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Original Article

The epidemiology and determinants of pregnancy-induced hypertension from 2010-2013: a population-based survey in northwestern China

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Abstract: Objective: To investigate the prevalence and risk factors for pregnancy-induced hypertension (PIH) in Shaanxi Province of Northwest China. A stratified multistage random sampling method was applied to recruit women of childbearing age (15-49 years) living in Shaanxi Province who gave birth from 2010-2013. The participants' characteristics were recorded using a structured questionnaire. A multilevel model was employed to evaluate the effect of the possible risk factors on PIH. Of the 29,184 women surveyed, the prevalence of PIH was 1.60% (95% CI: 1.46%-1.75%). A multilevel model analysis indicated that maternal age ≥35 years (OR=2.05, 95% CI: 1.55-2.70), unstable mental status (OR=1.49, 95% CI: 1.04-2.15), multiple pregnancies (OR=3.14, 95% CI: 1.82-5.45), gestational diabetes mellitus (OR=5.84, 95% CI: 2.42-14.11), and fetal malformation (OR=2.52, 95% CI: 1.61-3.92) were significantly associated with an increased risk of PIH. Healthcare professionals should strengthen their monitoring of high-risk pregnant women with these risk factors for PIH. Our findings provide clues about the etiology of PIH and useful evidence for formulating effective policies and health care programs for PIH intervention in northwest China.

Keywords: Pregnancy-induced hypertension, epidemiologic characteristics, gestational diabetes mellitus, fetal malformation, northwestern China

Introduction

Hypertensive disorders complicating pregnancy, also known as pregnancy-induced hypertension (PIH) syndrome [1-3], constitute a worldwide problem requiring prompt attention. PIH is classified into eclampsia, pre-eclampsia, gestational hypertension, pre-eclampsia complicated by chronic hypertension, and chronic hypertension complicating pregnancy [4, 5]. PIH is one of the main causes of death during the peripartum period worldwide and is particularly devastating in developing countries [6, 7]. Recent studies have reported that PIH is one of the main causes of maternal mortality in China [8, 9]. Furthermore, PIH is a risk factor for the development of coronary heart disease, stroke, kidney disease, diabetes, and chronic hypertension in pregnant women [10-15].

PIH is also associated with poor neonatal outcomes. Several articles have demonstrated the influence of PIH on preterm birth [16, 17]. Preterm birth is a key factor in neonatal mortality or morbidity over the past 20 years [18]. It is associated with an increased incidence of neonatal respiratory distress syndrome, sepsis, bronchopulmonary dysplasia, neurodevelopmental disorders, and intraventricular hemorrhage [19]. Recent systematic reviews and meta-analyses revealed that PIH was related to a reduced adjusted odds ratio of mortality, hearing loss, vision loss, and cerebral palsy among preterm infants [20]. Moreover, PIH is a predictor of low birth weight [21].

Despite extensive hospital-based research on the prevalence and risk factors for PIH [9], there is a lack of large community-based investiga-

tions among Chinese women in recent years. Moreover, some risk factors for PIH remain controversial [22], including gestational diabetes mellitus (GDM) and fetal malformation that have been insufficiently studied. Thus, the aim of this cross-sectional study was to present the epidemiologic and prevalence data of PIH and to investigate the controllable and relevant risk factors using a large population of women in Shaanxi Province. This research will provide useful evidence for formulating effective policies and health care programs for PIH intervention in northwest China.

Methods

Data sources and participants

The data in this current research was derived from a large population-based cross-sectional study aiming to investigate the prevalence and risk factors of birth defects which was executed in Shaanxi Province of northwest China between August and December 2013. We recruited women aged 15-49 from Shaanxi Province who gave birth from 2010-2013 with recorded pregnancy outcomes were enrolled in this study. A stratified, multistage, random sampling method was used. The study design used was based on the study by Liu et al. [23]. Based on the current fertility rates and population density, approximately 32,400 participants were expected to be included in this research.

