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Adverse pregnancy outcomes in Guangdong province, China, 2014-2017: a spatio-temporal analysis of 2.9 million births

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Abstract

Objectives Adverse birth outcomes pose a great threat to the public health and bring a heavy burden of disease in China. A comprehensive examination of the temporal and spatial trends of preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) epidemics can provide some elementary information for subsequent etiological and epidemiological studies. This study aimed to characterize the spatio-temporal features of PTB, LBW, and SGA based on a large cohort of live births in China.

Design Spatio-temporal descriptive analysis was performed in Guangdong province, China, from 2014 to 2017.

Setting Data involving 2,917,098 live births in Guangdong province, China from 2014 to 2017 was collected from Guangdong Birth Certificate System. Information was collected, including the date of birth, gestational age in week, birth weight, sex of the infant, age of the mother, and registered residence of the mother.

Results The estimated rate of PTB, LBW and SGA was 4.16%, 4.14% and 12.86%, respectively. For temporal trends, the rates of PTB, LBW and SGA showed seasonal fluctuations, especially for LBW and SGA. In addition, there were regional differences in the rates of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. From 2014 to 2017, the high rates of PTB and LBW expanded from the Pearl River Delta region to the Non-Pearl River Delta regions. However, compared with the Pearl River Delta region, the rate of SGA was higher in the Non-Pearl River Delta regions on the whole.

Conclusion The findings of this study contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA in south China.

Keywords: Preterm birth; Low birth weight; Small for gestational age; Spatial; Temporal

Strengths and limitations of this study

1. This study is one of the few studies based on a large cohort of newborns to reveal the current situation of adverse birth outcomes in China.
2. The findings of this study contribute to the better understanding of the characteristics of time trend and geographical distribution of adverse pregnancy outcomes in south China.
3. As a descriptive analysis, this study was unable to identify the causal relationship between spatio-temporal factors and adverse pregnancy outcomes.
4. Delays in reporting birth certificate data at small hospitals in different cities may cause bias.

Introduction

Previous studies [1, 2] suggested that severe infant morbidity and mortality partly resulted from adverse birth outcomes including preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA). PTB is defined as a live-birth infant with less than 37 complete weeks of gestation [3]. LBW is defined as a live-birth infant weighing less than 2,500 grams at birth [4]. SGA is defined as an infant whose birth weight falls below the 10thpercentile by sex and gestational week of all singleton live births [5]. With the development and progress of society and the continuous improvement of the level of medical care, the health condition of infants and young children has been significantly improved. However, adverse pregnancy outcomes such as PTB, LBW and SGA have not been effectively controlled, which has become an important risk factor for infant health. PTB rates were reported ranging from 6.2 % to 11.9% of live births in some developed and developing countries [6].In fact, the incidence of LBW in developed countries is still high, and even rising [7]. Among 135 million infants born in low and middle income countries in 2010, it is estimated that 29.7 million (22%) were term births of SGA, and 2.8 million (2.1%) were preterm births of SGA [8]. Overall, these adverse birth outcomes pose a great threat to the health of infants.

Additionally, the adverse outcomes of PTB, LBW and SGA may also increase the risk of chronic diseases or developmental outcomes later in life [9, 10]. These facts show that PTB, LBW and SGA are still challenging problems of public health in many countries. Thus further research is needed to investigate the epidemiology of these problems more comprehensively. Many previous studies described significant seasonal variations of PTB, LBW or SGA with remarkable differences between regions [11, 12]. However, some researches didn't detect an association between temperature and adverse pregnancy outcome [13-15]. In fact, the conditions of evidence differed among different regions and studies. The complexity of PTB, LBW, SGA and relevant risk factors in the individual, social and spatial levels often make the causal relationship between identified risks and responses non-stationary in space and time. A comprehensive examination of the temporal and spatial trends of PTB, LBW, and SGA can provide some basic elements for subsequent etiological and epidemiological studies.

Therefore, in order to fill in the gap, we performed a spatio-temporal analysis of PTB, LBW, and SGA, based on a large cohort involving approximately 3 million newborns in Guangdong province, China from 2014 to 2017. This study is more convincing because of the relatively large investigated samples. Additionally, this study analyzed regional differences of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. In general, the Pearl River Delta regions represent economically developed regions in Guangdong province, while Non-Pearl River Delta regions represent relatively underdeveloped regions. The findings of this study will contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA, and the design of prevention and intervention strategies for specific geographical areas and high-risk populations

Materials and methods

Patient and Public involvement

All birth data in this study was obtain from Guangdong Birth Certificate System and was only used for statistical analysis. Information of newborn and mothers across Guangdong province were collected in this study. No patients or public were involved in development of research question, study design, conduction of research and measurement of outcome. There are no plans of disseminating research results to participants. Ethical approval was obtained from ethics committee of Guangdong Woman & Children Hospital.

Data preparation

All birth data was collected from the Guangdong Birth Certificate System, which collects information of infants and young children from medical institutions in Guangdong province. After childbirth, obstetric medical staff put the baby on an electronic scale, record stable weight data. Health care workers or midwives fill out the delivery information of the newborn in the regional maternal and child information system. The logical settings of the system have been corrected to ensure the convincing records. Finally, the information will be transferred to the Guangdong Birth Certificate System. After the data being imported, the midwife director and the hospital doctor director need to confirm the birth information. Before the birth certificate is issued, the department of medical management and the parents should check the birth information again. All the information is verified by medical professionals. The birth registration database contains the date of birth, gestational age in week, birth weight, sex of the infant, parity, age of the mother, and registered residence of the mother. All live newborns were included in the study except for stillbirths, deaths within days of birth and permanent birth defects. To reduce bias, the subset of births was limited to singleton live births with 22-42 completed weeks gestation [16]. After further excluding births with implausible birth weights (less than 500 grams) [17] and verifying data, we included a total number of 2,914,198 births in our analysis.

Data analysis

We described basic characteristics of the newborns and mothers, and the rates of PTB, LBW and SGA according to the studied characteristics by year was estimated and compared using χ^2 test. In order to observe the temporal trends in the occurrence of PTB, LBW and SGA in the study site, we calculated daily rates of PTB (daily number of live births with gestational age less than 37 weeks/daily number of live births × 100%) [3], daily rates of LBW (daily number of live births with birth weight less than 2500 g / daily number of live births × 100%) [4], daily rates of SGA (daily number of live births with birth weight less than the 10th percentile of the normal average birth weight at the same gestational age/daily number of live births at the same gestational age × 100%) [18], respectively. We determined the season of birth based on the birth date (spring: March-May, summer: June-August; autumn: September-November, winter: December-February). Heatmaps of weekly average rates of PTB, LBW and

SGA were drew to investigate whether the rates exhibited an obvious seasonality.

According to economic conditions, Guangdong province can be divided into Pearl River Delta regions and Non-Pearl River Delta regions. Pearl River Delta regions are economically developed regions, including Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Zhaoqing, Huizhou and Jiangmen cities. By contrast, Non-Pearl River Delta regions are relatively underdeveloped regions, including Shantou, Chaozhou, Jieyang, Shanwei, Zhanjiang, Maoming, Yangjiang, Yunfu, Shaoguan, Qingyuan, Meizhou and Heyuan cities. Besides, city boundary shape files of Guangdong province were publicly obtained and used for mapping and spatial cluster detection of the adverse birth outcomes. We mapped the spatial distributions of rates for the adverse birth outcomes to investigate the spatial distributions pattern of the birth outcomes through 2014 to 2017. SAS software version 9.3 (SAS Institute Inc.; Cary, NC, the United States) was used for the statistical analyses. All statistical tests were 2-tailed. *P*-value less than 0.05 were considered to be statistically significant.

Results

Figure 1 shows the geographical locations of the study in Guangdong province. Guangdong province is located in southern China and is also currently the most populous province in China. From 2014 to 2017, there were 2,917,098 live newborns in Guangdong province, among which 1,254,102 were born in Pearl River Delta regions, accounting for 42.99%. There were 1,553,948 births (53.27%) were boys. There were 794,755 babies (27.24%) born in 2016, which accounts for a large proportion from 2014 to 2017. As illustrated in Table 1, the proportion of mothers who aged less than 20, 20 to 24, 25 to 29, 30 to 34, and over 35 years old was 2.68%, 22.78%, 39.87%, 23.38% and 11.29%, respectively. For the seasons of birth, the proportion of babies born in spring, summer, autumn and winter was 23.16%, 24.61%, 27.57% and 24.66%, respectively. There were 56,748 (42.96%) LBW of preterm births, while there were 63,968 (52.93%) LBW of term births. Regarding SGA infants, 2.47% were preterm births, while 97.53% were term births.

Table 2 reveals that the rates of PTB, LBW and SGA according to demographic characteristics, residence address and birth seasons by year. Infants born from women aged less than 35 years have higher rates of LBW and PTB outcomes than women younger than 35 years old. However, the rates of the difference were gradually decreasing from 2014 to 2017. From 2014 to 2016, there was a downward trend in the rates of SGA among pregnant women who were not less than 35 years old and less than 35 years old. In 2017, the rates for SGA by two groups of pregnant women rose slightly. Generally, infants who were born in the Pearl River Delta regions had higher rates of PTB and LBW than those who were born in Non-Pearl River Delta regions in Guangdong. However, infants who were born in the Pearl River Delta regions tended to have lower rates of SGA than those who were born in Non-Pearl River Delta regions. Boy and girl babies tended to be similar in the rates of the outcomes. We found the PTB rates of boys were higher than that of girls, among which the highest rate was in 2016 (5.02%). Besides, the LBW rates of girls were higher than that of boys, among which the highest rate was in 2017 (4.78%). For SGA, the highest rate was 14.46% in the girls group. In addition, the rates of PTB, LBW and SGA statistically varied among seasons of birth, respectively. For PTB, the highest rates were clustered in winter. For LBW, the highest rates did not show cluster tendency of season. However, for SGA, the highest rates were clustered in summer or autumn.

Figure 2 depicts daily time-series plots of the rates for the adverse pregnancy outcomes including PTB, LBW and SGA. Upon visual inspection, the rates of PTB, LBW and SGA show, to some degree, seasonal fluctuation trends, especially for the outcomes of PTB and SGA. In 2014, the rate of PTB ranged from 2.45% in October to 6.06% in February. The period of highest rates of PTB was between December and February. In 2015 and 2016, the rates of PTB in November were the lowest in the course of the year. In contrast, in 2016 and 2017, the highest rates of PTB were in October. In 2014, infants had a peak rate (5.61%) of LBW in September. Infants born from February to April were least likely to suffer from LBW, with the lowest rate

(2.55%) in March. In 2017, there was a similar pattern for LBW infants with the rate (2.80%) in February, which clearly lower than the figure between September and October. Additionally, the peak rate (6.30%) of LBW occurred in October. The average of daily rates of SGA was 14.30% in this study. During the period from 2014 to 2017, infants were least likely to suffer from SGA between January and March, which is similar to the outcome of LBW. In addition, infants were most likely to suffer from SGA between September and October.

Figure 3 depicts the heatmaps of weekly average rates for PTB, LBW and SGA across cities in Guangdong province, from 2014 to 2017. For most cities, there was a remarkable seasonality in the rates of the adverse pregnancy outcomes, especially for LBW and SGA.

Figure 4 shows the spatial distributions of PTB rates, as expressed in per 100 persons, in Guangdong, from 2014 to 2017. The figure revealed that the rates of PTB were relatively high in the Pearl River Delta regions. For the years of 2014 and 2015, the highest rates of PTB were in Zhongshan and Foshan cities, located in Pearl River Delta regions. In 2016, the city of Foshan had the highest rate of PTB. Additionally, we observed that Yunfu which was located near the Pearl River Delta region had a distinctly high rate of PTB in 2016. In 2017, the city of Zhongshan has the highest rate of PTB.

Figure 5 and 6 depict the maps of spatial distributions of rates for LBW and SGA in Guangdong, respectively. In the years of 2014 and 2015, the rates of LBW were relatively high in the cities including Zhongshan, Foshan, Dongguan and Guangzhou in Pearl River Delta regions. In 2016, the rates of LBW were relatively high in Guangzhou, Huizhou, Dongguan and Foshan. In 2017, the rates of LBW were relatively high in Zhongshan, Huizhou, and Guangzhou in the Pearl River Delta region. For the outcomes of SGA, the cities including Shantou, Zhaoqing, and Yunfu had higher rates than other cities from 2014 to 2017. In addition, the rate of SGA in

Foshan was also high in2017.

Discussion

Our study analyzed a total number of 2,917,098 live births to reveal the characteristics of the temporal trends and spatial distributions of PTB, LBW and SGA in Guangdong province from 2014 to 2017.

For PTB, Beck et al. [6] reported in a systematic review that 9.6% were preterm births among12.9 million births worldwide in 2005.A study estimated 14.9 million babies were preterm births in 2010, accounting for 11.1% of all live births worldwide, ranging from about 5% in several European countries to 18% in some African countries[19].A study revealed that PTB rate was around 4.75% among 10 counties and cities in China, based on Perinatal Healthcare Surveillance System from 1993 to 2005[20]. As the United Nations International Children's Emergency Fund (UNICEF) announced in 2007, the rates of LBW in China were still lower than those of some developed countries, such as the United States (8%), Australia (7%), the United Kingdom (8%), Canada (6%), and Japan (8%)[10]. However, the rate of LBW in China was slightly higher than the figure in South Korea (4%). According to a survey covering 14 provinces in China, the LBW rate in 1998 was 5.87%, and it decreased to 4.6% in 2006 [21]. For the worldwide rates of SGA, a previous study showed the rates were relatively high in Cambodia (18.8%), Nepal (17.9%), the Occupied Palestinian Territory (16.1%) and Japan (16.0%), while rates were relatively low in Afghanistan (4.8%), Uganda (6.6%) and Thailand (9.7%) [10]. In addition, a recent cross-sectional population-based study revealed that the rate of SGA was 12.93% from January 1, 2017 to October 31, 2017 in southern China [22]. However, the study was based on a relatively small size of data. Our study, based on a large size of data, revealed that the rates of PTB, LBW and SGA in Guangdong province were relatively low, compared with other countries in the world.

