

# Differences in epidemiology of patients with preeclampsia between China and the US (Review)

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**Abstract.** Preeclampsia (PE) is a complex complication that occurs during pregnancy. Studies indicated that morbidity from PE exhibits marked variations among geographical areas. Disparities in the incidence of PE between China and the US may be due to differences in ethnicity and genetic susceptibility, maternal age, sexual culture, body mass index, diet, exercise, multiple pregnancies and educational background. These epidemiological differences may give rise to differences between the two countries in terms of diagnostic and therapeutic criteria for PE. PE may be largely attributed to susceptibility genes and lifestyles, such as diet, body mass index and cultural norms regarding sexual relationships. The epidemiologic differences of patients with PE between the two countries indicated that appropriate prevention plans for PE require to be developed according to local conditions.

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## 1. Introduction

Preeclampsia (PE) is a common disorder associated with pregnancy, the symptoms of which are proteinuria and increased blood pressure that arises in previously normotensive females after 20 weeks of gestation and may influence multisystem function (1). Pre-eclampsia may cause issues in the brain, liver and kidneys, and aberrations in the clotting mechanism (2); it also represents a substantial risk for hypertension and associated cerebrovascular and cardiovascular disease (3). Worldwide, PE is one of the major causes of perinatal and maternal morbidity and mortality, particularly in middle- and low-income countries (4).

Worldwide, PE affects 2-8% of pregnancies. The incidence exhibits marked variations among countries and ethnicities (5). The present analysis suggested that the morbidity was higher in developing countries, particularly in Africa and Latin America (6,7), and that Asians may be a low-risk population for PE (8). Several studies have reported similar observations and a low incidence of preeclampsia in the Chinese of Asia, in New Zealand and in Asian Americans in comparison to Native Americans, African Americans and Europeans (9,7).

According to published data, during the last decade, the morbidity of PE reported in the US was higher than that in China (9,7). From 2004 to 2016, there was a decline in morbidity due to PE in China, while during 1980-2016, a yearly increase in morbidity was observed in the US (Fig. 1 and Table I) (10-18). These observations were in discordance with the previously determined higher incidence of PE in developing countries and led us to explore the reasons for this difference.

## 2. Pathological mechanisms of PE

According to the different onset of the condition, PE may be divided into early-( $<34$  weeks) and late-onset ( $>34$  weeks) PE (19). It is now recognized that early-onset and late-onset PE have different pathophysiologies, the former of which (also called placental PE), may be caused by the reduced

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maternal spiral arterial turnover in the first trimester and the latter (also called maternal PE) is related to reduced arterial turnover and increased placental perfusion (19). In early-onset PE, increased secretion of maternal serum angiogenic factor sFLT-1 and decreases in placental growth factor occur due to oxidative stress in the placenta (20). Fetal-derived trophoblast cells invade the maternal spiral artery and replace the endothelial cell layer in a normal pregnancy, which is called pseudo-angiogenesis or vascular mimicry process of vascular invasion, and trophoblasts differentiate from epithelial cells to endothelial cell phenotypes. However, in PE, trophoblasts cannot acquire the aggressive endothelial phenotypic characteristics, so the spiral arteries are insufficiently invasive, making them narrow and highly resistant (19). The changes of the above angiogenesis-related biomarkers are also used for monitoring and predicting PE (19). However, the above-mentioned highly recognized hypothesis does not appear to be directly related to the difference between the incidence and mortality of PE in China and the US. Subsequently, the potential risk factors were analyzed in the following context to help us prevent the occurrence of PE and even death due to PE.

### 3. Ethnic differences

A previous study indicated a variation in morbidity of PE among African Americans, Hispanics, Maori and Native Hawaiians (20). They then compared the rates of PE between Chinese living in Hawaii and Caucasians and the results indicated a higher risk of PE in the Chinese in Hawaii (20). However, the rates were also related to other factors, including the body mass index (BMI), maternal age, chronic hypertension, pregestational diabetes and smoking (20). Furthermore, a large retrospective cohort study from the UK observed that females of South Asia residing in the UK had an increased risk for PE compared with Caucasians (21). However, in another study performed from 2002 to 2011, in which 67,746 pregnant females participated, a lower prevalence of PE was observed in Chinese than in Caucasians (22). However, they did not distinguish between whether Caucasians were born or just lived in China. Furthermore, Chinese born in the US had a lower prevalence of PE than Chinese who lived in the US but were born in China (20). Besides the ethnic causes of the different rates of PE, other factors also contributed to increased risks of PE (20,22), which are summarized in Table II.