The sample size estimation was based on the formula: $N=\frac{z_{a/2}^2 p(1-p)}{d^2} * deff$, where d=20%p, a=0.05 ($z_{a/2}$=1.96), and deff=2. Considering that the prevalence of PIH was 4.20% among the pregnant women [17], the estimated sample size for the study was about 4,382.

Data collection

After the written informed consent was signed, trained skilled investigators personally conducted interviews with the participants using a structured questionnaire to collect demographic information, including their places of residence, dates of birth, educational levels, occupations, family economic statuses, pregnancy histories, prenatal care, lifestyles, and health statuses. Data about their offspring were also obtained, including sex, numbers of births, and fetal malformations. Xi'an Jiaotong University Health Science Center designed all the questionnaires, which were validated by the institution's supervisors to ensure completeness of the values and to minimize the logical errors to ensure the accuracy of the collected data.

Study outcomes

The primary outcome of this study was the presence of PIH. We defined PIH as a combination of clinical presentations in a patient with hypertension during pregnancy. The main clinical manifestations of PIH include hypertension, which may occasionally present with proteinuria, and even convulsions in severe cases. In each case, PIH was considered based on the self-reported symptoms of the pregnant woman combined with the diagnosis of her doctor from a local maternal and child health hospital.

Covariates

Information regarding the maternal sociodemographic characteristics including (1) maternal age (<35 or ≥35 years); (2) the mother's highest educational attainment (primary school and below, junior high school, or senior high school and above); (3) monthly household income (≤2000, 2000-4000, or ≥4000 yuan); (4) household classification (urban or rural); (5) region (southern Shaanxi, central Shaanxi, or northern Shaanxi); (6) lifestyle factors including second-hand smoke exposure (yes or no), and alcohol drinking (yes or no); (7) comorbidities including GDM (yes or no), and unstable mental status (yes or no); (8) healthcare utilization, including frequency of prenatal checkups (<5 or ≥5); (9) reproductive history including parity (1 or ≥2); and (10) neonatal characteristics including numbers of births (single gestation or multiple gestation), sex of the infant (boy or girl), and fetal malformation (yes or no) were evaluated as potential risk factors for PIH. The regional and household classifications in the research were defined according to China's household registration system. Passive smoking exposure was defined as inhaling tobacco smoke from others for more than 15 min/d [24].

Statistical analysis

EpiData3.1 was adopted to design the database and all the data entry was duplicated to ensure accuracy. The continuous variables were described using the mean ± standard

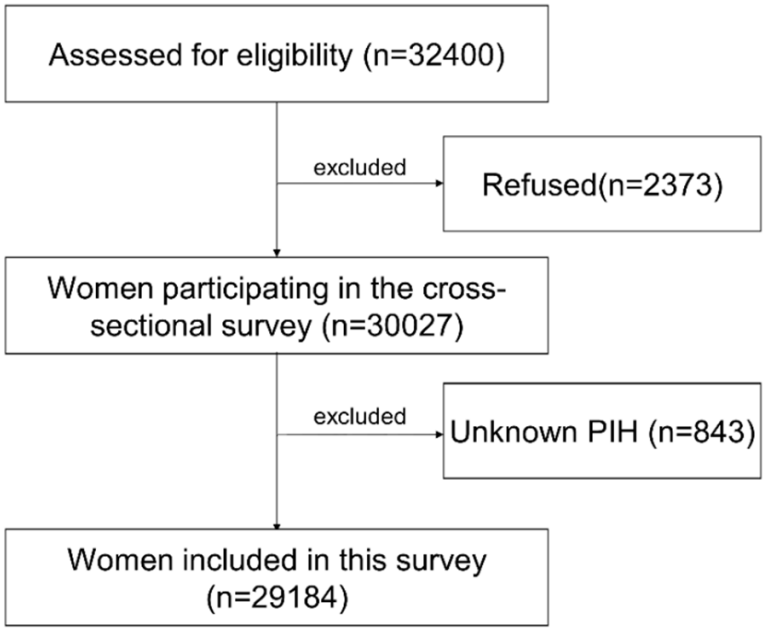

Figure 1. Flow diagram of the sampling strategy.

deviation (SD), and t-tests were used to compare the differences between groups. Counts and proportions were employed to show the characteristic of the categorical variables, and X^2 tests were used to compare the different groups.