The data represents statistically significant seasonal variations of births and adverse birth outcomes in Guangdong province, China. Seasonal patterns of birth outcomes were not consistent, which may reflect different etiologies and risk factors of time for each of the examined birth outcomes. For the rates of PTB, the highest number almost occurred in winter. Besides, for SGA, the highest rates were in summer or autumn from 2014 to 2017. Studies in developed countries such as Greece [23], Atlanta [24] and South Korea [25] revealed that PTB has a seasonal trend.LBW was also found seasonal trends[26]. A study revealed that PTB and SGA showed divergent patterns of seasonality in rural African community [27]. Seasonality of PTB, LBW and SGA was also found in Nepal. Our study indicated that the rate of PTB in November was the lowest in 2015 and 2016, while the rate in October was the highest in 2016 and 2017. Hughes et.al [28] also found infants were least likely to suffer from SGA from January to March. In contrast, Infants were most likely to suffer from SGA from June to August and in November. In our study, the rates of SGA peaked in the time period between September and October, and the rates were relatively low from January to March. In some countries, it was also reported that PTB had an obvious seasonal trend. In London [29], babies born in winter were more likely to suffer from PTB compared with those born in spring. In Gambia [27], the rates of PTB peaked twice in a year, once in the hunger season in July and once in October. However, a previous study from the United States reported no seasonality in the rates of PTB [30]. We speculate that the inconsistent results from different countries were partly due to the differences in the study population related to geography, culture and socio-economics. Environmental factors including temperature, humidity, and sunlight have been associated with birth outcomes. According to an animal model, a biological explanation for increasing the risk of PTB is that high temperatures increase the chances of dehydration [31]. This effect increases the risk of PTB due to decreased uterine blood flow and increased secretion of prostaglandins and oxytocin. Another hypothesis is that the effect of sunlight on vitamin D levels may affect fetal growth [32]. A study indicated that seasonal patterns are potential representatives of various environmental exposures [33].

In terms of spatial factors, the PTB, LBW and SGA rates in the Pearl River Delta region were significantly different from those in the non-Pearl River Delta region. A regional analysis in Japan revealed that incidence of PTB was 3.2% in coastal areas and 5.0% in inland areas, respectively, and the incidence of LBW was 6.5% in the coastal areas and 8.5% in the inland areas [34]. Our results of geographical distributions of the adverse pregnancy outcomes were basically consistent with the results from Brazilian regions, in which a higher LBW rates were observed in the developed regions compared with less developed regions [35]. Overall, from 2014 to 2017, the high rates of PTB and LBW expanded from the Pearl River Delta region to the Non-Pearl River Delta regions. The trend of LBW rates increased in less developed areas of Guangdong province year by year. Previous studies also suggested that PTB is often associated with LBW, and their risk factors are similar [36, 37]. Our study indicated that the rates of SGA in the non-Pearl River Delta regions were generally higher than the Pearl River Delta regions. In China, the Pearl River Delta region has better economic situation, education condition and nutritional support than the non-Pearl River Delta regions. Therefore, according to our actual situation, we need to pay more attention to relatively poor regions. We recommend increasing investment in its economic, medical and health resources. Previous study indicated that regional factors may affect birth outcomes through psychosocial processes associated with health behavior, physiological stress hormones, or increased susceptibility to infection [38]. In the future work, we hope to further explore this topic by introducing more variables into the spatio-temporal model, rather than just economic conditions. Because there are few reports on the regional distribution of adverse pregnancy outcomes in China, the contribution of this study is to analyze the characteristics of adverse pregnancy outcomes in Guangdong province from two aspects: time trend and geographical distribution.

In fact, it is often difficult for developing countries to obtain accurate and complete demographic data and medical records for maternal delivery. This present study made use of high quality data of birth certificate from a structured database of birth certificate in Guangdong province. The results of this study involving a large cohort of live births provide a clear description of temporal trends and spatial distributions of PTB, LBW and SGA in Guangdong province, which can be a high-quality baseline indicator for the researchers and decision makers of the public health.

This study does have several limitations. First, this study was just a descriptive analysis of temporal trends and spatial distributions of the adverse pregnancy outcomes, and unable to identify the causal relationship between spatio-temporal factors and adverse pregnancy outcomes. Although we used time trend profiles to roughly observe seasonal patterns, we did not consider potential factors that are difficult to measure, such as maternal infections and nutritional deficiencies. Second, it should note that there may have some delays in reporting birth certificate data at small hospitals in different cities, which can also have a potential impact on our study.

In summary, our study is one of the few studies based on a large cohort of newborns to understand the public health problem of adverse birth outcomes in China. The findings of this study contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA.

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Competing interests

The authors declare there is no conflict of interest regarding the publication of this paper.

Contributions

HZM, LW, FY contributed equally in this study and they are joint first authors. HZM, PG, BL, and QGZ conceived of or designed study.HZM, BL, FY, YLC, RYC, YTW, and PG performed research. HZM, PG, and FY analyzed data. PG, HZM, JML, and FY wrote and revised the paper. PG obtained the funding.

Patient consent

All data was collected from the Guangdong Birth Certificate System that collects information of infants and young children from medical institutions in Guangdong province. No patient consent form needed for data collection.

Ethics approval

This study was approved by the ethics committee of Guangdong Woman & Children Hospital (Shantou, China).

Data sharing

No additional data are available.

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Figure legends

Figure 1.Geographical locations of the study. Guangdong province is located in south China, and there are twenty-one cities including Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Zhaoqing, Huizhou, Jiangmen, Chaozhou, Shantou, Jieyang, Meizhou, Shanwei, Shaoguan, Heyuan, Qingyuan, Yunfu, Yangjiang, Maoming, and Zhanjiang included in this study. The Pearl River Delta regions were marked with pink, and the Non-Pearl River Delta regions were indicated by light blue.

Figure 2. Daily time-series plots of rates for the adverse pregnancy outcomes including preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) in Guangdong province, China, from 1 January 2014 to 31 December 2017.

Figure 3.Heatmaps of weekly counts for the adverse pregnancy outcomes including preterm birth, low birth weight and small for gestational age across cities in Guangdong province, China, from January 1, 2014 to December 31, 2017.

Figure 4. Spatial distributions of rates of preterm birth (PTB), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of PTB rates in 2014. (B) Spatial distributions of PTB rates in 2015. (C) Spatial distributions of PTB rates in 2016. (D) Spatial distributions of PTB rates in 2017.

Figure 5. Spatial distributions of rates of low birth weight (LBW), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of LBW rates in 2014. (B) Spatial distributions of LBW rates in 2015. (C) Spatial distributions of LBW rates in 2016. (D) Spatial distributions of LBW rates in 2017.

Figure 6. Spatial distributions of rates of small for gestational age (SGA), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of SGA rates in 2014. (B) Spatial distributions of SGA rates in 2015. (C) Spatial distributions of SGA rates in 2016. (D) Spatial distributions of SGA rates in 2017.

Tables

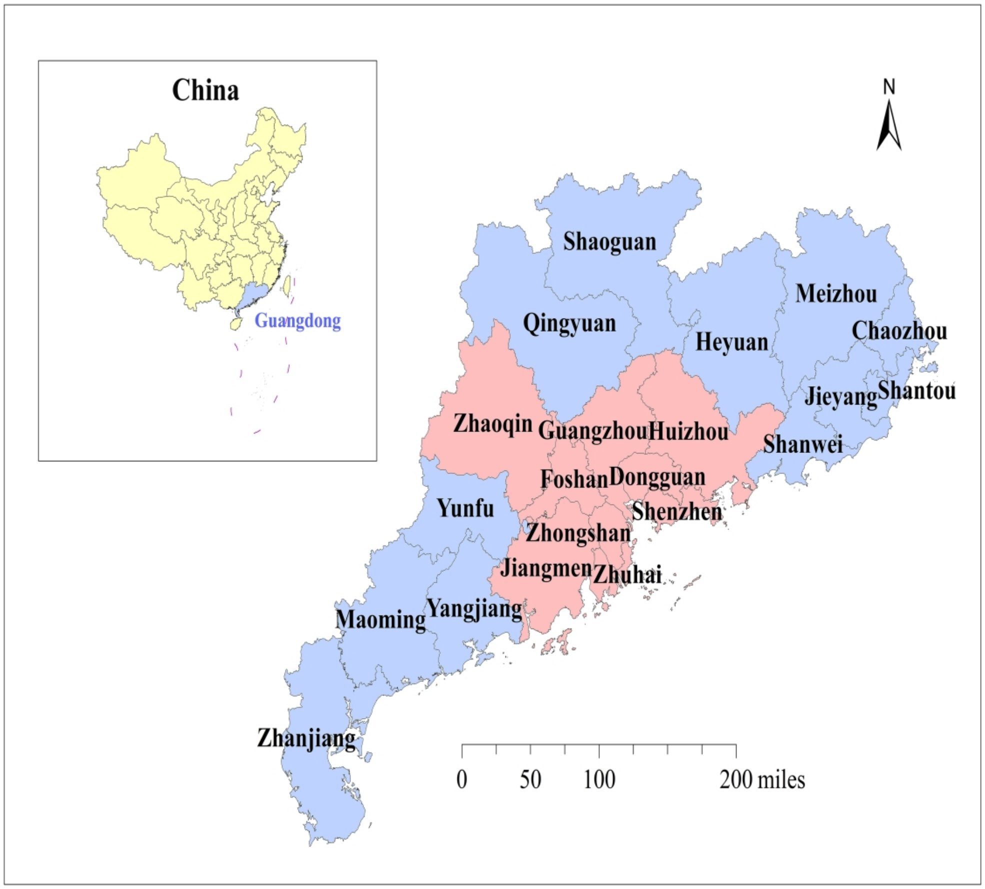
Table 1. Basic characteristics of the study participants.

Characteristic	Category	Frequency	Percentage
Maternal age (years)	< 20	78116	2.68
	20-24	664443	22.78
	25-29	1163071	39.87
	30-34	682067	23.38
	≥ 35	329378	11.29
	Missing	23	0.00
Inhabited city	Pearl River Delta region	1254102	42.99
	Non-Pearl River Delta region	1662996	57.01
Infant sex	Boy	1553948	53.27
	Girl	1363125	46.73
	Missing	25	0.00
Year of birth	2014	763518	26.17
	2015	627146	21.50
	2016	794755	27.24
	2017	731679	25.08
Season of birth	Spring	675595	23.16
	Summer	717762	24.61
	Autumn	804275	27.57
	Winter	719466	24.66
Preterm birth	Yes	121245	4.16
	No	2792953	95.74
	Missing	2900	0.10
Low birth weight (LBW)	Yes	120846	4.14
	No	2796122	95.85
	Missing	130	0.00
Small for gestational age (SGA)	Yes	384637	12.86
	No	2529522	82.88
	Missing	2939	4.26
Low birth weight (Yes)	Preterm	56748	46.96
	Full-term	63968	52.93
	Missing	130	0.11
Small for gestational age (Yes)	Preterm	9499	2.47
	Full-term	375138	97.53

Table 2. Rates of preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) according to demographic characteristics, residence address and birth season by year.

Year	Characteristic	Adverse pregnancy outcome		
		PTB (%)	LBW (%)	SGA (%)
2014	Maternal age (years)			
	< 35	3.79	4.04	14.39
	≥ 35	6.43	5.17	10.54
	Inhabited city			
	Pearl River Delta region	5.03	4.49	11.75
	Non-Pearl River Delta region	3.39	3.91	15.43
	Infant sex			
	Boy	4.43	3.63	13.81
	Girl	3.47	4.68	14.46
	Season of birth			
	Spring	3.78	3.96	13.85
	Summer	3.85	4.19	14.88
	Autumn	3.80	4.21	14.88
	Winter	4.48	4.10	12.80
2015	Maternal age (years)			
	< 35	3.79	4.05	14.09
	≥ 35	6.50	4.91	9.51
	Inhabited city			
	Pearl River Delta region	5.13	4.48	11.06
	Non-Pearl River Delta region	3.43	3.93	15.12
	Infant sex			
	Boy	4.51	3.68	13.43
	Girl	3.47	4.63	14.01
	Season of birth			
	Spring	4.02	4.08	13.36
	Summer	4.03	4.33	14.59
	Autumn	3.87	4.19	14.24
	Winter	4.20	3.87	12.53
2016	Maternal age (years)			
	< 35	4.24	3.98	12.40
	≥ 35	6.87	4.88	8.50
	Inhabited city			
	Pearl River Delta region	5.28	4.25	9.90
	Non-Pearl River Delta region	3.82	3.92	13.93
	Infant sex			
	Boy	5.02	3.61	11.70
	Girl	4.00	4.62	12.23
	Season of birth			

	Spring	4.49	4.02	11.76
	Summer	4.66	4.29	12.37
	Autumn	4.43	4.08	12.01
	Winter	4.60	3.93	11.58
2017	Maternal age (years)			
	< 35	3.67	4.11	13.85
	≥ 35	5.83	4.89	10.05
	Inhabited city			
	Pearl River Delta region	4.27	4.42	12.56
	Non-Pearl River Delta region	3.82	4.08	13.82
	Infant sex			
	Boy	4.53	3.78	13.13
	Girl	3.50	4.78	13.24
	Season of birth			
	Spring	3.91	4.14	12.57
	Summer	3.94	4.36	13.91
	Autumn	3.98	4.46	14.23
	Winter	4.36	4.04	12.02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Foshan
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Shenzhen
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Jiangmen
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Zhanjiang
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Fig 1