### 4. Susceptibility genes

In the pathogenesis of PE, a strong role for genetic factors is indicated by the ethnic groups' risk variations. Several genes have been determined to be associated with PE, such as inflammatory response, activation of endothelial cells and immunity (11,22,23); certain genes are susceptibility genes, while others are protective genes.

Studies of the Chinese Han population have reported that the vitamin D receptor gene with the G allele of rs2228570, the IL-10-1082A/G and -819T/C, IL-27 rs153109 and rs17855750 variants, as well as 11 $\beta$ -hydroxysteroid dehydrogenase and killer-cell immunoglobulin-like receptor genetic variations are related to PE (24-26). Cyclooxygenase-1195A homozygosity and variant growth arrest-specific 6 +1332 T allele were also

indicated to correlate with a reduced PE risk in the Chinese Han population (27-29).

The analysis of a subset of placentae with early-onset and severe PE indicated a racial variation in NK2 homeobox 5 expression, being higher expressed in Caucasians than in African Americans (30).

Best *et al.* (31) reported on the association between severe PE in a population of American Indians of Asian descent and a 3'UTR functional variant of the C-reactive protein (CRP) gene. They also indicated that the CRP variants rs876538 and rs3093068 were associated with PE in American Indians, additionally confirming a potential activity of CRP in PE (32).

### 5. Age

Various studies have explored the relationship of PE with advanced age of the mother (33,34). The risk of PE rises in an exponential manner with maternal age, particularly in females above the age of 40 years (35). Over the last few decades, a delayed maternal age at childbirth has been observed, particularly in high-income countries (36). There was an increase in the mean age of first-time mothers from 24.9 in 2000 to 26.3 in 2014 in the US (37). This trend was also observed in China and may be due to enhanced emancipation of females in these countries. The advanced maternal age (AMA) in China and the US over recent years was then compared. The usual definition of AMA is any pregnancy occurring when the mother's age exceeds 35 years (33,34). Fig. 2 indicates that more than 10 years later, the prevalence of AMA among patients with PE in China increased from 4.98 to 15.7% (35-42). By contrast, the prevalence of AMA in the USA decreased from 19.9 to 16.63% (43-45). Thus, as a rough estimate, AMA is more common in the US than in China.

### 6. Parity

The number of previous pregnancies with a gestational time of >20 weeks, irrespective of live birth or fetal death, is defined as parity. Several studies indicated that parous females experience an increased risk of PE compared with nulliparous females (46,47). Multiparity as a risk factor for PE was identified through a case-control study (odds ratio, 3.6; 95% CI: 2.6-5.0) (48). The shielding effect of multiparity remains to be fully elucidated and there may be a potential role of immune maladaptation and an immune reaction from the pregnant mother against paternal antigens resulting in PE (47). Furthermore, the risk of PE among multiparous females may possibly be lower due to desensitization after paternal antigen exposure in the placenta (49).

Most childbirths in China occur to nulliparous women due to the country's one-child policy. However, this policy was replaced by a universal two-child policy in October 2015 and the proportion of multipara began to increase and from 11.79% in 2005-2009 to 35.84% in 2015-2016 (50). However, the proportion of parturient females in China still exceeded that in the US (Fig. 3) (51,52).