The intra-class correlation (ICC) was found to be 0.015 (P<0.001) after running the empty models, which indicated that there was homogeneity in PIH. Studies have shown that even a small ICC can cause large Type I errors, which may erroneously reject a true statistical hypothesis. The traditional linear regression based on the ordinary least square method (OLS) assumes that observations are independent of each other, rendering it unsuitable for the analysis of this multi-layer data. Thus, compared with traditional linear regression, the multilevel model was more appropriate. A multilevel logistic regression was established to access the odds ratio (OR) and a 95% confidence interval (95% CI) was used to establish the relationship between PIH and the potential influencing factors, with districts set to level 2 and individuals set to level 1 using the PROC GLIMMIX procedure in the SAS 9.4 software. SAS software (version 9.4; SAS Institute Inc.) was applied to perform the statistical analysis. Statistical significance was defined as a two-tailed P<0.05.

Ethics statement

The study was carried out in accordance with the Declaration of Helsinki, and the Ethics Committee of Xi'an Jiaotong University Health Science Center approved all the procedures involving human subjects (No. 20120-008). The investigators read and explained the consent form to each of the participants and obtained a written informed consent from each one before conducting each in-person survey.

Results

Study subjects and demographic characteristics

In this large population study, 30,027 subjects agreed to participate in the survey, with a response rate of 92.68% (30027/32400). We removed 843 subjects due to unverified PIH statuses. Ultimately, a total of 29,184 women made up the study cohort (**Figure 1**). This sample size was sufficient for the data analysis.

Of the 29,184 women surveyed, the reproductive age was 28.04±4.86 years and those who were <35 years old accounted for 88.70%. In most cases, the highest educational levels attained by the participants were junior high school and senior high school and above (87.83%). The average monthly household income of the respondents was mainly concentrated in the ≥4000 yuan range (39.98%). Most of the participants (67.23%) resided in the rural areas. The subjects from the south, central, and north of Shaanxi accounted for 20.52%, 53.83%, and 25.64%, respectively. During pregnancy, 0.27% had GDM, and 5.68% suffered from an unstable mental status. Of the infants, 1.20% were multiple gestations, 54.79% were boys, and 2.18% had a malformation. Other demographic characteristics are presented in **Table 1**.

Prevalence of PIH

PIH was noted in 467 (1.60% [95% CI: 1.46%, 1.75%]) pregnant women. Older women (≥35

Table 1. Demographic characteristics of the participants

Baseline characteristics	Percent n (%)
Socio-demographic characteristics	
Maternal age, year*	
<35	25479 (88.70)
≥35	3245 (11.30)
Mother's highest educational attainment*	
Primary school and below	3543 (12.17)
junior school	14448 (49.62)
Senior school and above	11127 (38.21)
Monthly household income, yuan*	
≤2000	6582 (24.53)
2000-4000	9519 (35.48)
≥4000	10726 (39.98)
Household classification*	
Urban	9565 (32.77)
Rural	19619 (67.23)
Region*	
Southern Shaanxi	5990 (20.52)
Central Shaanxi	15710 (53.83)
Northern Shaanxi	7484 (25.64)
Lifestyles	
Second-hand smoke exposure*	
No	28542 (99.74)
Yes	77 (0.26)
Alcohol drinking*	
No	28810 (98.86)
Yes	332 (1.14)
Comorbidities	
Gestational diabetes mellitus*	
No	29104 (99.73)
Yes	80 (0.27)
Unstable mental status*	
No	27505 (94.32)
Yes	1656 (5.68)
Healthcare utilization	
Frequencies of prenatal checkups*	
<5	13544 (47.22)
≥5	15136 (52.78)
Reproductive history*	
Parity	
1	16673 (58.90)
≥2	11632 (41.10)
Neonatal characteristics	
Number of births*	
Single gestation	28833 (98.80)
Multiple gestation	351 (1.20)
Sex of the infant*	

years) had a higher risk of PIH (**Figure 2**). The prevalence of PIH among the participants from rural areas was lower than it was among the participants from urban areas (1.46% [95% CI: 1.29%-1.64%] vs. 1.89% [95% CI: 1.63%-2.19%], $P<0.001$). The prevalence of PIH was highest in women from southern Shaanxi, followed by central Shaanxi, then northern Shaanxi (1.97% [95% CI: 1.63-2.32%] vs. 1.63% [95% CI: 1.44-1.84] vs. 1.24% [95% CI: 1.00-1.52], $P<0.001$) (**Figure 3**).