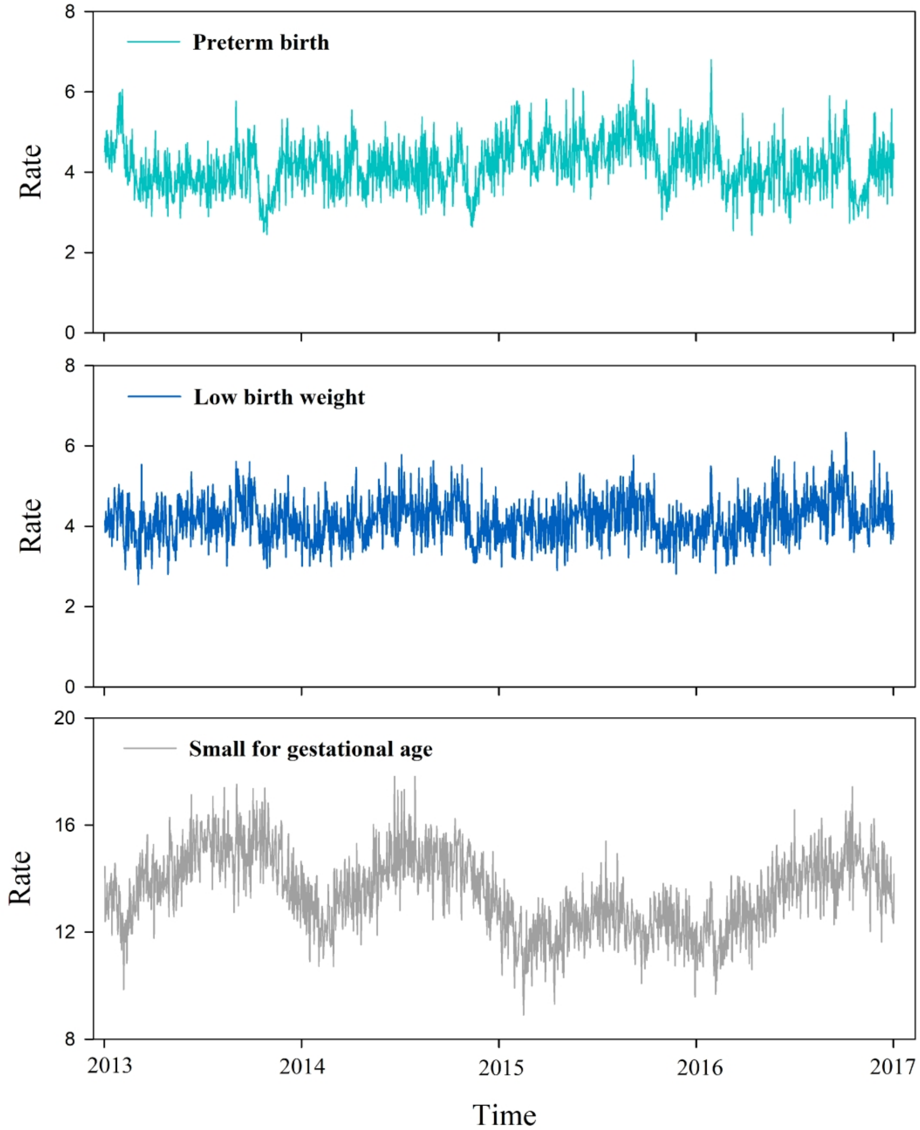
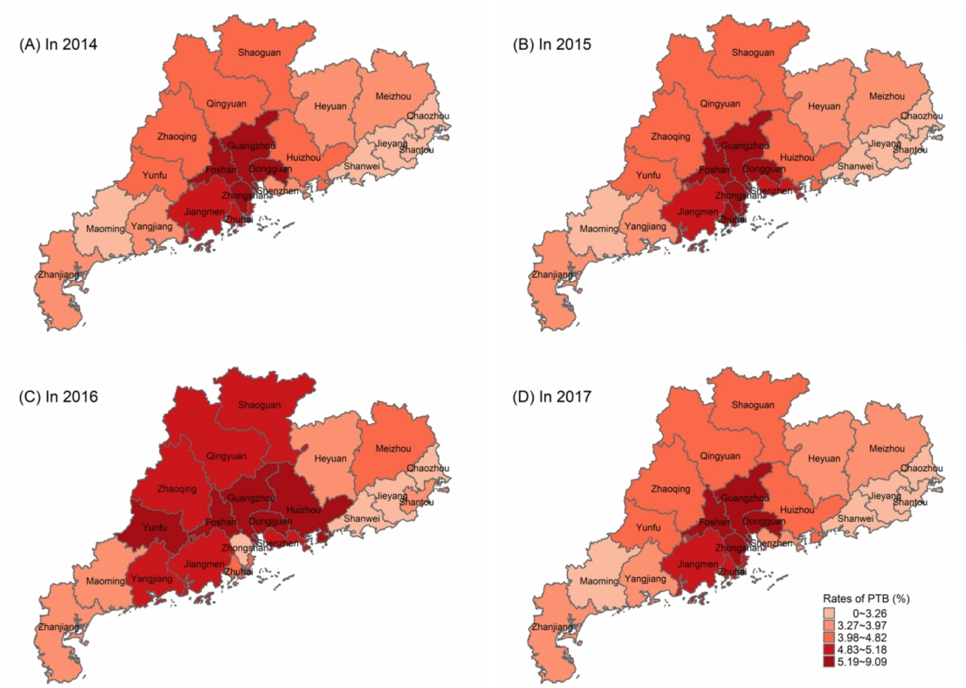

Preterm birth
Low birth weight
Small for gestational age
Rate
Rate
Rate
8
6
4
2
0
8
6
4
2
0
20
16
12
8
2013
2014
2015
2016
2017
Time

Fig 2


PTB
LBW
SGA
Zhuhai
Zhongshan
Zhaoqing
Zhanjian
Yunfu
Yangjiang
Shenzhen
Shaoguan
Shanwei
Shantou
Qingyuan
Meizhou
Maoming
Jieyang
Jiangmen
Huizhou
Heyuan
Guangzhou
Foshan
Dongguan
Chaozhou
2014
2015
2016
2017

Fig 3


(A) In 2014
(B) In 2015
(C) In 2016
(D) In 2017
Shaoguan
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Meizhou
Chaozhou
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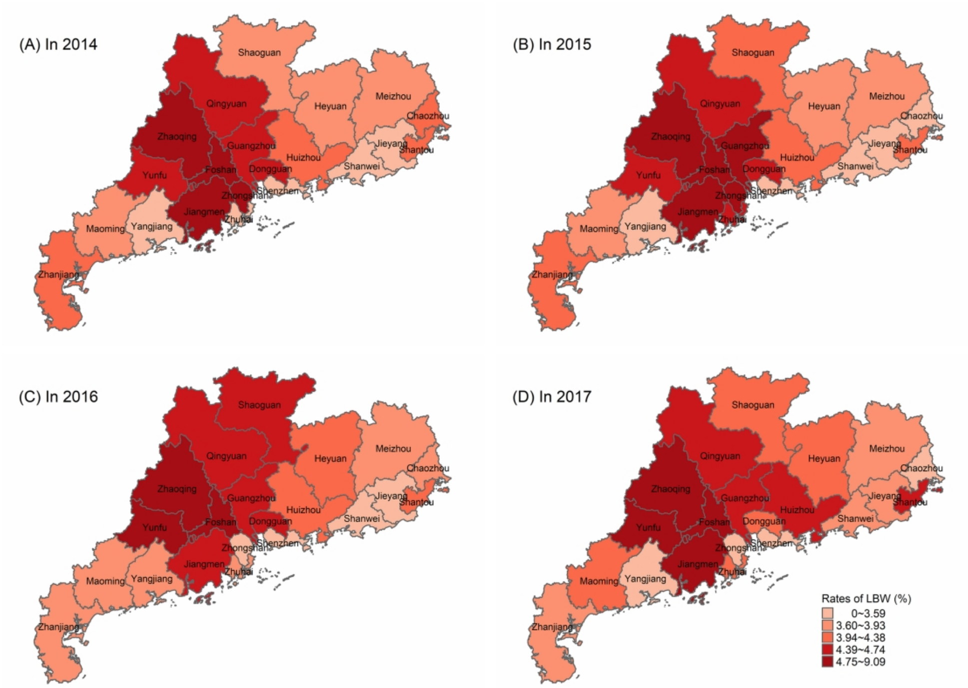
Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Zhongshan
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
Rates of PTB (%)
0~3.26
3.27~3.97
3.98~4.82
4.83~5.18
5.19~9.09

Fig 4


(A) In 2014
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(C) In 2016
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Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Zhongshan
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
Rates of LBW (%)
0~3.59
3.60~3.93
3.94~4.38
4.39~4.74
4.75~9.09

Fig 5

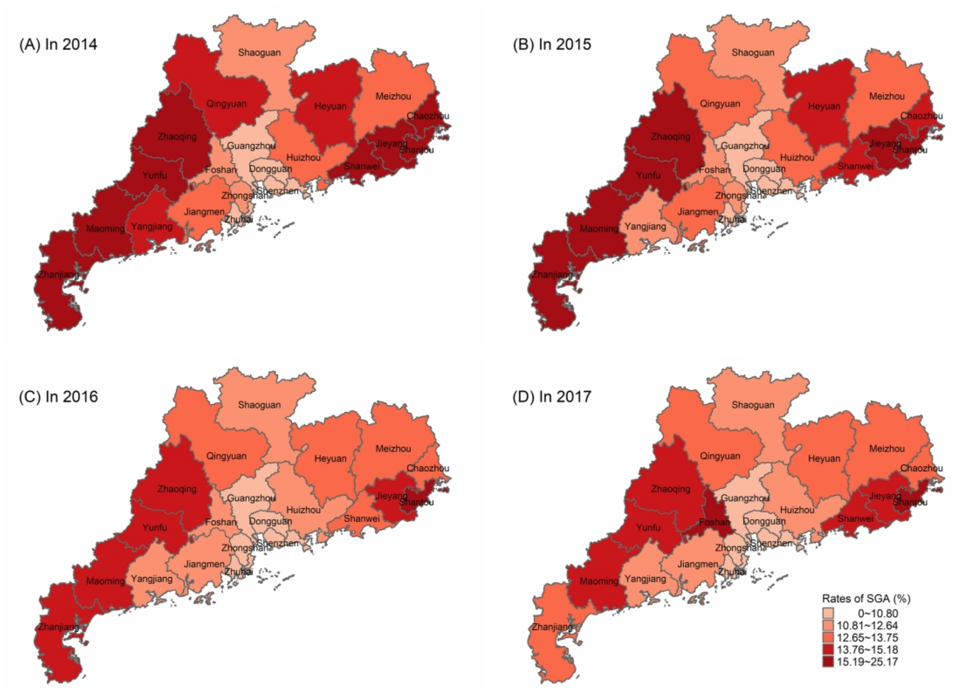
(A) In 2014
(B) In 2015
(C) In 2016
(D) In 2017
Shaoguan
Qingyuan
Heyuan
Meizhou
Chaozhou
Zhaoqing
Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Shenzhen
Zhongshan
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
Rates of SGA (%)
0~10.80
10.81~12.64
12.65~13.75
13.76~15.18
15.19~25.17

Fig 6

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Adverse birth outcomes in Guangdong province, China, 2014-2017: a spatio-temporal analysis of 2.9 million births

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Paediatrics
Keywords:	PUBLIC HEALTH, EPIDEMIOLOGY, Community child health < PAEDIATRICS

Adverse birth outcomes in Guangdong province, China, 2014-2017: a spatio-temporal analysis of 2.9 million births

Authors

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The manuscript word counts 3513 words.

Abstract

Objectives Adverse birth outcomes pose a great threat to the public health and bring a heavy burden of disease in China. A comprehensive examination of the temporal and spatial trends of preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) epidemics can provide some elementary information for subsequent etiological and epidemiological studies. This study aimed to characterize the spatio-temporal features of PTB, LBW, and SGA based on a large cohort of live births in China.

Design Spatio-temporal descriptive analysis was performed in Guangdong province, China, from 2014 to 2017.

Setting Data involving 2,917,098 live births in Guangdong province, China from 2014 to 2017 was collected from Guangdong Birth Certificate System. Information was collected, including the date of birth, gestational age in week, birth weight, sex of the infant, age of the mother, and registered residence of the mother.

Results The estimated rate of PTB, LBW and SGA was 4.16%, 4.14% and 12.86%, respectively. For temporal trends, the rates of PTB, LBW and SGA showed seasonal fluctuations, especially for LBW and SGA. In addition, there were regional differences in the rates of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. From 2014 to 2017, the high rates of PTB and LBW expanded from the Pearl River Delta region to the Non-Pearl River Delta regions. However, compared with the Pearl River Delta region, the rate of SGA was higher in the Non-Pearl River Delta regions on the whole.

Conclusion The findings of this study contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA in south China.

Keywords: Preterm birth; Low birth weight; Small for gestational age; Spatial; Temporal

Strengths and limitations of this study

- This study is a spatio-temporal descriptive analysis to reveal the current situation of adverse birth outcomes in Guangdong, south China.
- The study involves a cohort of nearly 2.9 million live births and further enhances our understanding of the temporal trend and spatial distribution of adverse pregnancy outcomes in south China.
- Multiple adverse pregnancy outcomes including preterm birth, low birth weight, and small for gestational age have been investigated and compared in terms of their temporal trend and spatial distribution.
- As a descriptive analysis, this study was unable to identify the causal relationship between spatio-temporal factors and adverse pregnancy outcomes.
- Delays in reporting birth certificate data at small hospitals in different cities may cause bias.

Introduction

Previous studies [1, 2] suggested that severe infant morbidity and mortality partly resulted from adverse birth outcomes including preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA). PTB is defined as a live-birth infant with less than 37 complete weeks of gestation [3]. LBW is defined as a live-birth infant weighing less than 2,500 grams at birth [4]. SGA is defined as an infant whose birth weight falls below the 10th percentile by sex and gestational week of all singleton live births in a region [5]. With the development and progress of society and the continuous improvement of the level of medical care, the health condition of infants and young children has been significantly improved. However, adverse pregnancy outcomes such as PTB, LBW and SGA have not been effectively controlled, which has become an important risk factor for infant health. PTB rates were reported ranging from 6.2 % to 11.9% of live births in some developed and developing countries [6]. In fact, the incidence of LBW in developed countries is still high, and even rising [7]. Among 135 million infants born in low and middle income countries in 2010, it is estimated that 29.7 million (22%) were term births of SGA, and 2.8 million (2.1%) were PTBs of SGA [8]. In Guangzhou city of south China, a PTB rate of 5.6% has been reported in a previous study [9]. A retrospective study involving 39 hospitals of different levels from 14 provinces and autonomous regions in China throughout 2011 reported that a total of 7474 cases were diagnosed as LBW (incidence = 7.2%) [10]. Overall, these adverse birth outcomes pose a great threat to the health of infants.

Additionally, the adverse outcomes of PTB, LBW and SGA may also increase the risk of chronic diseases or developmental outcomes later in life [11, 12]. These facts show that PTB, LBW and SGA are still challenging problems of public health in many countries. Thus further research is needed to investigate the epidemiology of these problems more comprehensively. Many previous studies described significant seasonal variations of PTB, LBW or SGA with remarkable differences between regions [13, 14]. However, some researches didn't detect an association between temperature and adverse pregnancy outcome [15-17]. In fact, the conditions of evidence differed among different regions and studies. The complexity of PTB, LBW, SGA and relevant risk factors in the individual, social and spatial levels often make the causal relationship between identified risks and responses non-stationary in space and time. A comprehensive examination of the temporal and spatial trends of PTB, LBW, and SGA can provide some basic elements for subsequent etiological and epidemiological studies.

As the southern gate of China, Guangdong province has the most developed economic and social level in South China. However, there are still regional differences in the industrial development, the degree of medical care and the level of education of the local residents that cannot be ignored. These factors may have an impact on the fertility status of local residents in Guangdong province. In addition, more recent data about the fertility status of local residents have not been reported. There is an urgent need to provide an overall description of the fertility situation of the local population in order to carry out some other follow-up exploratory studies. Therefore, in order to fill in the gap, we performed a spatio-temporal analysis of PTB, LBW, and SGA, based on a large cohort involving approximately 3 million newborns in Guangdong province, China from 2014 to 2017. This study is more convincing because of the relatively large investigated samples. Additionally, this study analyzed regional differences of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. In general, the Pearl River Delta regions represent economically developed regions in Guangdong province, while Non-Pearl River Delta regions represent relatively underdeveloped regions. The findings of this study will contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA, and the design of prevention and intervention strategies for specific geographical areas and high-risk populations.