### 7. Sexual culture

Further evidence demonstrates a role of the father in the onset of PE (52,53). Multiparous females who change partners are

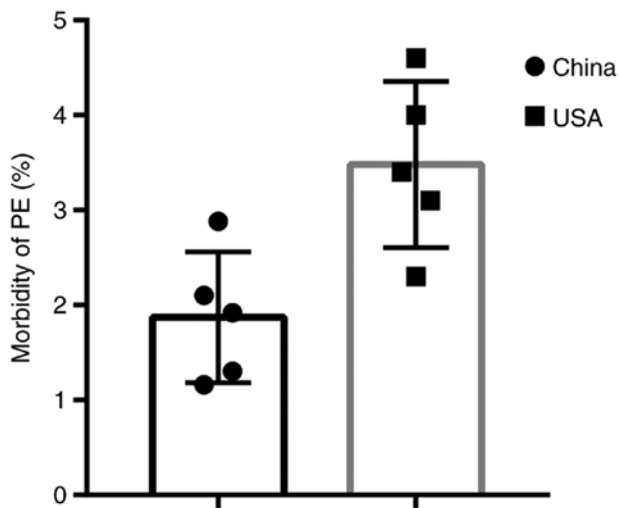


Figure 1. Morbidity of PE in China and the US. PE, preeclampsia.

frequently at an increased risk of PE in the following pregnancy in comparison to females who are multiparous and with the same partner (54). The PE risk increases in females who have no history of pregnancy and who changed partners; however, this risk decreases in females who already have a history of the condition (55). This is more or less universally accepted due to immunological tolerance.

Studies from the US indicated that 19% of females between the ages of 41 and 49 have more than one partner (49); however, due to the different cultures, there may be fewer partners for Chinese females than American females. Prior to conceiving, a stable sexual relationship is maintained by a majority of Chinese females for more than a year, usually with the same partner (11).

## 8. Obesity

In western countries, obesity with a BMI  $\geq 30$  kg/m<sup>2</sup> is a major health issue, which, in the 21st century, is prevalent at a rate of 20% in the US (54). Compared with American pregnant females, obesity is less prevalent in Chinese pregnant females (49,54-56). The percentage of obesity between Chinese and American populations was determined using the classification suggested by the World Health Organization (WHO). The population of patients with PE among pregnant women was categorized into four groups based on the BMI as follows: Underweight, BMI  $< 18.5$ ; normal,  $18.5 \leq \text{BMI} < 25$ ; overweight,  $25 \leq \text{BMI} < 30$ ; obese, BMI  $\geq 30$  (Fig. 4) (57,58).

The risk of PE is increased in obesity (59,60). Obesity and metabolic factors associated with obesity may bring about ischemia of the placenta and maternal vascular dysfunction to support the onset of PE (61).

The distribution of the BMI was different between Chinese and US Americans (Fig. 4), as obesity was more common in the US; however, the impact of a high BMI on PE in females from China was greater than that in Caucasians (46). This may be because of the higher body fat percentage in Chinese and the metabolic mechanism causing PE may be apparent even at a lower BMI in Chinese (62).

Table I. Incidence of preeclampsia in China and the US.

A, China			
Years	Cases	Morbidity (%)	(Refs.)
2004-2008	13273	2.10	(10)
2002-2011	67746	1.92	(11)
2011	112386	2.88	(12)
2005-2012	1208559	1.16	(13)
2013-2016	21577	1.30	(14)
Average		1.34	
B, US			
Years	Cases	Morbidity (%)	(Refs.)
2007	312207	4.00	(10)
1980-2010	1200000	3.40	(15)
2002-2010	36537061	2.30	(16)
2007-2011	2138012	3.10	(17)
2007-2016	1846535	4.60	(18)
Average		2.49	

## 9. Diet

The dietary patterns have a relationship with the risk of PE (63). Vegetables and Mediterranean diets are more protective against PE, while high meat/salt/fat diets increase the risk of PE (64,65).

The characteristic diet pattern in the US includes a high intake of white bread, potatoes, margarine and mixed meat, which is high in salt and calories. Compared to Americans, the Chinese have a lower fat intake and their diet includes higher amounts of vegetables, grains and soy and comparatively lower amounts of sweets, alcohol and meat. The differences in their intake may be the cause of the variations in the incidence of PE and a different BMI distribution.

Nutritional factors were indicated to be related to PE. Particularly supplementation of calcium has a vital role in preventing PE among females with nutrient deficiency (66). The WHO recommends that pregnant females take calcium supplements, particularly in the populations at high risk and with a low-calcium diet (67), as compared to Americans, the Chinese consume fewer dairy products, which are high in calcium.