Determinants of PIH

A univariate analysis showed that maternal age, household classification, region, GDM, unstable mental status, frequency of prenatal checkups, parity, multiple gestation, and fetal malformations were strong predictors of PIH (**Table 2**).

In the multilevel model, the PIH and the characteristics of the mothers and their infants during pregnancy were used as the independent and the dependent variables, respectively. Older women had a higher risk of PIH (OR=2.05, 95% CI: 1.55-2.70). Women with GDM or an unstable mental status were more likely to suffer from PIH (OR=5.84, 95% CI: 2.42-14.11; vs. OR=1.49, 95% CI: 1.04-2.15, respectively). Participants with multiple gestations or fetal malformations were associated with a higher risk of PIH (OR=3.14, 95% CI: 1.82-5.45; vs. OR=2.52, 95% CI: 1.61-3.92) (**Table 3**).

Discussion

This study aimed to present the epidemiologic and prevalence data of PIH and its associated risk factors from a large population of pregnant women in Shaanxi Province. We found that the prevalence of PIH in women from Shaanxi Province is 1.67%. We noted that the risk factors for PIH include older age, GDM, unstable mental status, multiple gestation, and fetal malformation.

Despite the publication of several studies involving Chinese women, there remains a lack of large sample community-based investigations analyzing this topic. A multicenter cross-sectional retrospective study from China in 2011 indicated that the rate of PIH syndrome was 5.22% [25]. Another cross-sectional study of 16,954 mothers analyzed from 2006-2008

Boy	15984 (54.79)
Girl	13187 (45.21)
Fetal malformation*	
No	28549 (97.82)
Yes	635 (2.18)

*: *P* values <0.001.

in five Chinese cities showed a prevalence rate of 16.1 per 10000 [26]. A population-based study from America noted that the prevalence of PIH increased from 3.0% in 1990 to 3.9% in 2004 [27]. In Japan, PIH prevalence was reported to be 3.1% according to a cross-sectional study of 2,348 women [28]. Another cross-sectional study conducted in Zimbabwe reported a PIH prevalence of 19.4% [29]. Thus, our study observed that the prevalence of PIH was similar to studies from China, but the prevalence was lower than it was in the United States, Japan, and Zimbabwe. A possible reason for this discrepancy may be due to a recall bias secondary to the limited amount of time, manpower, material, and financial resources that hindered an exhaustive review of the disease history or medical records available. Our questionnaires relied on the recall memory of the participating women, inevitably underdiagnosing some women with PIH. In addition, most of the investigated population were from the rural areas, with low medical resources and a consequently low detection rate. All of these could result in an underestimated prevalence rate of PIH.

The results of this research indicated that older age, GDM, unstable mental status, multiple gestation, and fetal malformation were risk factors for PIH. Bener et al. [30] reported that a higher maternal age >30 years was positively associated with an increased risk for PIH in Arab subjects. Owiredu et al. [22] revealed that Ghanaian women aged 35-39 years were more likely to suffer from PIH compared to women aged 25-29 years (OR=9.2, 95% CI: 2.5-34.7). Similarly, our study showed that women aged ≥35 years had a higher risk of PIH compared with women aged <35 years (OR=2.05, 95% CI: 1.55-2.70). The association between higher maternal age and hypertensive disorders of pregnancy (HDP) was also evident in Chinese women aged 35-39 years with a 1.84-fold higher risk of HDP, and those aged ≥40 years had a 2.39-fold higher risk than those aged 25-29 years [25]. Further, they found that the prevalence rate of PIH increased proportionately with maternal age. Our study has similar results. However, Umesawa et al. reported no association between maternal age and the risk of PIH, pre-eclampsia (PE), or HDP; and a study conducted in America reported no association between older age and the prevalence of PE [22]. Confounding factors owing to the relationship of lower maternal age with nulliparity [31] and the variation between the study population's characteristics in both groups might explain the discrepancy.

