529 (85.3)	129 (83.8)	51,400 (85.3)	
Poor	622 (1.0)	3 (1.9)	619 (1.0)	
Very poor	27 (0.0)	1 (0.6)	26 (0.0)	
Number of miscarriages, mean (SD)	0.44 (0.81)	0.60 (0.92)	0.44 (0.81)	0.014
Breast feeding, *n* (%)				
Yes	57,698 (95.5)	145 (94.2)	57,553 (95.5)	0.527
No	2699 (4.5)	9 (5.8)	2690 (4.5)	
Menopause, *n* (%)				
Yes	17,833 (29.5)	96 (62.3)	17,737 (29.4)	<0.001
No	42,564 (70.5)	58 (37.7)	42,506 (70.6)	

Continued

Risk factor	Overall (*N*=60,397)	Case (*N*=154)	Control (*N*=60,243)	*P* value*
Dysmenorrhea, *n* (%)				
Yes	47,855 (79.2)	123 (79.9)	47,732 (79.2)	0.924
No	12,542 (20.8)	31 (20.1)	12,511 (20.8)	
Breast hyperplasia, *n* (%)				
No	56,179 (93.0)	148 (96.1)	56,031 (93.0)	0.178
Yes	4,218 (7.0)	6 (3.9)	4,212 (7.0)	
Bean product, *n* (%)				
Almost every day	2,494 (4.1)	9 (5.8)	2,485 (4.1)	0.085
3–4 days a week	12,266 (20.3)	32 (20.8)	12,234 (20.3)	
1–2 days a week	26,792 (44.4)	54 (35.1)	26,738 (44.4)	
Almost never	18,845 (31.2)	59 (38.3)	18,786 (31.2)	
Sleep satisfaction, *n* (%)				
Very satisfied	11,345 (18.8)	22 (14.3)	11,323 (18.8)	0.04
Satisfied	42,765 (70.8)	106 (68.8)	42,659 (70.8)	
Not satisfied	6,133 (10.2)	25 (16.2)	6,108 (10.1)	
Very dissatisfied	154 (0.3)	1 (0.6)	153 (0.3)	
Nightmare, *n* (%)				
No	57,681 (95.5)	141 (91.6)	57,540 (95.5)	0.03
Yes	2,716 (4.5)	13 (8.4)	2,703 (4.5)	
Exercise, *n* (%)				
Yes	3,421 (5.7)	10 (6.5)	3,411 (5.7)	0.786
No	56,976 (94.3)	144 (93.5)	56,832 (94.3)	
Life satisfaction degree, *n* (%)				
<25	41,350 (68.5)	75 (48.7)	41,275 (68.5)	<0.001
≥25	19,047 (31.5)	79 (51.3)	18,968 (31.5)	
Behavioral prevention degree, *n* (%)				
<1	45,018 (74.5)	90 (58.4)	44,928 (74.6)	<0.001
≥1	15,379 (25.5)	64 (41.6)	15,315 (25.4)	
Awareness of BC degree, *n* (%)				
<8	49,180 (81.4)	107 (69.5)	49,073 (81.5)	<0.001
≥8	11,217 (18.6)	47 (30.5)	11,170 (18.5)	

Note: This table shows only the important variables in Supplementary Figure S3 as well as some essential variables; other insignificant variables are omitted. The omitted variables include marital status, number of birth, number of pregnancies, number of term pregnancies, age at 1st pregnancy at term, full-term birth, breast feeding duration (month), history of contraceptive use, age of menarche, menstruation regular, family history of breast, menstrual period, menstrual cycle, benign breast disease history, nipple discharge, mamma accessoria, nipple retraction, cervical cancer history, ovarian cancer history, ovarian cyst history, diabetes mellitus, hypertension, coronary heart disease, nephritis, fresh beans, red meat, dairy products, corn, carrot, fried foods, colored vegetables or fruit, garlic, ham, pickles, sleep duration, smoking, drinking, passive smoking, tea, insomnia, waking up early, and sleeping late. For numerical risk factors, the numbers and numbers within parentheses indicate the mean and SD, respectively; for categorical risk factors, the numbers and numbers within parentheses indicate the numbers of people and their percentages of the cohort size respectively. es of the cohort size respectively.
Abbreviation: BMI=Body mass index; WHR=Waist-to-hip ratio; BC=Breast cancer; SD=Standard deviation.
* The *P* value of Comparing groups for statistical differences. T-Test was used for numerical risk factors and Chi-squared test for Categorical risk factors, respectively.vely.
† Age of the case group is their age at diagnosis of breast cancer; age of the control group is the initial age at the start of follow-up.
§ A Chinese unit of length, which is equal to one third of a meter.

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