## 10. Exercise

Studies have indicated the beneficial effects of exercise performed by pregnant females in preventing complications, such as PE (68,69). Exercising may prevent obesity, improve endothelial function, decrease oxidative stress and promote placental growth and vascular development (70).

Compared with American females, Chinese females are more sedentary throughout the whole pregnancy. This may be due to psychological fears specific to pregnancy such as

Table II. Summary of factors contributing to increased risk of preeclampsia.

Risk factor	Mean RR (95% CI)
Genetic susceptibility	Increased <sup>a</sup>
Lifestyle	Increased <sup>a</sup>
Diet (high salt and calories, low calcium)	
Physical activity (sedentary)	
Sexual culture (more than one partner)	
Low education	Increased <sup>a</sup>
Previous preeclampsia	7.19 (5.85-8.83)
Insulin-dependent diabetes	3.56 (2.54-4.99)
Multiple pregnancies	2.93 (2.04-4.21)
Nulliparity	2.91 (1.28-6.61)
Family history of preeclampsia	2.90 (1.70-4.93)
Obesity	2.47 (1.66-3.67)
Age >40 years	1.96 (1.34-2.87)
Preexisting hypertension	1.38 (1.01-1.87)

RR, risk ratio. <sup>a</sup>Risk for preeclampsia increased, but by how much is unknown.

miscarriage and physical factors such as increased stomach size and fatigue. Furthermore, in China, the excessive diagnosis of threatened abortion and preterm labor is common and has led numerous pregnant females to opt for bed rest.

### 11. Educational background

Evidence indicates that less-educated females are more likely to suffer from hypertensive disorders of pregnancy than those who are highly educated (71). A similar distribution of educational background was revealed in China and in the US (Fig. 5) (72,73).

### 12. Diagnosis

PE is defined as new-onset hypertension with a blood pressure of  $\geq 140$  mmHg (systolic) or  $\geq 90$  mmHg (diastolic) beyond pregnancy of 20 weeks along with the occurrence of the following new-onset conditions, alone or combined (74): i) Proteinuria albumin: Creatinine  $\geq 8$  mg/mmol or urine protein/creatinine ratio  $\geq 30$  mg/mmol or on dipstick testing  $\geq 1$  g/l [2+]; ii) Other dysfunctions of maternal organs, such as involvement of liver or kidney, hematological or neurological issues or dysfunction of the uterus or the placenta including aberrant umbilical artery Doppler waveform analysis, and restriction of growth of the fetus or stillbirth.

The classical criteria for diagnosing PE are proteinuria and hypertension. From 2002, there has been an important change in the criteria of the American College of Obstetricians and Gynecologists (ACOG) definition of PE, i.e., confirmation of proteinuria is not required if evidence of other organ damage is present (75). In China, the guidelines for PE were in accordance with the ACOG criteria; however, the new guidelines

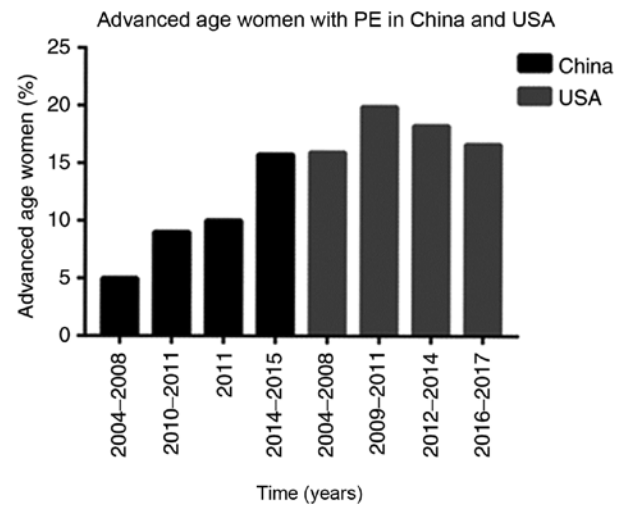


Figure 2. Percentage of patients with advanced maternal age in China and the US for over a decade. PE, preeclampsia. The X axis represents the years and references.

were implemented later in China than in the US and in certain areas of China, positive proteinuria is also required to diagnose PE (76). Indicators of organ damage such as headache, blurred vision and pain in the abdomen may be present and these observations may influence the reported incidence of PE in different countries (77).