Materials and methods

Patient and public involvement

All birth data in this study was obtain from Guangdong Birth Certificate System and was only used for statistical analysis. Information of newborn and mothers across Guangdong province were collected in this study. No patients or public were involved in development of research question, study design, conduction of research and measurement of outcome. There are no plans of disseminating research results to participants.

Ethics statement

Ethical approval was obtained from ethics committee of Guangdong Woman and Children Hospital. The approval number is 201601011.

Data preparation

All birth data was collected from the Guangdong Birth Certificate System, which collects information of infants and young children from medical institutions in Guangdong province. After childbirth, obstetric medical staff put the baby on an electronic scale, record stable weight data. Health care workers or midwives fill out the delivery information of the newborn in the regional maternal and child information system. The logical settings of the system have been corrected to ensure the convincing records. Finally, the information will be transferred to the Guangdong Birth Certificate System. After the data being imported, the midwife director and the hospital doctor director need to confirm the birth information. Before the birth certificate is issued, the department of medical management and the parents should check the birth information again. All the information is verified by medical professionals. The birth registration database contains the date of birth, gestational age in week, birth weight, sex of the infant, parity, age of the mother, and registered residence of the mother. All live newborns were included in the study except for stillbirths, deaths within days of birth and birth defects. To reduce bias, the subset of births was limited to singleton live births with 22-42 completed weeks gestation [18]. After further excluding births with implausible birth weights (less than 500 grams) [19] and verifying data, we included a total number of 2,914,198 births in our analysis.

Data analysis

We described basic characteristics of the newborns and mothers, and the rates of PTB, LBW and SGA according to the studied characteristics by year was estimated and compared using χ^2 test. In order to observe the temporal trends in the occurrence of PTB, LBW and SGA in the study site, we calculated daily rates of PTB (daily number of live births with gestational age less than 37 weeks/daily number of live births × 100%) [3], daily rates of LBW (daily number of live births with birth weight less than 2500 g / daily number of live births × 100%) [4], daily rates of SGA (daily number of live births with birth weight less than the 10th percentile of the normal average birth weight at the same gestational age/daily number of live births at the same gestational age × 100%) [20], respectively. We determined the season of birth based on the birth date (spring: March-May, summer: June-August; autumn: September-November, winter: December-February). Heatmaps of weekly average rates of PTB, LBW and SGA were drew to investigate whether the rates exhibited an obvious seasonality. SAS software version 9.3 (SAS Institute Inc.; Cary, NC, the United States) was used for the statistical analyses.

According to economic conditions, Guangdong province can be divided into Pearl River Delta regions and Non-Pearl River Delta regions. Pearl River Delta regions are economically developed regions, including Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Zhaoqing, Huizhou and Jiangmen cities. By contrast, Non-Pearl River Delta regions are relatively underdeveloped regions, including Shantou, Chaozhou, Jieyang, Shanwei, Zhanjiang, Maoming, Yangjiang, Yunfu, Shaoguan, Qingyuan, Meizhou and Heyuan cities. Besides, city boundary shape files of Guangdong province were publicly obtained from the National Geomatics Center of China (http://www.ngcc.cn/ngcc/) and used for disease mapping. We mapped the spatial distributions of rates for the adverse birth outcomes to investigate the spatial distributions pattern of the birth outcomes through 2014 to 2017. In addition, we calculated the Kulldorff's spatial scan statistic using the DCluster package within R software for purely spatial cluster detection of the adverse birth outcomes. All statistical tests were 2-tailed. *P*-value less than 0.05 were considered to be statistically significant.

Results

Figure 1 shows the geographical locations of the study in Guangdong province. Guangdong province is located in southern China and is also currently the most populous province in China. There were a total of 2,917,098 births in Guangdong province during the study period, 1,553,948 (53.27%) were boys. Approximately 22% (627,146) babies were born in 2015, which is the lowest population of all births between 2014 and 2017. As illustrated in Table 1, the proportion of mothers who aged less than 20, 20 to 24, 25 to 29, 30 to 34, and over 35 years old was 2.68%, 22.78%, 39.87%, 23.38% and 11.29%, respectively. For the seasons of birth, the proportion of babies born in spring, summer, autumn and winter was 23.16%, 24.61%, 27.57% and 24.66%, respectively. There were 56,748 (42.96%) LBW of preterm births, while there were 63,968 (52.93%) LBW of term births. Regarding SGA infants, 2.47% were preterm births, while 97.53% were term births.

Table 2 reveals that the rates of PTB, LBW and SGA according to demographic characteristics, residence address and birth seasons by year. Infants born from women aged less than 35 years have higher rates of LBW and PTB outcomes than women younger than 35 years old (all *P*-values < 0.05). However, the rates of the difference were gradually decreasing from 2014 to 2017. From 2014 to 2016, there was a downward trend in the rates of SGA among pregnant women who were not less than 35 years old and less than 35 years old. In 2017, the rates for SGA by two groups of pregnant women rose slightly. Generally, infants who were born in the Pearl River Delta regions had higher rates of PTB and LBW than those who were born in Non-Pearl River Delta regions in Guangdong (all *P*-values < 0.05). However, infants who were born in the Pearl River Delta regions tended to have lower rates of SGA than those who were born in Non-Pearl River Delta regions (all *P*-values < 0.05). Boy and girl babies tended to be similar in the rates of the outcomes. We found the PTB rates of boys were higher than that of girls (all P-values < 0.05), among which the highest rate was in 2016 (5.02%). Besides, the LBW rates of girls were higher than that of boys (all P-values < 0.05), among which the highest rate was in 2017 (4.78%). For SGA, the highest rate was 14.46% in the girls group. In addition, the rates of PTB, LBW and SGA statistically varied among seasons of birth, respectively (all P-values < 0.05). For PTB, the highest rates were clustered in winter. For LBW, the highest rates did not show cluster tendency of season. However, for SGA, the highest rates were clustered in summer or autumn.

Figure 2 depicts daily time-series plots of the rates for the adverse pregnancy outcomes including PTB, LBW and SGA. Upon visual inspection, the rates of PTB, LBW and SGA show, to some degree, seasonal fluctuation trends, especially for the outcomes of PTB and SGA. In 2014, the rate of PTB ranged from 2.45% in October to 6.06% in February. The period of highest rates of PTB was between December and February. In 2015 and 2016, the rates of PTB in November were the lowest in the course of the year. In contrast, in 2016 and 2017, the highest rates of PTB were in October. In 2014, infants had a peak rate (5.61%) of LBW in September. Infants born from February to April were least likely to suffer from LBW, with the lowest rate (2.55%) in March. In 2017, there was a similar pattern for LBW infants with the rate (2.80%) in February, which clearly lower than the figure between September and October. Additionally, the peak rate (6.30%) of LBW occurred in October. The average of daily rates of SGA was 14.30% in this study. During the period from 2014 to 2017, infants were least likely to suffer from SGA between January and March, which is similar to the outcome of LBW. In addition, infants were most likely to suffer from SGA between September and October.

Figure 3 depicts the heatmaps of weekly average rates for PTB, LBW and SGA across cities in Guangdong province, from 2014 to 2017. For most cities, there was a remarkable seasonality in the rates of the adverse pregnancy outcomes, especially for LBW and SGA.

Figure 4 shows the spatial distributions of PTB rates, as expressed in per 100 persons, in Guangdong, from 2014 to 2017. The figure revealed that the rates of PTB were relatively high in the Pearl River Delta regions. For the years of 2014 and 2015, the highest rates of PTB were in Zhongshan and Foshan cities, located in Pearl River Delta regions. In 2016, the city of Foshan had the highest rate of PTB. Additionally, we observed that Yunfu which was located near the Pearl River Delta region had a distinctly high rate of PTB in 2016. In 2017, the city of Zhongshan has the highest rate of PTB. We observed spatial heterogeneity of PTB outcome across the study time period in Guangdong province (Fig S1 and Table S1), and the most likely cluster appearing in the Pearl River Delta was detected.

Similarly, the spatial heterogeneity of LBW and SGA was also observed in Guangdong province (Fig S2, Fig S3 and Table S1). Figure 5 and 6 depict the maps of spatial distributions of rates for LBW and SGA in Guangdong, respectively. In the years of 2014 and 2015, the rates of LBW were relatively high in the cities including Zhongshan, Foshan, Dongguan and Guangzhou in Pearl River Delta regions. In 2016, the rates of LBW were relatively high in Guangzhou, Huizhou, Dongguan and Foshan. In 2017, the rates of LBW were relatively high in Zhongshan, Huizhou, and Guangzhou in the Pearl River Delta region. For the outcomes of SGA, the cities including Shantou, Zhaoqing, and Yunfu had higher rates than other cities from 2014 to 2017. In addition, the rate of SGA in Foshan was also high in2017.

Discussion

Our study analyzed a total number of 2,917,098 live births to reveal the characteristics of the temporal trends and spatial distributions of PTB, LBW and SGA in Guangdong province from 2014 to 2017. This study reveals the overall situation and regional differences of fertility among local residents in Guangdong province, and provides more recent data about the reproductive status of local pregnant women. These findings will be beneficial to subsequently explore on the causes of differences in the fertility in Guangdong province.

For PTB, Beck et al. [6] reported in a systematic review that 9.6% were preterm births among 12.9 million births worldwide in 2005. A study estimated 14.9 million babies were preterm births in 2010, accounting for 11.1% of all live births worldwide, ranging from about 5% in several European countries to 18% in some African countries [21]. A study revealed that PTB rate was around 4.75% among 10 counties and cities in China, based on Perinatal Healthcare Surveillance System from 1993 to 2005 [22]. As the United Nations International Children's Emergency Fund (UNICEF) announced in 2007, the rates of LBW in China were still lower than those of some developed countries, such as the United States (8%), Australia (7%), the United Kingdom (8%), Canada (6%), and Japan (8%) [10]. However, the rate of LBW in China was slightly higher than the figure in South Korea (4%). According to a survey covering 14 provinces in China, the LBW rate in 1998 was 5.87%, and it decreased to 4.6% in 2006 [23]. For the worldwide rates of SGA, a previous study showed the rates were relatively high in Cambodia (18.8%), Nepal (17.9%), the Occupied Palestinian Territory (16.1%) and Japan (16.0%), while rates were relatively low in Afghanistan (4.8%), Uganda (6.6%) and Thailand (9.7%) [12]. In addition, a recent cross-sectional population-based study revealed that the rate of SGA was 12.93% from January 1, 2017 to October 31, 2017 in southern China [24]. However, the study was based on a relatively small size of data. Our study, based on a large size of data, revealed that the rates of PTB, LBW and SGA in Guangdong province were relatively low, compared with other countries in the world.

The data represents statistically significant seasonal variations of births and adverse birth outcomes in Guangdong province, China. Seasonal patterns of birth outcomes were not consistent, which may reflect different etiologies and risk factors of time for each of the examined birth outcomes. For the rates of PTB, the highest number almost occurred in winter. Besides, for SGA, the highest rates were in summer or autumn from 2014 to 2017. Studies in developed countries such as Greece [25], Atlanta [26] and

South Korea [27] revealed that PTB has a seasonal trend. LBW was also found seasonal trends [28]. A study revealed that PTB and SGA showed divergent patterns of seasonality in rural African community [29]. Seasonality of PTB, LBW and SGA was also found in Nepal. Our study indicated that the rate of PTB in November was the lowest in 2015 and 2016, while the rate in October was the highest in 2016 and 2017. Hughes et. al [30] also found infants were least likely to suffer from SGA from January to March. In contrast, Infants were most likely to suffer from SGA from June to August and in November. In our study, the rates of SGA peaked in the time period between September and October, and the rates were relatively low from January to March. In some countries, it was also reported that PTB had an obvious seasonal trend. In London [31], babies born in winter were more likely to suffer from PTB compared with those born in spring. In Gambia [29], the rates of PTB peaked twice in a year, once in the hunger season in July and once in October. However, a previous study from the United States reported no seasonality in the rates of PTB [32]. We speculate that the inconsistent results from different countries were partly due to the differences in the study population related to geography, culture and socio-economics. Environmental factors including temperature, humidity, and sunlight have been associated with birth outcomes. According to an animal model, a biological explanation for increasing the risk of PTB is that high temperatures increase the chances of dehydration [33]. This effect increases the risk of PTB due to decreased uterine blood flow and increased secretion of prostaglandins and oxytocin. Another hypothesis is that the effect of sunlight on vitamin D levels may affect fetal growth [34]. A study indicated that seasonal patterns are potential representatives of various environmental exposures [35].

In terms of spatial factors, the PTB, LBW and SGA rates in the Pearl River Delta region were significantly different from those in the non-Pearl River Delta region. A regional analysis in Japan revealed that incidence of PTB was 3.2% in coastal areas and 5.0% in inland areas, respectively, and the incidence of LBW was 6.5% in the coastal areas and 8.5% in the inland areas [36]. Our results of geographical distributions of the adverse pregnancy outcomes were basically consistent with the results from

Brazilian regions, in which a higher LBW rates were observed in the developed regions compared with less developed regions [37]. Overall, from 2014 to 2017, the high rates of PTB and LBW expanded from the Pearl River Delta region to the Non-Pearl River Delta regions. The trend of LBW rates increased in less developed areas of Guangdong province year by year. Previous studies also suggested that PTB is often associated with LBW, and their risk factors are similar [38, 39]. Our study indicated that the rates of SGA in the non-Pearl River Delta regions were generally higher than the Pearl River Delta regions. Previous study suggested that adverse pregnancy outcomes can be increased by preconception risk factors and lifestyles [40]. As we known, there are obvious regional differences in the social and economic level, diet structure and educational level in Guangdong province. These regional factors may have a direct impact on the fertility status and reproductive outcome of the local population. In China, the Pearl River Delta region has better economic situation, education condition and nutritional support than the non-Pearl River Delta regions. Therefore, according to our actual situation, we need to pay more attention to relatively poor regions. We recommend increasing investment in its economic, medical and health resources. Previous study indicated that regional factors may affect birth outcomes through psychosocial processes associated with health behavior, physiological stress hormones, or increased susceptibility to infection [41]. In the future work, we hope to further explore this topic by introducing more variables into the spatio-temporal model, rather than just economic conditions. Because there are few reports on the regional distribution of adverse pregnancy outcomes in China, the contribution of this study is to analyze the characteristics of adverse pregnancy outcomes in Guangdong province from two aspects: time trend and geographical distribution.

