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Title:

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Date:

2020-12-12

Citation:

Jing, S., Chen, C., Gan, Y., Vogel, J. & Zhang, J. (2020). Incidence and trend of preterm birth in China, 1990-2016: A systematic review and meta-analysis. *BMJ Open*, 10 (12), <https://doi.org/10.1136/bmjopen-2020-039303>.

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BMJ Open Incidence and trend of preterm birth in China, 1990–2016: a systematic review and meta-analysis

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To cite: Jing S, Chen C, Gan Y, *et al.* Incidence and trend of preterm birth in China, 1990–2016: a systematic review and meta-analysis. *BMJ Open* 2020;**10**:e039303. doi:10.1136/bmjopen-2020-039303

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-039303>).

SJ, CC and YG contributed equally.

SJ, CC and YG are joint first authors.

Received 10 April 2020

Revised 19 October 2020

Accepted 24 November 2020



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ABSTRACT

Objectives To update the WHO estimate of preterm birth rate in China in 1990–2016 and to further explore variations by geographic regions and years of occurrence.

Design Systematic review and meta-analysis.

Data sources Pubmed, Embase, Cochrane Library and Sinomed databases were searched from 1990 to 2018.

Eligibility criteria Studies were included if they provided preterm birth data with at least 500 total births. Reviews, case–control studies, intervention studies and studies with insufficient information or published before 1990 were excluded. We estimated pooled incidence of preterm birth by a random effects model, and preterm birth rate in different year, region and by livebirths or all births in subgroup analyses.

Results Our search identified 3945 records. After the removal of duplicates and screening of titles and abstracts, we reviewed 254 studies in full text and excluded 182, leaving 72 new studies. They were combined with the 82 studies included in the WHO report (154 studies, 187 data sets in total for the meta-analysis), including 24 039 084 births from 1990 to 2016. The pooled incidence of preterm birth in China was 6.09% (95% CI 5.86% to 6.31%) but has been steadily increasing from 5.36% (95% CI 4.89% to 5.84%) in 1990–1994 to 7.04% (95% CI 6.09% to 7.99%) in 2015–2016. The annual rate of increase was about 1.05% (95% CI 0.85% to 1.21%). Northwest China appeared to have the highest preterm birth rate (7.3%, 95% CI 4.92% to 9.68% from 1990 to 2016).

Conclusions The incidence of preterm birth in China has been rising gradually in the past three decades. It was 7% in 2016. Preterm birth rate varied by region with the West having the highest occurrence.

INTRODUCTION

Preterm birth before 37 completed weeks of gestation¹ is often considered as one of the indicators reflecting a country's health level and social development. Complications of preterm birth is the leading cause of child under-5 mortality globally and ranked first in the causes of perinatal mortality in China.^{2–3} The survival of preterm infants is at a greater risk of health problems both in the short and longer terms.⁴ In addition to the direct health problems and parenting psychological stress,⁵ preterm birth also causes enormous health-care costs.^{6,7} Data from Germany showed that

Strengths and limitations of this study

- This systematic review focused on the current status of preterm birth in China and summarised preterm birth rate over the past three decades.
- The meta-analysis updated the estimate of preterm birth rate over time and compared among geographic regions in China.
- The inclusion of stillbirth increased preterm birth rate, which calls for a standardised definition for international comparisons.
- Most included studies lacked information on the subtypes of preterm birth and the method of gestational age estimation, causing in-depth analysis difficult.

the average health costs of a preterm infant in the first year were €9717 EUR higher than that of a full-term infant.⁸ In 2005, it was estimated by the Institute of Medicine that the socioeconomic burden associated with preterm birth was at least US\$26 billion per year in the USA.⁹