Our study also found a link between adverse mental state and PIH. Pregnant women are susceptible to external stimuli or negative events, making them prone to suffer from stress, anxiety, mood swings, depression, and other extreme emotions, causing an increase in catecholamines and other substances. These neuroendocrine substances are closely related to PIH [32].

The results of our study reported that fetal malformation was closely related to an increased risk of PIH. Although PIH is common during pregnancy, there are few published studies on the relationship between PIH and fetal malformation. One study [33] reported that Latin American and Caribbean women who delivered infants with fetal malformation had a positive correlated with PE risk. Nelson et al. [34] also found that preeclampsia, but not gestational hypertension, was related to an increased incidence of malformation compared with normotensive women. The underlying pathogenetic mechanism of this association remains unknown. Impaired placental perfusion was proposed to be the common etiology for fetal malformation and PIH [33].

We found that the participants with multiple pregnancies were more likely to suffer from PIH, which was consistent with previous research. Chun et al. [25] reported that pregnant Chinese women with multiple gestations were more likely to suffer from HDP (OR=3.68, 95% CI: 3.26-4.16). Rui et al. also reported that multiple gestations had a 3.31 times higher risk of PIH than singleton pregnancies [35]. Another study found an association between PE and multiple pregnancies [36]. The underlying mechanism for the increased incidence of PIH in multiple pregnancies may be due to a

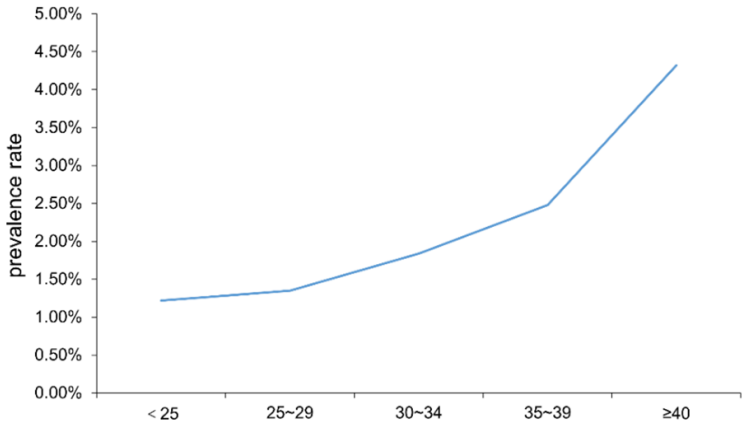

Figure 2. The prevalence rate of PIH by age group.

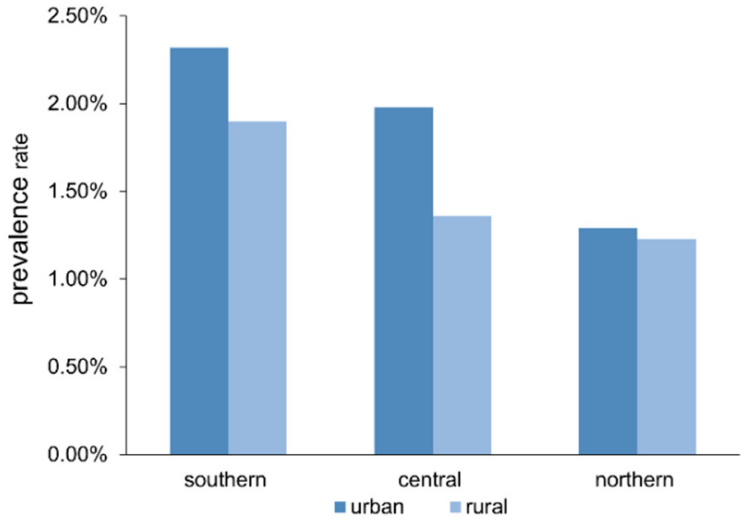

Figure 3. The prevalence rate of PIH by region and household classification.

greater demand of the multiple fetuses competing for oxygen and blood supply, but the exact pathology remains unclear [37].