In fact, it is often difficult for developing countries to obtain accurate and complete demographic data and medical records for maternal delivery. This present study made use of high quality data of birth certificate from a structured database of birth certificate in Guangdong province. The results of this study involving a large cohort of live births provide a clear description of temporal trends and spatial distributions of

PTB, LBW and SGA in Guangdong province, which can be a high-quality baseline indicator for the researchers and decision makers of the public health.

This study does have several limitations. First, this study was just a descriptive analysis of temporal trends and spatial distributions of the adverse pregnancy outcomes, and unable to identify the causal relationship between spatio-temporal factors and adverse pregnancy outcomes. Although we used time trend profiles to roughly observe seasonal patterns, we did not consider potential factors that are difficult to measure, such as maternal infections and nutritional deficiencies. Second, it should note that there may have some delays in reporting birth certificate data at small hospitals in different cities, which can also have a potential impact on our study.

In summary, our study is one of the few studies based on a large cohort of newborns to understand the public health problem of adverse birth outcomes in China. The findings of this study contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA.

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Competing interests

The authors declare there is no conflict of interest regarding the publication of this paper.

Contributions

HZM, LW, BL, FY contributed equally in this study and they are joint first authors. HZM, PG and QGZ conceived of or designed study. HZM, BL, FY, YLC, RYC,

YTW, and PG performed research. HZM, PG, and FY analyzed data. PG, HZM, JML, and FY wrote and revised the paper. PG obtained the funding.

Patient consent

All data was collected from the Guangdong Birth Certificate System that collects information of infants and young children from medical institutions in Guangdong province. No patient consent form needed for data collection.

Ethics approval

This study was approved by the ethics committee of Guangdong Woman & Children Hospital (Shantou, China).

Data sharing

No additional data are available.

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Figure legends

Figure 1. Geographical locations of the study. Guangdong province is located in south China, and there are twenty-one cities including Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Zhaoqing, Huizhou, Jiangmen, Chaozhou, Shantou, Jieyang, Meizhou, Shanwei, Shaoguan, Heyuan, Qingyuan, Yunfu, Yangjiang, Maoming, and Zhanjiang included in this study. The Pearl River Delta regions were marked with pink, and the Non-Pearl River Delta regions were indicated by light blue.

Figure 2. Daily time-series plots of rates for the adverse pregnancy outcomes including preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) in Guangdong province, China, from 1 January 2014 to 31 December 2017.

Figure 3. Heatmaps of weekly counts for the adverse pregnancy outcomes including preterm birth, low birth weight and small for gestational age across cities in Guangdong province, China, from January 1, 2014 to December 31, 2017.

Figure 4. Spatial distributions of rates of preterm birth (PTB), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of PTB rates in 2014. (B) Spatial distributions of PTB rates in 2015. (C) Spatial distributions of PTB rates in 2016. (D) Spatial distributions of PTB rates in 2017.

Figure 5. Spatial distributions of rates of low birth weight (LBW), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of LBW rates in 2014. (B) Spatial distributions of LBW rates in 2015. (C) Spatial distributions of LBW rates in 2016. (D) Spatial distributions of LBW rates in 2017.

Figure 6. Spatial distributions of rates of small for gestational age (SGA), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of SGA rates in 2014. (B) Spatial distributions of SGA rates in 2015. (C) Spatial distributions of SGA rates in 2016. (D) Spatial distributions of SGA rates in 2017.

Tables

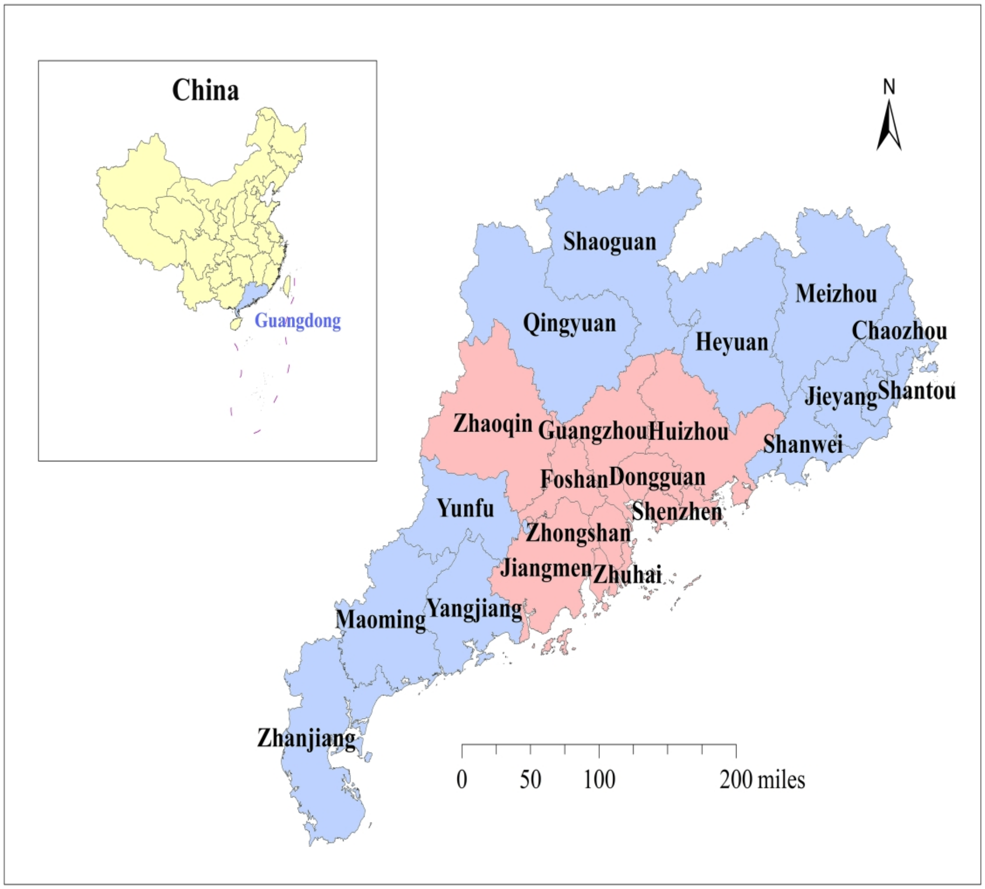
Table 1. Basic characteristics of the study participants.

Characteristic	Category	Frequency	Percentage
Maternal age (years)	< 20	78116	2.68
	20-24	664443	22.78
	25-29	1163071	39.87
	30-34	682067	23.38
	≥ 35	329378	11.29
	Missing	23	0.00
Inhabited city	Pearl River Delta region	1254102	42.99
	Non-Pearl River Delta region	1662996	57.01
Infant sex	Boy	1553948	53.27
	Girl	1363125	46.73
	Missing	25	0.00
Year of birth	2014	763518	26.17
	2015	627146	21.50
	2016	794755	27.24
	2017	731679	25.08
Season of birth	Spring	675595	23.16
	Summer	717762	24.61
	Autumn	804275	27.57
	Winter	719466	24.66
Preterm birth	Yes	121245	4.16
	No	2792953	95.74
	Missing	2900	0.10
Low birth weight (LBW)	Yes	120846	4.14
	No	2796122	95.85
	Missing	130	0.00
Small for gestational age (SGA)	Yes	384637	12.86
	No	2529522	82.88
	Missing	2939	4.26
Low birth weight (Yes)	Preterm	56748	46.96
	Full-term	63968	52.93
	Missing	130	0.11
Small for gestational age (Yes)	Preterm	9499	2.47
	Full-term	375138	97.53

Table 2. Rates of preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) according to demographic characteristics, residence address and birth season by year.

Year	Characteristic	Adverse pregnancy outcome					
		PTB (%)	*P*-value	LBW (%)	*P*-value	SGA (%)	*P*-value
2014	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	3.79		4.04		14.39	
	≥ 35	6.43		5.17		10.54	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	5.03		4.49		11.75	
	Non-Pearl River Delta region	3.39		3.91		15.43	
	Infant sex		<0.0001		<0.0001		<0.0001
	Boy	4.43		3.63		13.81	
	Girl	3.47		4.68		14.46	
	Season of birth		<0.0001		0.0003		<0.0001
	Spring	3.78		3.96		13.85	
	Summer	3.85		4.19		14.88	
	Autumn	3.8		4.21		14.88	
	Winter	4.48		4.1		12.8	
2015	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	3.79		4.05		14.09	
	≥ 35	6.5		4.91		9.51	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	5.13		4.48		11.06	
	Non-Pearl River Delta region	3.43		3.93		15.12	
	Infant sex		<0.0001		<0.0001		<0.0001
	Boy	4.51		3.68		13.43	
	Girl	3.47		4.63		14.01	
	Season of birth		<0.0001		<0.0001		<0.0001
	Spring	4.02		4.08		13.36	
	Summer	4.03		4.33		14.59	
	Autumn	3.87		4.19		14.24	
	Winter	4.2		3.87		12.53	
2016	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	4.24		3.98		12.4	
	≥ 35	6.87		4.88		8.5	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	5.28		4.25		9.9	
	Non-Pearl River Delta region	3.82		3.92		13.93	
	Infant sex		<0.0001		<0.0001		<0.0001
	Boy	5.02		3.61		11.7	
	Girl	4		4.62		12.23	

	Season of birth		0.0011		<0.0001		<0.0001
	Spring	4.49		4.02		11.76	
	Summer	4.66		4.29		12.37	
	Autumn	4.43		4.08		12.01	
	Winter	4.6		3.93		11.58	
2017	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	3.67		4.11		13.85	
	≥ 35	5.83		4.89		10.05	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	4.27		4.42		12.56	
	Non-Pearl River Delta region	3.82		4.08		13.82	
	Infant sex		<0.0001		<0.0001		0.1572
	Boy	4.53		3.78		13.13	
	Girl	3.5		4.78		13.24	
	Season of birth		<0.0001		<0.0001		<0.0001
	Spring	3.91		4.14		12.57	
	Summer	3.94		4.36		13.91	
	Autumn	3.98		4.46		14.23	
	Winter	4.36		4.04		12.02	


China
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200 miles

Fig 1

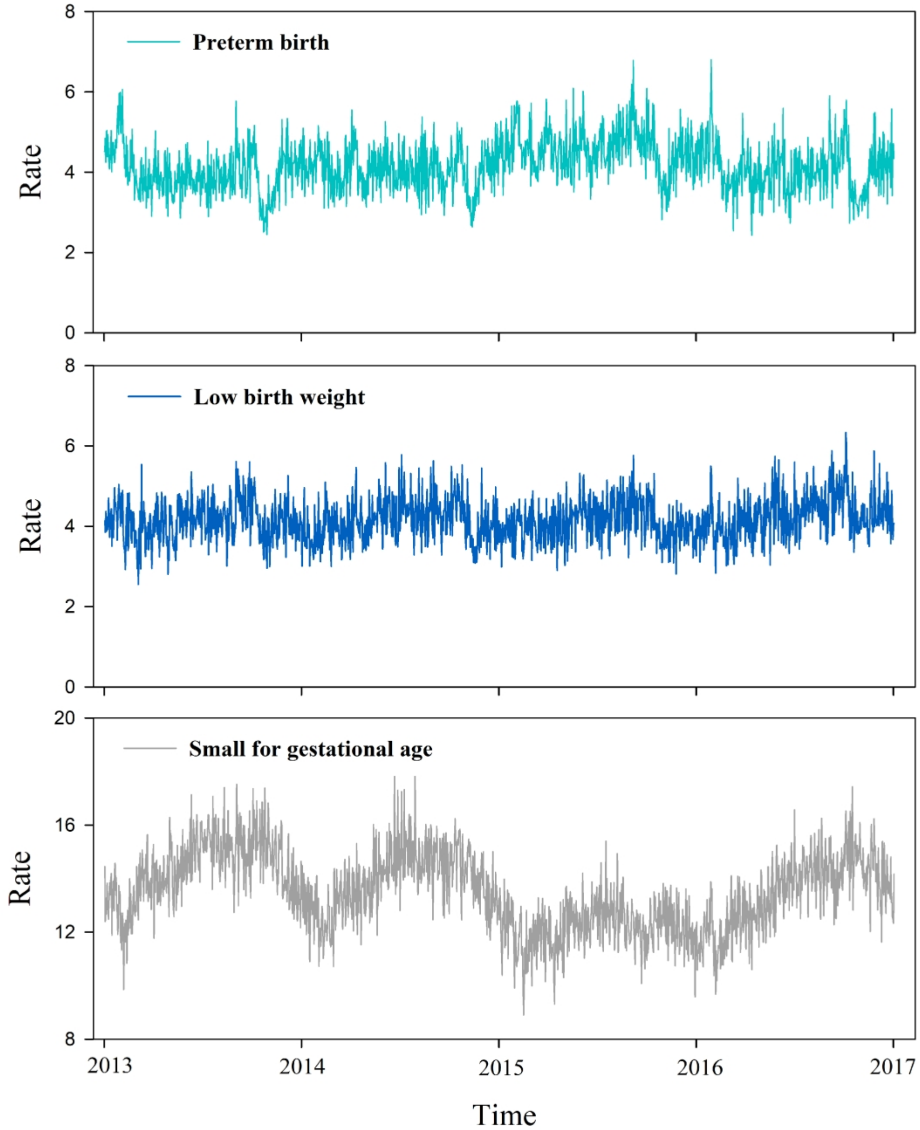

Preterm birth
Low birth weight
Small for gestational age
Rate
Rate
Rate
8
6
4
2
0
8
6
4
2
0
20
16
12
8
2013
2014
2015
2016
2017
Time

Fig 2


PTB
LBW
SGA
Zhuhai
Zhongshan
Zhaoqing
Zhanjian
Yunfu
Yangjiang
Shenzhen
Shaoguan
Shanwei
Shantou
Qingyuan
Meizhou
Maoming
Jieyang
Jiangmen
Huizhou
Heyuan
Guangzhou
Foshan
Dongguan
Chaozhou
2014
2015
2016
2017