The WHO estimates that the global preterm birth rate was 9.8% (uncertainty interval (UI): 8.3%–10.9%) in 2000, 11.1% (UI: 9.1%–13.4%) in 2010 and 10.6% (UI: 9.0%–12.0%) in 2014.^{10,11} Increasing preterm birth rates are affected by multiple factors, including an increasing proportion of pregnant women over 34 years old, greater use of assisted reproduction technology and increasing number of multiple births.¹² Improvement in maternal and perinatal healthcare increases survival of extremely preterm and very preterm infants, who otherwise might have been stillbirths.^{13,14} A 2005 study from 16 provinces in China showed that the incidence of preterm birth among 42 139 livebirths was 7.8%.¹⁵ In 2011, Zou *et al* conducted a multicentre survey including 107 905 livebirths from 14 provinces in China reporting a preterm birth rate of 7.1%,¹⁶ which differed substantially from the incidence of 11.0% of singleton livebirths from

63 tertiary hospitals in 23 provinces in China between 2011 and 2014.¹⁷ Yet our multicentre cross-sectional survey involving 89 hospitals in 25 provinces in China has showed that the incidence of preterm birth was 7.3% between 2015 and 2016.¹⁸ In addition to the variations among different studies, the trend of preterm birth rate in China over the past three decades remains unclear. It is also worth noting that China opened two-child policy in 2015.¹⁹ As more families choose to have a second baby, whether the incidence of preterm birth is impacted needs to be explored. Therefore, our study aims to update the WHO estimate of preterm birth rate in China from 2014 to 2016 and to further explore variations by geographic regions and years of occurrence.

METHODS

This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (online supplemental table S1).

Search strategy

Recently, WHO published a review on global, regional and national estimates of levels of preterm birth rate in 2014.¹¹ Of note, the literature search was performed in February 2016 and articles published from 1990 to 2016 were screened. Our team participated in the study and conducted literature review of Chinese literature. This study is an update of the estimate for China. We followed the same search strategy and data extraction method as the previous paper for the maximal compatibility. In February 2019, we searched articles published from 2016 to 2018 in the same databases, including Pubmed, Embase, Cochrane Library and Sinomed using the same term as 'preterm birth', 'preterm labour', 'preterm delivery', 'premature labour', 'premature birth', 'premature delivery', 'pprom' or 'premature foetus membrane rupture', cross-referenced with 'China', without language restrictions but restricted to the six most highly cited Chinese medical journals in the Sinomed database. The search strategy is found in online supplemental table S2. Since the publication year of articles in our search had overlapped with WHO's search, we removed the duplicate articles in the title and abstract screening step. It should also be noted that there was, on average, a 2-year time lag between the study year and publication year. Thus, while our literature search was up to 2018, the study year was up to 2016.

Selection criteria

Studies were eligible if preterm birth rate was reported in at least 500 total births in Chinese population.²⁰ Reports using livebirths or all births as the denominator were all eligible. We excluded reviews, case-control studies, experimental studies or those lacking sufficient information to determine the preterm birth rate. Studies collected before 1990 (or where the time period of collection was not reported) were not eligible. Where there

were multiple reports from the same study population, we used only the data with most comprehensive information. Studies focusing on high-risk population only or reporting preterm birth rate less than 3% were also excluded on the basis of biological implausibility.²¹

Data extraction and quality assessments

After removing duplicates, two reviewers screened all titles and abstracts and then assessed the full text of potentially eligible articles independently. For each eligible report, extracted data including author, publication year, region, study design, year of data collection, method of estimating gestational age (GA), definition of preterm birth (per 100 livebirths or all births, singletons or singletons and multiples) and rate of preterm birth. A midpoint year was assigned to each study. Any disagreements were resolved by discussion or a third reviewer.

We assessed the quality of the included studies by the scales recommended by the Agency for Healthcare Research and Quality (AHRQ). For cross-sectional studies, we used a scoring approach of 11 items to grade quality, and publications scored 8–11 points were deemed to be of high quality, whereas a score of 4–7 represented moderate quality and a score of 0–3 represented low quality.²² For cohort studies, we used the Newcastle-Ottawa Scale recommended by AHRQ to grade quality, which contains three perspectives including the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or the outcome of interest.²³ Publications with a total score of 7–11 were deemed to be of high quality.