### 13. Individual therapy for PE

The only effective way to eradicate PE is delivery, which increases the rate of preterm delivery. However, the modes of delivery vary between China and the US. In the US, the cesarean section rate was reported to be 62.1% in patients with severe PE (78), although a retrospective cohort study reported no obvious benefit from urgent delivery through cesarean on the outcomes of the mother and the infant among patients with severe PE (12). Furthermore, as per the ACOG recommendations, severe PE is not a complete contraindication to a labor induction clinical trial. However, in China, the rate of cesarean delivery among patients with severe PE was as high as ~88% (79).

To prevent the occurrence of PE, various options were put forward, such as a low-Na<sup>+</sup> diet, diuretics, as well as supplementation of Ca<sup>2+</sup> and Vitamin C and E (80). Among high-risk patients, administration of aspirin is advised at 11-14 weeks of gestation until 36 weeks due to the moderately reduced incidence of another type of PE, preterm PE (81). It is also worth mentioning that the approach proposed by the Aspirin for Evidence-based PE Prevention Trial for patients with preterm PE, comprising a single intervention of daily aspirin, may be beneficial but not suitable for pregnant females with chronic hypertension; however, there was no evidence of heterogeneity in the effects of aspirin in subgroups defined by maternal characteristics and obstetric history (81). According to the above-mentioned differences between the two countries, therapeutic or prevention measures may be implemented based on individual characteristics, e.g. in view of the differences between the two countries, including a lower proportion of individuals with AMA, multipara and obese patients among

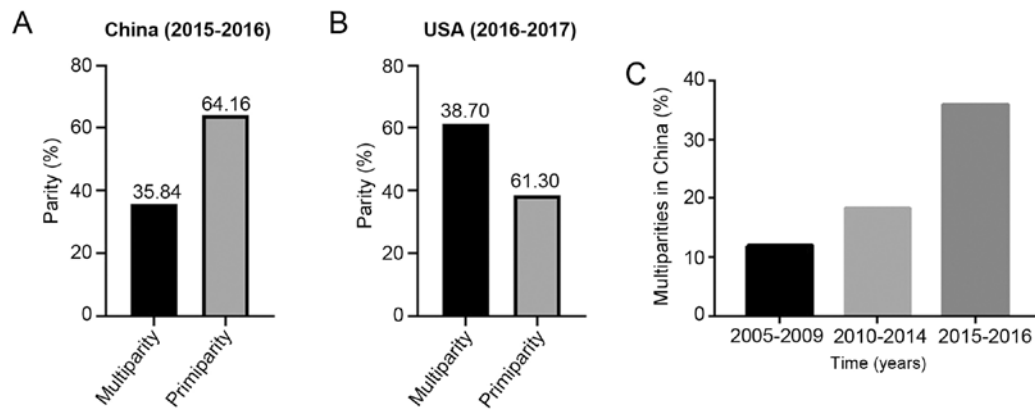


Figure 3. Proportion of multiparas in China and the US. The percentage of multipara and primipara with PE in (A) China from 2015 to 2016, and (B) the US from 2016 to 2017. (C) Proportion of multipara with PE in China from 2005 to 2016. PE, preeclampsia.

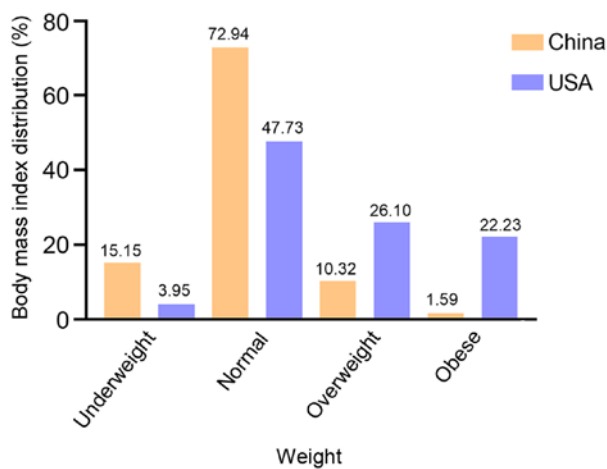


Figure 4. Body mass index distribution in Chinese and American patients with PE from 2014 to 2015. Compared with that in Chinese patients with PE, more obesity is observed in American patients with PE. PE, preeclampsia.