Fig 3

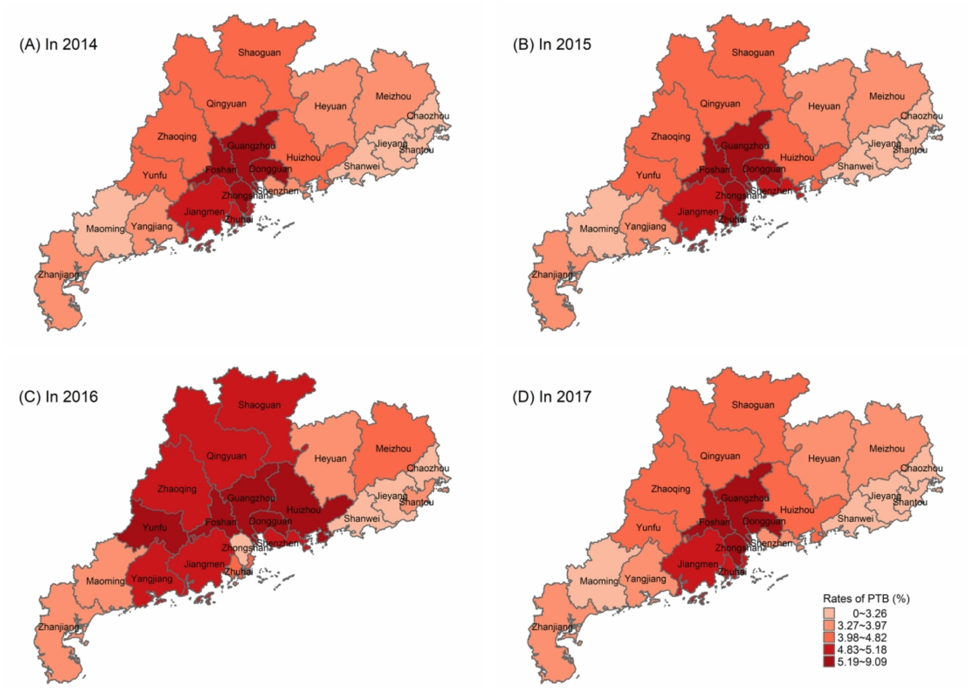
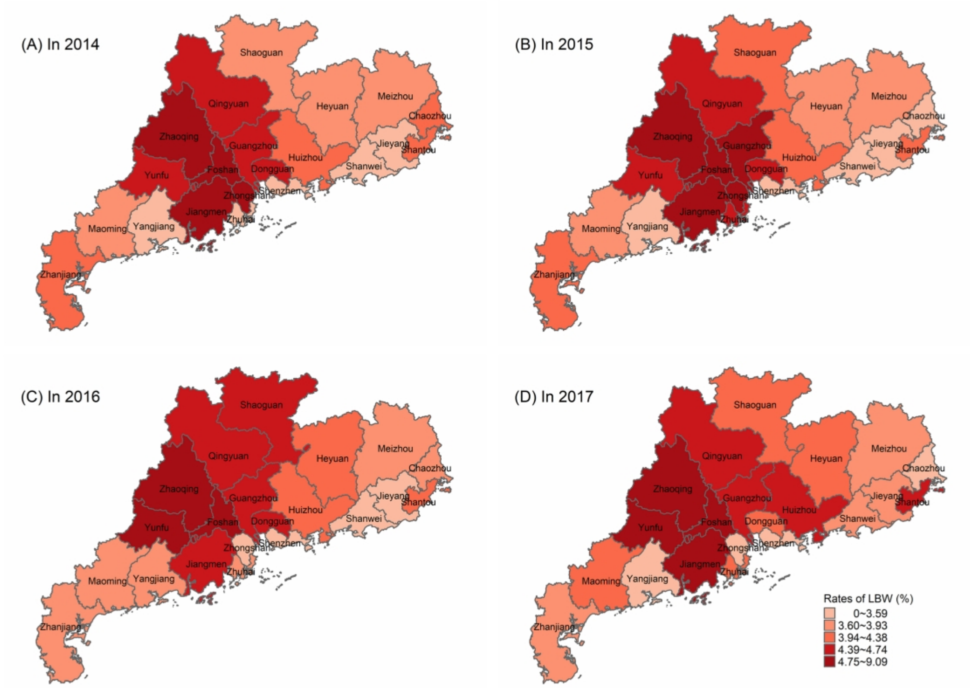

(A) In 2014
(B) In 2015
(C) In 2016
(D) In 2017
Shaoguan
Qingyuan
Heyuan
Meizhou
Chaozhou
Zhaoqing
Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Zhongshan
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
Rates of PTB (%)
0~3.26
3.27~3.97
3.98~4.82
4.83~5.18
5.19~9.09

Fig 4


(A) In 2014
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(B) In 2015
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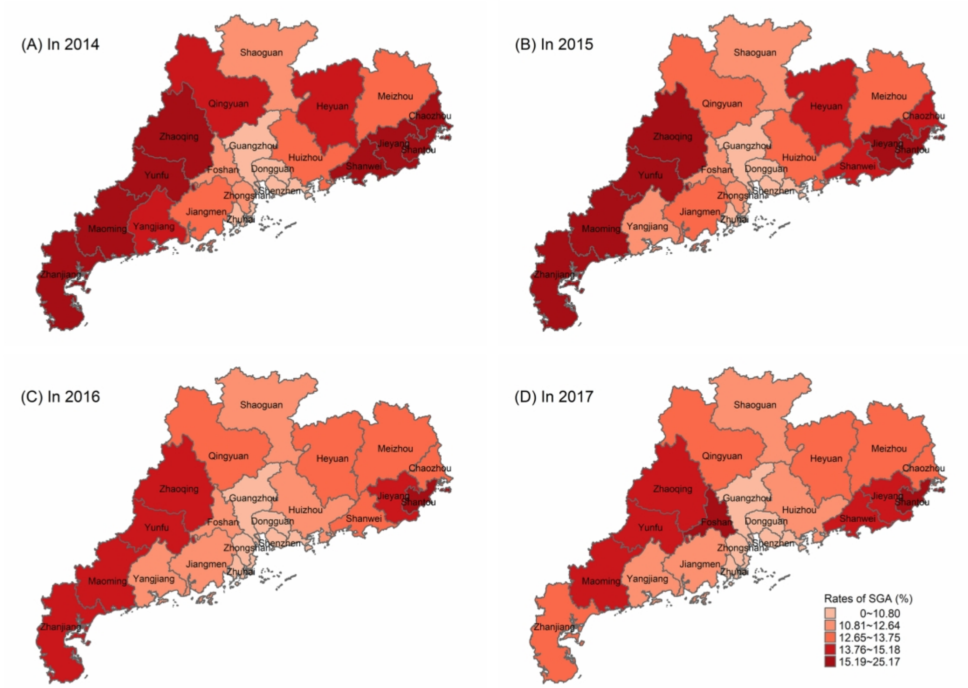
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
(C) In 2016
Shaoguan
Meizhou
Heyuan
Qingyuan
Chaozhou
Zhaoqing
Guangzhou
Jieyang
Shantou
Huizhou
Yunfu
Foshan
Dongguan
Shanwei
Zhongshan
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
(D) In 2017
Shaoguan
Meizhou
Heyuan
Qingyuan
Chaozhou
Zhaoqing
Guangzhou
Jieyang
Shantou
Huizhou
Yunfu
Foshan
Dongguan
Shanwei
Zhongshan
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
Rates of LBW (%)
0~3.59
3.60~3.93
3.94~4.38
4.39~4.74
4.75~9.09

Fig 5


(A) In 2014
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Heyuan
Meizhou
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Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Shenzhen
Zhongshan
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
(B) In 2015
(C) In 2016
(D) In 2017
Rates of SGA (%)
0~10.80
10.81~12.64
12.65~13.75
13.76~15.18
15.19~25.17

Fig 6

Supplementary File

Figure S1. The results of purely spatial clustering of preterm births according to the Kulldorff's spatial scan statistic. The most likely cluster identified was marked with red.

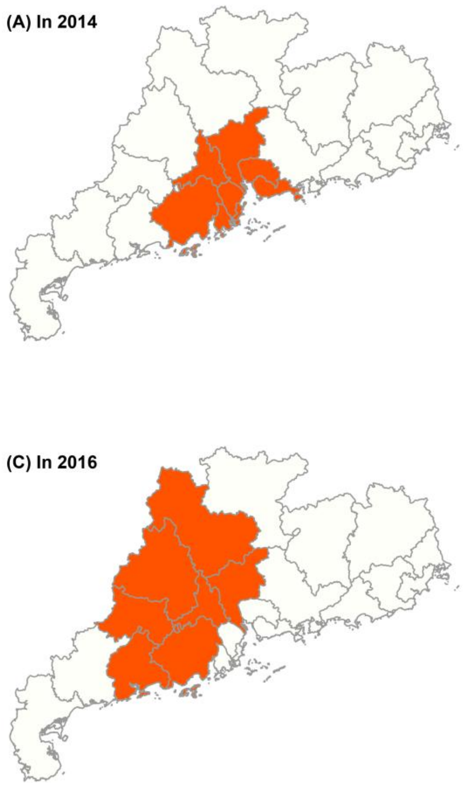

Figure S2. The results of purely spatial clustering of low birth weight infants according to the Kulldorff's spatial scan statistic. The most likely cluster identified was marked with red.

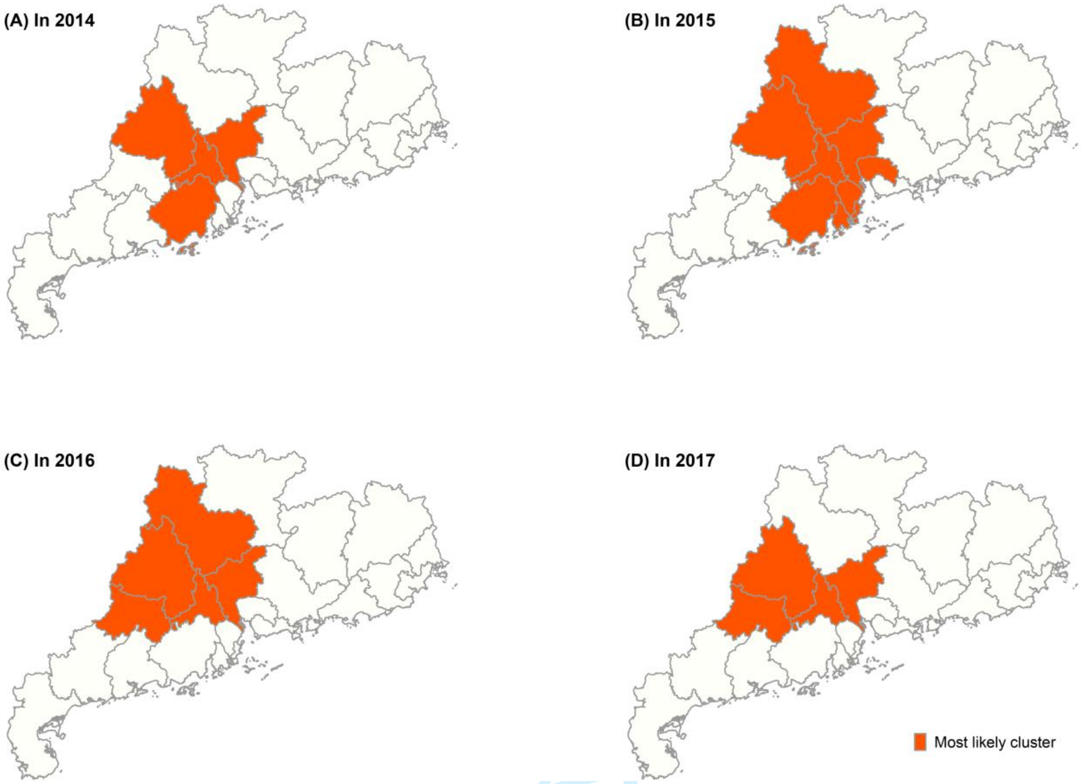

Figure S3. The results of purely spatial clustering of small-for-gestational-age infants according to the Kulldorff's spatial scan statistic. The most likely cluster identified was marked with red.

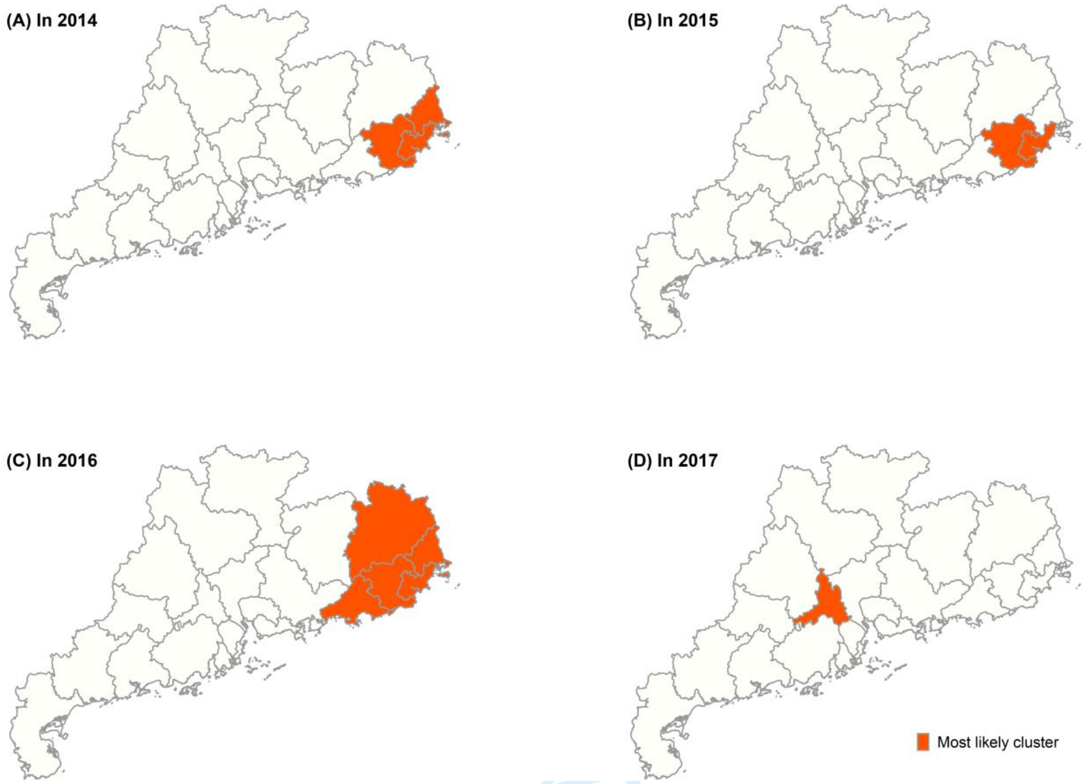

Table S1. The results of purely spatial clustering according to the Kulldorff's spatial scan statistic. The results of the most likely cluster by adverse birth outcome are shown.