Statistical analyses

To calculate the preterm birth rate in China, we conducted a meta-analysis of the included studies using R V.3.4.4. We evaluated the heterogeneity among studies using both the Cochran Q test statistic and I² statistic and assumed a random effects model because of a clear heterogeneity in the included studies. Subgroup analyses and meta-regression were conducted to explain the potential sources of heterogeneity. Factors that were investigated included the midpoint year of data collection, administrative region, method of estimating GA and the definition of preterm birth. In our analysis, we calculated the preterm birth rate in livebirths from the reports using livebirths as the denominator and all births from the reports using all births as the denominator, respectively. All studies (regardless of denominator population) were used to calculate the preterm birth rate. Publication bias was assessed by funnel plot and Egger's linear regression tests. The annual rate of increase = $(PTB_{2015-2016}/PTB_{1990-1994})^{(1/26)} - 1$ ($PTB_{2015-2016}$: the preterm birth rate in 2015–2016, $PTB_{1990-1994}$: the preterm birth rate in 1990–1994).

Patient and public involvement

There was no involvement of patients or the public in any part of this research.

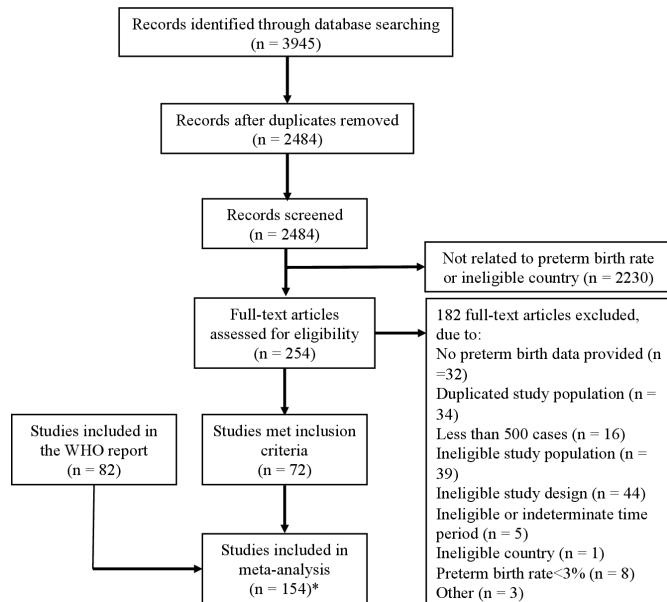


Figure 1 Study selection. *The 154 eligible studies included 187 datasets.

RESULTS

A total of 3945 records were identified. After removal of duplicates and initial screening on the basis of the title and abstract, we reviewed 254 studies in full text. Of these publications, 182 articles were excluded, including 44 were ineligible study design, 39 investigated patients with high-risk for preterm birth, 34 had a duplicated population with other studies, 32 did not provide preterm birth data, 16 had a sample size fewer than 500 patients, 8 had a preterm birth rate less than 3%, 5 had ineligible or unknown year of data collection and 4 were from out of China or had other reasons. After exclusions, we kept 154 studies in the meta-analysis, 82 of which were included in the WHO report¹¹ while 72 studies were new. These studies employed 187 data sets (figure 1 and online supplemental table S3).^{16 17 24–175}

These studies were conducted in seven administrative regions of China, including 41 from the East, 40 from the North, 18 from the South, 16 from the Central, 9 from the Southwest, 6 from the Northwest, 1 from the Northeast, 17 from Hong Kong, Macau and Taiwan and the rest of 39 from multiple provinces. Of the 187 data sets, 110 calculated preterm birth rate in livebirths only, 15 in all births (livebirths and stillbirths) and other 62 data sets did not specify live birth or all births. In terms of epidemiological design, 61 were cross-sectional studies and 93 were cohort studies. According to the quality criteria recommended by AHRQ, 42 studies were high quality, 100 were moderate quality and the remaining 12 were low quality. All included studies defined preterm birth as a delivery before 37 weeks of gestation. Thirty-nine studies estimated GA by last menstrual period (LMP) combined with ultrasound, 39 studies estimated GA by LMP, 5 studies estimated by ultrasound. Among 154 studies, 97 studies included singletons only, 25 studies

included both singletons and multiples and 32 studies are unknown.