GDM is one of the most common diseases to occur during pregnancy, and it often occurs in combination with PIH. Our study demonstrated that GDM is strongly related to an increased risk of PIH, corroborating findings from earlier reports. GDM is associated with an 87% increase in the risk of gestational hypertension in Australian women [38], a 148% increase in the risk of HDP in Chinese women [25], and a 93% increase in the risk of PE in the Latin American and Caribbean populations [33]. Increasingly, evidence indicates that insulin resistance is the common pathway of GDM and PIH [39].

Strengths and limitations

Our research has several strengths. First, this investigation provided updated information on the status of PIH in the Shaanxi Province of northwest China. Additionally, our large sample size, which accounted for 9% of all the newborns in Shaanxi province, provided sufficient power to evaluate the association between maternal and fetal characteristics and PIH. This study was the largest representative study in Shaanxi Province that provides the current status and potential risk factors for PIH in this geographical region. Several variables were analyzed that allowed us to control the effects of several possible risk factors and even analyze those risk factors with a low prevalence, including second-hand smoke exposure, alcohol drinking, multiple gestation, GDM, and fetal malformations.

Our study has several limitations. First, our questionnaire-based research, which relied on self-reported parameters to diagnose PIH may have resulted in a recall bias. We have taken a series of measures to reduce this bias, such as uniform training before the investigation and a pilot study. Second, most of the subjects were from rural areas that may have resulted in a low PIH detection rate. Third, other factors affecting PIH that were previously reported in the literature, such as pre-pregnancy BMI, maternal physical activity during pregnancy, or a familial history of PIH, were not included in this study. Medical histories were also not included in the questionnaire, such as histories of hypertension or diabetes, that may affect the correlation. A history of hypertension has been proved to be an important risk factor for PIH [22]. Although the mechanism between diabetes mellitus and PIH is unclear, women with diabetes mellitus seem to have a higher risk of PIH [22]. The relationship between medical history and PIH and its

Table 2. Univariate analysis of the determinants of PIH in Shaanxi Province

Baseline characteristics	NO-PIH n (%)	PIH n (%)	χ^2	*P* Values
Socio-demographic characteristics				
Maternal age, year			39.54	<0.001
<35	25115 (88.85)	364 (79.48)		
≥35	3151 (11.15)	94 (20.52)		
Mother's highest educational attainment			0.75	0.686
Primary school and below	3481 (12.15)	62 (13.30)		
junior school	14224 (49.64)	224 (48.07)		
Senior school and above	10947 (38.21)	180 (38.63)		
Monthly household income, yuan			5.64	0.060
≤2000	6469 (24.51)	13 (26.16)		
2000-4000	9349 (35.42)	170 (39.35)		
≥4000	10577 (40.07)	149 (34.49)		
Household classification			7.71	0.005
Urban	9384 (32.68)	181 (38.76)		
Rural	19333 (67.32)	286 (61.24)		
Region			11.36	0.003
Southern Shaanxi	5872 (20.45)	118 (25.27)		
Central Shaanxi	15454 (53.81)	256 (54.82)		
Northern Shaanxi	7391 (25.74)	93 (19.91)		
Lifestyles				
Second-hand smoke exposure				1.000*
No	28542 (99.73)	464 (99.78)		
Yes	76 (0.27)	1 (0.22)		
Alcohol drinking			1.40	0.236
No	28352 (98.87)	458 (98.28)		
Yes	324 (1.13)	8 (1.72)		
Comorbidities				
Gestational diabetes mellitus				0.000*
No	28646 (99.75)	458 (98.1)		
Yes	71 (0.25)	9 (1.93)		
Unstable mental status			11.13	0.001
No	27082 (94.38)	423 (90.77)		
Yes	1613 (5.62)	43 (9.23)		
Healthcare utilization				
Frequencies of prenatal checkups			5.60	0.018
<5	13351 (47.31)	193 (41.77)		
≥5	14867 (52.69)	269 (58.23)		
Reproductive history				
Parity			4.01	0.045
1	16423 (58.98)	250 (54.35)		
≥2	11422 (41.02)	210 (45.65)		
Neonatal characteristics				
Number of births			28.08	0.000
Single gestation	28384 (98.84)	449 (96.15)		
Multiple gestation	333 (1.16)	18 (3.85)		
Sex of the infant			0.21	0.647
Boy	15733 (54.81)	251 (53.75)		