pregnant females in China compared with those in the US. For American pregnant females, it may be useful to prevent PE by lowering the age of pregnancy, reducing multipara, reducing weight appropriately and controlling weight gain during pregnancy. Furthermore, psychological stress may be a risk factor for pregnant females (82,83), which may be related to educational background and work intensity (which may be reflected by their salary). The present results indicated that Chinese females have a similar educational level distribution to Americans. Hence, regardless of whether pregnant females are Chinese or American, attention should be paid to adjusting their pace of life to reduce the potential risk of mental stress.

Once PE becomes severe and develops into eclampsia, antispasmodic therapy is required, i.e. magnesium sulfate therapy in the short term (<48 h), which features a rapid onset of action, an easily available antidote (calcium gluconate), lack of sedation and low cost (84).

#### 14. Limitations

Of note, the present study had certain limitations. First, China lacks a large-scale epidemiological investigation regarding the incidence of PE and most of the published data focused on

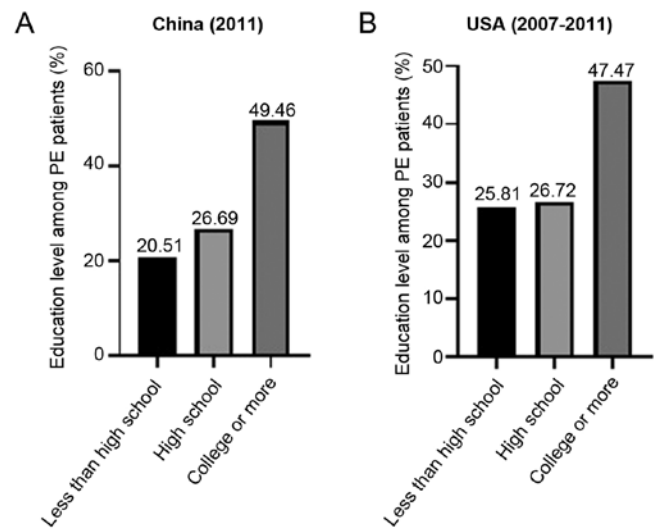


Figure 5. Level of education in (A) Chinese patients with PE in 2011 and (B) American patients with PE from 2007 to 2011. The educational background was nearly similar between Chinese and American patients with PE. PE, preeclampsia.

specific regions of China, which exhibit a wide geographical variation, such as smog/high air pollution. The occurrence of hypertensive disorders during pregnancy in central China was 1.23%, while it was 7.44% in Northern China, which may relate to the economic and medical status of the region (71). Thus, the incidences presented in this review may not reflect the total incidence of PE in China. Furthermore, the risk factors between China and the US require to be compared in the same period. It is difficult to obtain data for the same period and with the development of the economy and medical technology, the current corresponding data may be different. Finally, the present study was a comparative review and not a meta-analysis, and therefore, it is important to consider the heterogeneity among the studies and the bias risk for the published selected articles.

#### 15. Conclusions

The reasons for the variation in the incidence of PE between China and the US still remain to be fully elucidated. Certain

risk factors such as age and BMI may be involved, while others may be less conclusive for the Chinese population. Therefore, further exhaustive research is still required. PE may be mostly attributed to gene polymorphisms and life-style factors such as diet, BMI and cultural norms pertaining to sexual relationships. These risk factors may give rise to epidemiological differences among countries and may suggest that prevention measures, such as exercise and weight and stress reduction, should be scheduled according to local conditions.

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### Availability of data and materials

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### Authors' contributions

PS and LZ conceptualized the study and performed data analysis. NZ conceptualized the study, performed the literature search, collected and analyzed data and wrote the manuscript. SY, JZ and JL analyzed data. SY and BX performed the literature review and revised the manuscript. XC and SY performed the literature search. All authors have read and approved the final manuscript. Data authentication is not applicable.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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