The estimated pooled preterm birth rate in China from 1990 to 2016 was 6.09% (95% CI 5.86% to 6.31%) overall, ranging from 3% to 16.28%, with considerable heterogeneity ($I^2=99.8\%$, $p<0.0001$). The estimated preterm birth rate by region was as follows: 5.67% (95% CI 4.26% to 7.09%) in the Central, 6.19% (95% CI 5.66% to 6.73%) in the East, 5.48% (95% CI 4.96% to 6.01%) in the North, 3.8% (95% CI 2.4% to 5.21%) in the Northeast, 7.3% (95% CI 4.92% to 9.68%) in the Northwest, 6.14% (95% CI 5.96% to 6.32%) in the South, 6.96% (95% CI 4.94% to 8.99%) in the Southwest and 6.13% (95% CI 5.55% to 6.71%) in Hong Kong, Macau and Taiwan. Only one study was from the Northeast, thus the preterm birth rate may not be reliable. (figure 2)

The pooled preterm birth rate in China was 6.00% (95% CI 5.69% to 6.3%) for livebirths and 7.01% (95% CI 5.9% to 8.12%) for all births (livebirths and stillbirths). The rate has been increasing in the past three decades, from 5.36% (95% CI 4.89% to 5.84%) in 1990–1994 to 7.04% (95% CI 6.09% to 7.99%) in 2015–2016 (table 1). The average annual rate of increase was 1.05% (95% CI 0.85% to 1.21%).

Univariate meta-regression analysis suggested that the midpoint year ($p<0.001$), administration region ($p=0.009$), definition of preterm birth (livebirths/all births ($p=0.021$), singletons or singletons and multiples ($p=0.013$)) and method of estimating GA ($p=0.095$) might have contributed to the heterogeneity, whereas we detected no significant differences in quality level of study ($p=0.376$). We further conducted multivariate meta-regression, which showed that midpoint year, administration region, and definition of preterm birth (singletons or singletons and multiples) might be sources of heterogeneity. The funnel plot did not suggest any publication bias ($p=0.097$) (figure 3).

We performed a sensitivity analysis where the low-quality studies were excluded. The results remained essentially the same (online supplemental table S4), confirming that the results were unlikely confounded by the quality of studies.

DISCUSSION

Our study shows that the pooled preterm birth rate in China was 6.09% (95% CI 5.86% to 6.31%) between 1990 and 2016. The incidence of preterm birth has been increasing in China in the past three decades, from 5.36% (95% CI 4.89% to 5.84%) in 1990–1994 to 7.04% (95% CI 6.09% to 7.99%) in 2016. The annual rate of increase was 1.05% (95% CI 0.85% to 1.21%). Preterm birth rate differed by regions, among which West China showed the highest preterm birth rate.

Preterm birth is officially defined as a delivery between 28 and 37 completed weeks of gestation in China.¹⁷⁶ With the development and popularisation of prenatal diagnosis and perinatal care, more and more compromised