Girl	12971 (45.19)	216 (46.25)		
Fetal malformation			32.54	0.000
No	28110 (97.89)	439 (94.00)		
Yes	607 (2.11)	28 (6.00)		

*analyzed using Fisher's exact probability test. PIH: pregnancy-induced hypertension.

Table 3. Predictors of PIH in Shaanxi Province using a multilevel model

Predictors	*β*	$S_{\overline{X}}$	*t*	*P* Values	*OR* (95% CI)
Socio-demographic characteristics					
Maternal age, year					
<35					1.00
≥35	0.72	0.14	5.27	<0.001	2.05 (1.55~2.70)
Mother's highest educational attainment					
Primary school and below					1.00
junior school	0.02	0.16	0.10	0.92	1.02 (0.73~1.41)
Senior school and above	0.03	0.19	0.17	0.87	1.03 (0.71~1.50)
Monthly household income, yuan					
≤2000					1.00
2000-4000	0.09	0.13	0.73	0.47	1.10 (0.85~1.42)
≥4000	-0.22	0.14	-1.51	0.14	0.81 (0.61~1.07)
Household classification					
Urban					1.00
Rural	-0.36	0.18	-1.98	0.06	0.70 (0.48~1.01)
Region					
Southern Shaanxi					1.00
Central Shaanxi	-0.24	0.21	-1.15	0.26	0.79 (0.51~1.21)
Northern Shaanxi	-0.35	0.25	-1.40	0.17	0.71 (0.42~1.18)
Lifestyles					
Second-hand smoke exposure					
No					1.00
Yes	-0.37	1.03	-0.36	0.72	0.69 (0.08~5.88)
Alcohol drinking					
No					1.00
Yes	0.15	0.43	0.34	0.74	1.16 (0.48~2.77)
Comorbidities					
Gestational diabetes mellitus					
No					1.00
Yes	1.77	0.42	4.24	<0.001	5.84 (2.42~14.11)
Unstable mental status					
No					1.00
Yes	0.40	0.18	2.24	0.03	1.49 (1.04~2.15)
Healthcare utilization					
Frequencies of prenatal checkups					
<5					1.00
≥5	0.07	0.12	0.56	0.58	1.07 (0.84~1.36)
Reproductive history					
Parity					
1					1.00

≥2	-0.01	0.12	-0.06	0.95	0.99 (0.78~1.26)
Neonatal characteristics					
Number of births					
Single gestation					1.00
Multiple gestation	1.15	0.27	4.27	<0.001	3.14 (1.82~5.45)
Sex of the infant					
Boy					1.00
Girl	0.05	0.10	0.47	0.64	1.05 (0.85~1.29)
Fetal malformation					
No					1.00
Yes	0.92	0.22	4.25	<0.001	2.52 (1.61~3.92)

PIH: pregnancy-induced hypertension. OR: odds ratio, 95% CI: 95% confidence interval.

mechanism should be analyzed in future studies.

Conclusion

Our findings reveal that there is a significant correlation between PIH and GDM, unstable mental status, maternal age, multiple gestation, and fetal malformations. Our study emphasizes that healthcare professionals should strengthen the monitoring of high-risk pregnant women with these risk factors for PIH. Our findings provide valuable clues about the etiology of PIH based on data from community-based populations and useful evidence to formulate effective policies and health care programs for PIH interventions in northwest China.

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Disclosure of conflict of interest

None.

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