Outcome	Year	Coordinates	Observed cases	Expected cases	LLR	*P*-value
PTB	2014	22.5160N, 113.3926E	9439	8669.02	560.61	0.00
	2015	22.5603N, 113.1110E	10716	9995.57	456.72	0.00
	2016	23.0710N, 112.0032E	11809	10390.57	320.46	0.00
	2017	22.5533N, 113.8831E	8892	8530.58	780.61	0.00
LBW	2014	22.9003N, 112.8926E	8037	6820.77	133.05	0.00
	2015	22.9003N, 112.8926E	12099	10424.63	135.78	0.00
	2016	23.1582N, 112.5671E	9840	8510.90	162.32	0.00
	2017	23.1582N, 112.5671E	7792	6677.31	73.06	0.00
SGA	2014	23.4624N, 116.6781E	5943	6331.37	404.23	0.00
	2015	23.2503N, 116.4331E	5013	5357.05	430.82	0.00
	2016	23.4624N, 116.6781E	9158	10061.89	691.66	0.00
	2017	22.9203N, 112.8926E	1824	1464.99	3260.36	0.00

PTB: Preterm birth; LBW: Low birth weight; SGA: small for gestational age; LLR: Log likelihood ratio.

Coordinates: The coordinates of the most likely cluster.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Adverse birth outcomes in Guangdong province, China, 2014-2017: a spatio-temporal analysis of 2.9 million births

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Paediatrics
Keywords:	PUBLIC HEALTH, EPIDEMIOLOGY, Community child health < PAEDIATRICS

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Adverse birth outcomes in Guangdong province, China, 2014-2017: a spatio-temporal analysis of 2.9 million births

Authors

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The manuscript word counts 4155 words.

Abstract

Objectives Adverse birth outcomes pose a great threat to the public health and bring a heavy burden of disease in China. A comprehensive examination of the temporal and spatial trends of preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) epidemics can provide some elementary information for subsequent etiological and epidemiological studies. This study aimed to characterize the spatio-temporal features of PTB, LBW, and SGA based on a large cohort of live births in China.

Design Spatio-temporal descriptive analysis was performed in Guangdong province, China, from 2014 to 2017.

Setting Data involving 2,917,098 live births in Guangdong province, China from 2014 to 2017 was collected from Guangdong Birth Certificate System. Information was collected, including the date of birth, gestational age in week, birth weight, sex of the infant, age of the mother, and registered residence of the mother.

Results The estimated rate of PTB, LBW and SGA was 4.16%, 4.14% and 12.86%, respectively. For temporal trends, the rates of PTB, LBW and SGA showed seasonal fluctuations, especially for LBW and SGA. In addition, there were regional differences in the rates of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. From 2014 to 2017, the high rates of PTB and LBW expanded from the Pearl River Delta region to the Non-Pearl River Delta regions. However, compared with the Pearl River Delta region, the rate of SGA was higher in the Non-Pearl River Delta regions on the whole.

Conclusion The findings of this study contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA in south China.

Keywords: Preterm birth; Low birth weight; Small for gestational age; Spatial; Temporal

Strengths and limitations of this study

- This study is a spatio-temporal descriptive analysis to reveal the current situation of adverse birth outcomes in Guangdong, south China.
- The study involves a cohort of nearly 2.9 million live births and further enhances our understanding of the temporal trend and spatial distribution of adverse pregnancy outcomes in south China.
- Multiple adverse pregnancy outcomes including preterm birth, low birth weight, and small for gestational age have been investigated and compared in terms of their temporal trend and spatial distribution.
- As a descriptive analysis, this study was unable to identify the causal relationship between spatio-temporal factors and adverse pregnancy outcomes.
- Delays in reporting birth certificate data at small hospitals in different cities may cause bias.

Introduction

Previous studies [1, 2] suggested that severe infant morbidity and mortality partly resulted from adverse birth outcomes including preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA). PTB is defined as a live-birth infant with less than 37 complete weeks of gestation [3]. LBW is defined as a live-birth infant weighing less than 2,500 grams at birth [4]. SGA is defined as an infant whose birth weight falls below the 10th percentile by sex and gestational week of all singleton live births in a region [5]. With the development and progress of society and the continuous improvement of the level of medical care, the health condition of infants and young children has been significantly improved. However, adverse pregnancy outcomes such as PTB, LBW and SGA have not been effectively controlled, which has become an important risk factor for infant health. PTB rates were reported ranging from 6.2 % to 11.9% of live births in some developed and developing countries [6]. In fact, the incidence of LBW in developed countries is still high, and even rising [7]. Among 135 million infants born in low and middle income countries in 2010, it is estimated that 29.7 million (22%) were term births of SGA, and 2.8 million (2.1%) were PTBs of SGA [8]. In Guangzhou city of south China, a PTB rate of 5.6% has been reported in a previous study [9]. A retrospective study involving 39 hospitals of different levels from 14 provinces and autonomous regions in China throughout 2011 reported that a total of 7474 cases were diagnosed as LBW (incidence = 7.2%) [10]. Overall, these adverse birth outcomes pose a great threat to the health of infants.

Additionally, the adverse outcomes of PTB, LBW and SGA may also increase the risk of chronic diseases or developmental outcomes later in life [11, 12]. These facts show that PTB, LBW and SGA are still challenging problems of public health in many countries. Thus further research is needed to investigate the epidemiology of these problems more comprehensively. Many previous studies described significant seasonal variations of PTB, LBW or SGA with remarkable differences between regions [13, 14]. However, some researches didn't detect an association between temperature and adverse pregnancy outcome [15-17]. In fact, the conditions of evidence differed among different regions and studies. The complexity of PTB, LBW, SGA and relevant risk factors in the individual, social and spatial levels often make the causal relationship between identified risks and responses non-stationary in space and time. A comprehensive examination of the temporal and spatial trends of PTB, LBW, and SGA can provide some basic elements for subsequent etiological and epidemiological studies.

As the southern gate of China, Guangdong province has the most developed economic and social level in South China [18]. However, there are still regional differences in the industrial development, the degree of medical care and the level of education of the local residents that cannot be ignored. These factors may have an impact on the fertility status of local residents in Guangdong province. In addition, more recent data about the fertility status of local residents have not been reported. There is an urgent need to provide an overall description of the fertility situation of the local population in order to carry out some other follow-up exploratory studies. Therefore, in order to fill in the gap, we performed a spatio-temporal analysis of PTB, LBW, and SGA, based on a large cohort involving approximately 3 million newborns in Guangdong province, China from 2014 to 2017. This study is more convincing because of the relatively large investigated samples. Additionally, this study analyzed regional differences of PTB, LBW and SGA between the Pearl River Delta and Non-Pearl River Delta regions. In general, the Pearl River Delta regions represent economically developed regions in Guangdong province, while Non-Pearl River Delta regions represent relatively underdeveloped regions. The findings of this study will contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA, and the design of prevention and intervention strategies for specific geographical areas and high-risk populations.

Materials and methods

Patient and public involvement

All birth data in this study was obtain from Guangdong Birth Certificate System and was only used for statistical analysis. Information of newborn and mothers across Guangdong province were collected in this study. No patients or public were involved in development of research question, study design, conduction of research and measurement of outcome. There are no plans of disseminating research results to participants.

Ethics statement

Ethical approval was obtained from ethics committee of Guangdong Woman and Children Hospital. The approval number is 201601011.

Data preparation

All birth data was collected from the Guangdong Birth Certificate System, which collects information of infants and young children from medical institutions in Guangdong province. After childbirth, obstetric medical staff put the baby on an electronic scale, record stable weight data. Health care workers or midwives fill out the delivery information of the newborn in the regional maternal and child information system. The logical settings of the system have been corrected to ensure the convincing records. Finally, the information will be transferred to the Guangdong Birth Certificate System. After the data being imported, the midwife director and the hospital doctor director need to confirm the birth information. Before the birth certificate is issued, the department of medical management and the parents should check the birth information again. All the information is verified by medical professionals. The birth registration database contains the date of birth, gestational age in week, birth weight, sex of the infant, parity, age of the mother, and registered residence of the mother. All live newborns were included in the study except for stillbirths, deaths within days of birth and birth defects. To reduce bias, the subset of births was limited to singleton live births with 22-42 completed weeks gestation [19]. After further excluding births with implausible birth weights (less than 500 grams) [20] and verifying data, we included a total number of 2,914,198 births in our analysis.

Data analysis

We described basic characteristics of the newborns and mothers, and the rates of PTB, LBW and SGA according to the studied characteristics by year and compared the estimates using χ^2 test. In order to observe the temporal trends in the occurrence of PTB, LBW and SGA in the study site, we calculated daily rates of PTB (daily number of live births with gestational age less than 37 weeks/daily number of live births × 100%) [3], daily rates of LBW (daily number of live births with birth weight less than 2500 g / daily number of live births × 100%) [4], daily rates of SGA (daily number of live births with birth weight less than the 10th percentile of the normal average birth weight at the same gestational age/daily number of live births at the same gestational age × 100%) [21], respectively. We determined the season of birth based on the birth date (spring: March-May, summer: June-August; autumn: September-November, winter: December-February). Heatmaps of weekly average rates of PTB, LBW and SGA were drew to investigate whether the rates exhibited an obvious seasonality. SAS software version 9.3 (SAS Institute Inc.; Cary, NC, the United States) was used for the statistical analyses.

According to economic conditions, Guangdong province can be divided into Pearl River Delta regions and Non-Pearl River Delta regions. Pearl River Delta regions are economically developed regions, including Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Zhaoqing, Huizhou and Jiangmen cities. By contrast, Non-Pearl River Delta regions are relatively underdeveloped regions, including Shantou, Chaozhou, Jieyang, Shanwei, Zhanjiang, Maoming, Yangjiang, Yunfu, Shaoguan, Qingyuan, Meizhou and Heyuan cities. Besides, city boundary shape files of Guangdong province were publicly obtained from the National Geomatics Center of China (http://www.ngcc.cn/ngcc/) and used for disease mapping. We mapped the spatial distributions of rates for the adverse birth outcomes to investigate the spatial distributions pattern of the birth outcomes through 2014 to 2017. In addition, we calculated the Kulldorff's spatial scan statistic using the DCluster package within R software for purely spatial cluster detection of the adverse birth outcomes. All statistical tests were 2-tailed. *P*-value less than 0.05 were considered to be statistically significant.

Results

Figure 1 shows the geographical locations of the study in Guangdong province. Guangdong province is located in southern China and is also currently the most populous province in China. There were a total of 2,917,098 births in Guangdong province during the study period, 1,553,948 (53.27%) were boys. Approximately 22% (627,146) babies were born in 2015, which is the lowest population of all births between 2014 and 2017. As illustrated in Table 1, the proportion of mothers who aged less than 20, 20 to 24, 25 to 29, 30 to 34, and over 35 years old was 2.68%, 22.78%, 39.87%, 23.38% and 11.29%, respectively. For the seasons of birth, the proportion of babies born in spring, summer, autumn and winter was 23.16%, 24.61%, 27.57% and 24.66%, respectively. There were 56,748 (42.96%) LBW of preterm births, while there were 63,968 (52.93%) LBW of term births. Regarding SGA infants, 2.47% were preterm births, while 97.53% were term births.

Table 2 reveals that the rates of PTB, LBW and SGA according to demographic characteristics, residence address and birth seasons by year. Infants born from women aged less than 35 years have higher rates of LBW and PTB outcomes than women younger than 35 years old (all *P*-values < 0.05). However, the rates of the difference were gradually decreasing from 2014 to 2017. From 2014 to 2016, there was a downward trend in the rates of SGA among pregnant women who were not less than 35 years old and less than 35 years old. In 2017, the rates for SGA by two groups of pregnant women rose slightly. Generally, infants who were born in the Pearl River Delta regions had higher rates of PTB and LBW than those who were born in Non-Pearl River Delta regions in Guangdong (all *P*-values < 0.05). However, infants who were born in the Pearl River Delta regions tended to have lower rates of SGA than those who were born in Non-Pearl River Delta regions (all *P*-values < 0.05). Boy and girl babies tended to be similar in the rates of the outcomes. We found the PTB rates of boys were higher than that of girls (all P-values < 0.05), among which the highest rate was in 2016 (5.02%). Besides, the LBW rates of girls were higher than that of boys (all P-values < 0.05), among which the highest rate was in 2017 (4.78%). For SGA, the highest rate was 14.46% in the girls group. In addition, the rates of PTB, LBW and SGA statistically varied among seasons of birth, respectively (all P-values < 0.05). For PTB, the highest rates were clustered in winter. For LBW, the highest rates did not show cluster tendency of season. However, for SGA, the highest rates were clustered in summer or autumn.

Figure 2 depicts daily time-series plots of the rates for the adverse pregnancy outcomes including PTB, LBW and SGA. Upon visual inspection, the rates of PTB, LBW and SGA show, to some degree, seasonal fluctuation trends, especially for the outcomes of PTB and SGA. In 2014, the rate of PTB ranged from 2.45% in October to 6.06% in February. The period of highest rates of PTB was between December and February. In 2015 and 2016, the rates of PTB in November were the lowest in the course of the year. In contrast, in 2016 and 2017, the highest rates of PTB were in October. In 2014, infants had a peak rate (5.61%) of LBW in September. Infants born from February to April were least likely to suffer from LBW, with the lowest rate (2.55%) in March. In 2017, there was a similar pattern for LBW infants with the rate (2.80%) in February, which clearly lower than the figure between September and October. Additionally, the peak rate (6.30%) of LBW occurred in October. The average of daily rates of SGA was 14.30% in this study. During the period from 2014 to 2017, infants were least likely to suffer from SGA between January and March, which is similar to the outcome of LBW. In addition, infants were most likely to suffer from SGA between September and October.

Figure 3 depicts the heatmaps of weekly average rates for PTB, LBW and SGA across cities in Guangdong province, from 2014 to 2017. For most cities, there was a remarkable seasonality in the rates of the adverse pregnancy outcomes, especially for LBW and SGA.

Figure 4 shows the spatial distributions of PTB rates, as expressed in per 100 persons, in Guangdong, from 2014 to 2017. The figure revealed that the rates of PTB were relatively high in the Pearl River Delta regions. For the years of 2014 and 2015, the highest rates of PTB were in Zhongshan and Foshan cities, located in Pearl River Delta regions. In 2016, the city of Foshan had the highest rate of PTB. Additionally, we observed that Yunfu which was located near the Pearl River Delta region had a distinctly high rate of PTB in 2016. In 2017, the city of Zhongshan has the highest rate of PTB. We observed spatial heterogeneity of PTB outcome across the study time period in Guangdong province (Fig S1 and Table S1), and the most likely cluster appearing in the Pearl River Delta was detected.