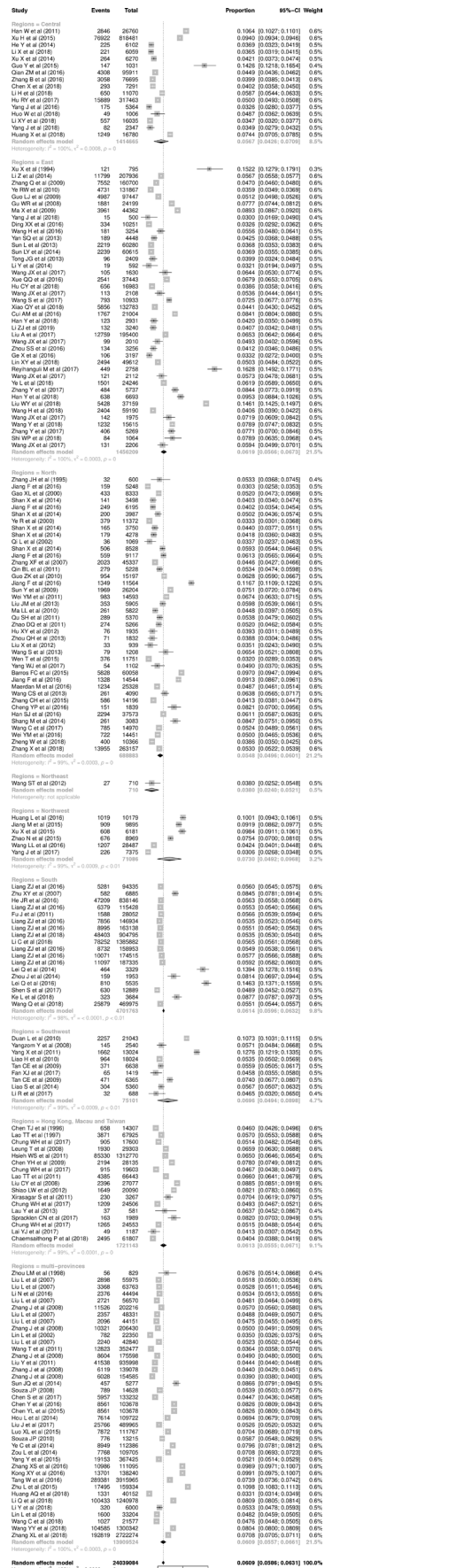


Figure 2 Random effects meta-analysis of preterm birth in China.

fetuses are recognised and born even before 28 weeks of gestation. Many of these extremely preterm births can now survive and included in the statistics of preterm birth. Iatrogenic preterm birth related to medical intervention accounted for a large proportion of preterm birth in China,¹⁸ which may be one of the reasons for the gradual increase in preterm birth rate in recent years. In addition, inclusion of stillbirths in the denominator population increased the overall preterm birth rate. Similarly, Morisaki *et al* found that in a multicountry analysis of the WHO Multi-Country Survey on Maternal and Newborn Health that compared with the preterm birth rate based on livebirths alone, the inclusion of stillbirths had substantially increased the preterm birth rate, which could reflect international disparities in perinatal health more accurately.¹⁷⁷ Their findings are in line with our finding in our univariate meta-regression that preterm birth rate was higher in all births (7.01%, 95% CI 5.9% to 8.12%) than that in livebirths only (6.0%, 95% CI 5.69% to 6.3%), indicating that preterm birth as a public health problem may be more severe than expected. Not only appropriate prevention and management strategies but also more research on aetiology and pathogenesis are needed to reduce preterm birth rate in China.

Assisted reproductive technology (ART) is being increasingly used in China. One nationwide survey of ART from 178 reproductive centres and 13 sperm banks demonstrated that total ART cycle procedures of in vitro fertilisation increased from 78 002 during 1981–2004 to 393 538 during 2005–2011 in China.¹⁷⁸ ART is a known risk factor for preterm birth for both singleton and multiple pregnancies.¹⁷⁹ Meanwhile, the risk of prematurity is much higher in twins than in singletons.¹⁸⁰ Therefore, the popularity of ART may also be one of the possible reasons for the gradual increase in preterm birth rate in China since 1990. Recently installed two-child policy may also be a factor for the increasing preterm birth rate since 2015 as women who had second child were often in advanced age, which is a risk factor for preterm birth.¹⁷⁹

Subgroup analysis in different administration regions showed that the preterm birth rate was highest in the West, of which the preterm birth rate was 7.3% (95% CI 4.92% to 9.68%) in the Northwest and 6.96% (95% CI 4.94% to 8.99%) in the Southwest. The preterm birth rate in Hong Kong, Macau and Taiwan was estimated to be 6.13% (95% CI 5.55% to 6.71%), which was close to that in the Central and North China. The high preterm rate in the West may be associated with a lower socioeconomic status.¹⁸¹ On the other hand, the Northeast appeared to have the lowest preterm birth rate. Although only one study was included in our meta-analysis, the preterm birth rate in Northeast (3.8%, 95% CI 2.4% to 5.21%) was in line with our multi-centre survey in which the preterm birth rate was 5.2% (95% CI 4.4% to 6.0%).¹⁸ Studies showed that height is inversely associated with the risk of preterm birth.¹⁸² Since women in Northeast China is generally taller,¹⁸³ this may partially explain the lowest preterm birth rate in that region. It is also a possibility that as the fetuses there tend

Table 1 Pooled incidence of preterm birth in China, 1990–2016

Characteristic	Number of studies	Number of births	Preterm birth rate (%)		Heterogeneity		Multivariate meta-regression*	
			Estimate	95% CI	I ² (%)	Coefficient	95% CI	
Administration region†								
Central	16	1414665	5.67	4.26 to 7.09	99.9	Ref	Ref	Ref
East	41	1456209	6.19	5.66 to 6.73	99.5	0.007	0.007	−0.002 to 0.016
North	40	688883	5.48	4.96 to 6.01	98.7	−0.003	−0.003	−0.013 to 0.006
Northwest	6	71086	7.3	4.92 to 9.68	99.4	0.021	0.021	0.007 to 0.035
South	18	4701763	6.14	5.96 to 6.32	98.1	0.015	0.015	0.005 to 0.025
Southwest	9	75101	6.96	4.94 to 8.99	99.1	0.014	0.014	0.001 to 0.026
Hong Kong, Macau and Taiwan	17	1721143	6.13	5.55 to 6.71	99.1	0.010	0.010	−0.001 to 0.022
Multiprovinces	39	13909524	6.09	5.57 to 6.61	99.9	0.012	0.012	0.003 to 0.022
Year								
1990–1994	9	417378	5.36	4.89 to 5.84	96.5	Ref	Ref	Ref
1995–1999	21	1644484	4.6	4.25 to 4.95	99.1	−0.012	−0.012	−0.024 to 0.0001
2000–2004	13	2774165	5.68	4.91 to 6.45	99.8	−0.001	−0.001	−0.014 to 0.012
2005–2009	42	5012931	6.54	6.08 to 6.99	99.7	0.006	0.006	−0.005 to 0.017
2010–2014	88	13288977	6.17	5.85 to 6.48	99.8	0.005	0.005	−0.006 to 0.016
2015–2016	14	901149	7.04	6.09 to 7.99	99.6	0.016	0.016	0.003 to 0.029
Denominator‡								
Live births only	110	17931691	6.00	5.69 to 6.3	99.9	Ref	Ref	Ref
All births	15	661838	7.01	5.9 to 8.12	99.7	0.004	0.004	−0.005 to 0.012
Unknown births	62	5445555	6.02	5.68 to 6.36	99.5	0.004	0.004	−0.001 to 0.009
Method of estimating GA								
LMP	54	15903912	5.79	5.39 to 6.20	99.9	Ref	Ref	Ref
Ultrasound	5	176565	5.47	3.96 to 6.99	99.4	−0.011	−0.011	−0.016 to 0.013
LMP and ultrasound	40	5517976	6.59	6.06 to 7.13	99.8	0.004	0.004	−0.003 to 0.011
Unknown	88	2440631	6.09	5.74 to 6.44	99.2	0.003	0.003	−0.003 to 0.009
Singletons/multiples								
Singletons only	121	15766450	5.84	5.58 to 6.10	99.8	Ref	Ref	Ref
Singletons and multiples	33	1653911	6.69	5.81 to 7.57	99.8	0.015	0.015	0.008 to 0.022
Unknown	33	6618723	6.44	5.95 to 6.94	99.8	0.006	0.006	−0.0001 to 0.012

*Adjusted variable: quality level of studies.

†Only one study was from Northeast China, in which the preterm birth rate was 3.8% (95% CI: 2.4% to 5.21%). The meta-regression showed no significant difference between Northeast and Central China.

‡All births: livebirths and stillbirths. Unknown births: does not specify live birth or all births. GA, gestational age; LMP, last menstrual period.

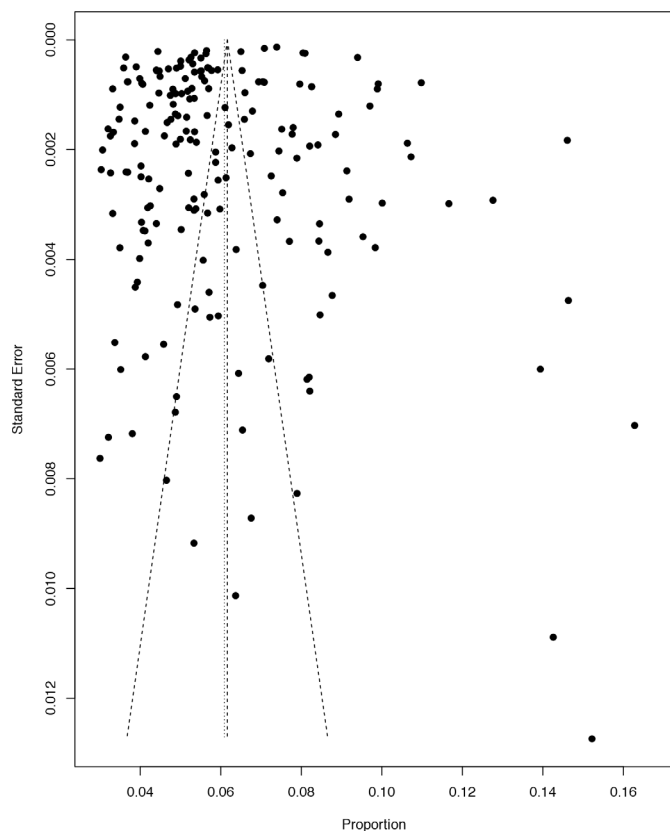


Figure 3 Funnel plot of preterm birth prevalence as a function of prevalence estimate SE.

to be larger, ultrasound might overestimate the GA, and therefore reduce the incidence of preterm birth.

Our meta-analysis has some limitations. First, although the upper limit of the definition of preterm birth is globally accepted as 36 weeks+6 days, the lower limit ranges from 20 to 28 weeks in different part of the world.¹¹ Many reports in our study did not provide a clear lower limit of gestational week. Second, ultrasound early in pregnancy is considered the gold standard for assessment of GA, but many studies did not specify the method of assessing GA. Though LMP combined with ultrasound to assess GA was predominant assessment method in China, no specific data are available. However, it is likely that the degree of ultrasound use in pregnancy varies with availability of medical resources in different settings and regions. Women only relied on the first day of the LMP might bias the preterm birth rate. The high preterm birth rate in low socioeconomic regions may result from both misclassification and truly higher preterm birth rate. Third, most studies did not provide more detailed information on the subtypes of preterm birth (spontaneous onset, iatrogenic and rupture of the membranes) or the causes of preterm birth, making more in-depth analysis difficult.

Subgroup analysis did not explain the specific causes of heterogeneity ($I^2 > 50\%$). We conducted univariate meta-regression analysis on various sources and identified significant differences in year, regions and definition of preterm birth, suggesting that these factors might be the main cause of heterogeneity in this meta-analysis.

Meanwhile, multivariate meta-regression showed that the West had a higher preterm birth rate than other regions. Compared with 1990–1994, preterm birth rate was higher in 2015–2016. Additionally, the rate was higher in all births than in singletons only. Method of estimating GA was not associated with heterogeneity.

In summary, our meta-analysis showed that the preterm birth rate has been rising in China over the past three decades. It was around 7% in 2016. Preterm birth rate varied by region with the West having the highest occurrence.

Contributors JZ and JV conceived and designed the study. Screening was carried out by SJ, CC and YG. SJ and CC analysed the data and drafted the manuscript. All author commented and revised the final version of this article.

Funding This work was supported by the Shanghai Municipal Health Commission (GWIV.26) and the Shanghai Jiao Tong University School of Medicine Doctoral Student Innovation Fund, grant number BXJ201907.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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