Similarly, the spatial heterogeneity of LBW and SGA was also observed in Guangdong province (Fig S2, Fig S3 and Table S1). Figure 5 and 6 depict the maps of spatial distributions of rates for LBW and SGA in Guangdong, respectively. In the years of 2014 and 2015, the rates of LBW were relatively high in the cities including Zhongshan, Foshan, Dongguan and Guangzhou in Pearl River Delta regions. In 2016, the rates of LBW were relatively high in Guangzhou, Huizhou, Dongguan and Foshan. In 2017, the rates of LBW were relatively high in Zhongshan, Huizhou, and Guangzhou in the Pearl River Delta region. For the outcomes of SGA, the cities including Shantou, Zhaoqing, and Yunfu had higher rates than other cities from 2014 to 2017. In addition, the rate of SGA in Foshan was also high in2017.

Discussion

Our study analyzed a total number of 2,917,098 live births to reveal the characteristics of the temporal trends and spatial distributions of PTB, LBW and SGA in Guangdong province from 2014 to 2017. This study reveals the overall situation and regional differences of fertility among local residents in Guangdong province, and provides more recent data about the reproductive status of local pregnant women. These findings will be beneficial to subsequently explore on the causes of differences in the fertility in Guangdong province.

For PTB, Beck et al. [6] reported in a systematic review that 9.6% were preterm births among 12.9 million births worldwide in 2005. A study estimated 14.9 million babies were preterm births in 2010, accounting for 11.1% of all live births worldwide, ranging from about 5% in several European countries to 18% in some African countries [22]. A study revealed that PTB rate was around 4.75% among 10 counties and cities in China, based on Perinatal Healthcare Surveillance System from 1993 to 2005 [23]. As the United Nations International Children's Emergency Fund (UNICEF) announced in 2007, the rates of LBW in China were still lower than those of some developed countries, such as the United States (8%), Australia (7%), the United Kingdom (8%), Canada (6%), and Japan (8%) [10]. However, the rate of LBW in China was slightly higher than the figure in South Korea (4%). According to a survey covering 14 provinces in China, the LBW rate in 1998 was 5.87%, and it decreased to 4.6% in 2006 [24]. For the worldwide rates of SGA, a previous study showed the rates were relatively high in Cambodia (18.8%), Nepal (17.9%), the Occupied Palestinian Territory (16.1%) and Japan (16.0%), while rates were relatively low in Afghanistan (4.8%), Uganda (6.6%) and Thailand (9.7%) [12]. In addition, a recent cross-sectional population-based study revealed that the rate of SGA was 12.93% from January 1, 2017 to October 31, 2017 in southern China [25]. However, the study was based on a relatively small size of data. Our study, based on a large size of data, revealed that the rates of PTB, LBW and SGA in Guangdong province were relatively low, compared with other countries in the world.

The data represents statistically significant seasonal variations of births and adverse birth outcomes in Guangdong province, China. Seasonal patterns of birth outcomes were not consistent, which may reflect different etiologies and risk factors of time for each of the examined birth outcomes. For the rates of PTB, the highest number almost occurred in winter. Besides, for SGA, the highest rates were in summer or autumn from 2014 to 2017. Studies in developed countries such as Greece [26], Atlanta [27] and

South Korea [28] revealed that PTB has a seasonal trend. LBW was also found seasonal trends [29]. A study revealed that PTB and SGA showed divergent patterns of seasonality in rural African community [30]. Seasonality of PTB, LBW and SGA was also found in Nepal. Our study indicated that the rate of PTB in November was the lowest in 2015 and 2016, while the rate in October was the highest in 2016 and 2017. Hughes et Al. [31] also found infants were least likely to suffer from SGA from January to March. In contrast, Infants were most likely to suffer from SGA from June to August and in November. In our study, the rates of SGA peaked in the time period between September and October, and the rates were relatively low from January to March. In some countries, it was also reported that PTB had an obvious seasonal trend. In London [32], babies born in winter were more likely to suffer from PTB compared with those born in spring. In Gambia [30], the rates of PTB peaked twice in a year, once in the hunger season in July and once in October. However, a previous study from the United States reported no seasonality in the rates of PTB [33]. We speculate that the inconsistent results from different countries were partly due to the differences in the study population related to geography, culture and socio-economics. Environmental factors including temperature, humidity, and sunlight have been associated with birth outcomes. According to an animal model, a biological explanation for increasing the risk of PTB is that high temperatures increase the chances of dehydration [34]. This effect increases the risk of PTB due to decreased uterine blood flow and increased secretion of prostaglandins and oxytocin. Another hypothesis is that the effect of sunlight on vitamin D levels may affect fetal growth [35]. A study indicated that seasonal patterns are potential representatives of various environmental exposures [36].

In terms of spatial factors, the PTB, LBW and SGA rates in the Pearl River Delta region were significantly different from those in the non-Pearl River Delta region. A regional analysis in Japan revealed that incidence of PTB was 3.2% in coastal areas and 5.0% in inland areas, respectively, and the incidence of LBW was 6.5% in the coastal areas and 8.5% in the inland areas [37]. Our results of geographical distributions of the adverse pregnancy outcomes were basically consistent with the results from

Brazilian regions, in which a higher LBW rates were observed in the developed regions compared with less developed regions [38]. Overall, from 2014 to 2017, the high rates of PTB and LBW expanded from the Pearl River Delta region to the Non-Pearl River Delta regions. The trend of LBW rates increased in less developed areas of Guangdong province year by year. Previous studies also suggested that PTB is often associated with LBW, and their risk factors are similar [39, 40]. Our study indicated that the rates of SGA in the non-Pearl River Delta regions were generally higher than the Pearl River Delta regions. Previous study suggested that adverse pregnancy outcomes can be increased by preconception risk factors and lifestyles [41]. As we known, there are obvious regional differences in the level of social-economic development in Guangdong province [42]. These regional factors may have a direct impact on the fertility status and reproductive outcome of the local population. In China, the Pearl River Delta region has better economic situation, education condition and nutritional support than the non-Pearl River Delta regions. Therefore, according to our actual situation, we need to pay more attention to relatively poor regions. We recommend increasing investment in its economic, medical and health resources. Previous study indicated that regional factors may affect birth outcomes through psychosocial processes associated with health behavior, physiological stress hormones, or increased susceptibility to infection [43]. In the future work, we hope to further explore this topic by introducing more variables into the spatio-temporal model, rather than just economic conditions. Because there are few reports on the regional distribution of adverse pregnancy outcomes in China, the contribution of this study is to analyze the characteristics of adverse pregnancy outcomes in Guangdong province from two aspects: time trend and geographical distribution.

In fact, it is often difficult for developing countries to obtain accurate and complete demographic data and medical records for maternal delivery. This present study made use of high quality data of birth certificate from a structured database of birth certificate in Guangdong province. The results of this study involving a large cohort of live births provide a clear description of temporal trends and spatial distributions of

PTB, LBW and SGA in Guangdong province, which can be a high-quality baseline indicator for the researchers and decision makers of the public health.

This study does have several limitations. First, this study was just a descriptive analysis of temporal trends and spatial distributions of the adverse pregnancy outcomes, and unable to identify the causal relationship between spatio-temporal factors and adverse pregnancy outcomes. Although we used time trend profiles to roughly observe seasonal patterns, we did not consider potential factors that are difficult to measure, such as maternal infections and nutritional deficiencies. Second, it should note that there may have some delays in reporting birth certificate data at small hospitals in different cities, which can also have a potential impact on our study.

In summary, our study is one of the few studies based on a large cohort of newborns to understand the public health problem of adverse birth outcomes in China. The findings of this study contribute to the understanding of the etiology and epidemiology of PTB, LBW and SGA.

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Competing interests

The authors declare there is no conflict of interest regarding the publication of this paper.

Contributions

HZM, LW, BL, FY contributed equally in this study and they are joint first authors. HZM, PG and QGZ conceived of or designed study. HZM, BL, LW, FY, YLC, RYC, YTW, and PG performed research. HZM, PG, and FY analyzed data. PG, HZM, JML, FY and QGZ wrote and revised the paper. PG obtained the funding.

Patient consent

All data was collected from the Guangdong Birth Certificate System that collects information of infants and young children from medical institutions in Guangdong province. No patient consent form needed for data collection.

Ethics approval

This study was approved by the ethics committee of Guangdong Woman & Children Hospital (Shantou, China).

Data sharing

No additional data are available.

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Figure legends

Figure 1. Geographical locations of the study. Guangdong province is located in south China, and there are twenty-one cities including Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Zhaoqing, Huizhou, Jiangmen, Chaozhou, Shantou, Jieyang, Meizhou, Shanwei, Shaoguan, Heyuan, Qingyuan, Yunfu, Yangjiang, Maoming, and Zhanjiang included in this study. The Pearl River Delta regions were marked with pink, and the Non-Pearl River Delta regions were indicated by light blue.

Figure 2. Daily time-series plots of rates for the adverse pregnancy outcomes including preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) in Guangdong province, China, from 1 January 2014 to 31 December 2017.

Figure 3. Heatmaps of weekly counts for the adverse pregnancy outcomes including preterm birth, low birth weight and small for gestational age across cities in Guangdong province, China, from January 1, 2014 to December 31, 2017.

Figure 4. Spatial distributions of rates of preterm birth (PTB), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of PTB rates in 2014. (B) Spatial distributions of PTB rates in 2015. (C) Spatial distributions of PTB rates in 2016. (D) Spatial distributions of PTB rates in 2017.

Figure 5. Spatial distributions of rates of low birth weight (LBW), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of LBW rates in 2014. (B) Spatial distributions of LBW rates in 2015. (C) Spatial distributions of LBW rates in 2016. (D) Spatial distributions of LBW rates in 2017.

Figure 6. Spatial distributions of rates of small for gestational age (SGA), in Guangdong province, China, from January 1, 2014 to December 31, 2017. (A) Spatial distributions of SGA rates in 2014. (B) Spatial distributions of SGA rates in 2015. (C) Spatial distributions of SGA rates in 2016. (D) Spatial distributions of SGA rates in 2017.

Tables

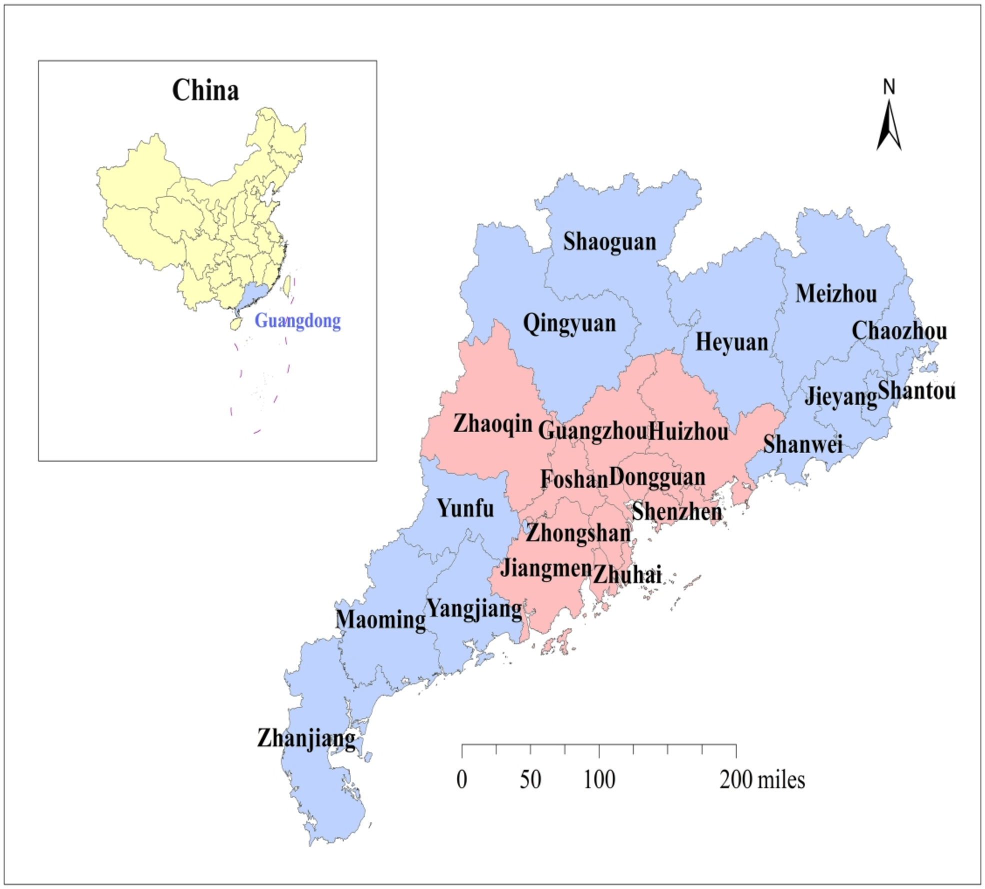
Table 1. Basic characteristics of the study participants.

Characteristic	Category	Frequency	Percentage
Maternal age (years)	< 20	78116	2.68
	20-24	664443	22.78
	25-29	1163071	39.87
	30-34	682067	23.38
	≥ 35	329378	11.29
	Missing	23	0.00
Inhabited city	Pearl River Delta region	1254102	42.99
	Non-Pearl River Delta region	1662996	57.01
Infant sex	Boy	1553948	53.27
	Girl	1363125	46.73
	Missing	25	0.00
Year of birth	2014	763518	26.17
	2015	627146	21.50
	2016	794755	27.24
	2017	731679	25.08
Season of birth	Spring	675595	23.16
	Summer	717762	24.61
	Autumn	804275	27.57
	Winter	719466	24.66
Preterm birth	Yes	121245	4.16
	No	2792953	95.74
	Missing	2900	0.10
Low birth weight (LBW)	Yes	120846	4.14
	No	2796122	95.85
	Missing	130	0.00
Small for gestational age (SGA)	Yes	384637	12.86
	No	2529522	82.88
	Missing	2939	4.26
Low birth weight (Yes)	Preterm	56748	46.96
	Full-term	63968	52.93
	Missing	130	0.11
Small for gestational age (Yes)	Preterm	9499	2.47
	Full-term	375138	97.53

Table 2. Rates of preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) according to demographic characteristics, residence address and birth season by year.

Year	Characteristic	Adverse pregnancy outcome					
		PTB (%)	*P*-value	LBW (%)	*P*-value	SGA (%)	*P*-value
2014	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	3.79		4.04		14.39	
	≥ 35	6.43		5.17		10.54	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	5.03		4.49		11.75	
	Non-Pearl River Delta region	3.39		3.91		15.43	
	Infant sex		<0.0001		<0.0001		<0.0001
	Boy	4.43		3.63		13.81	
	Girl	3.47		4.68		14.46	
	Season of birth		<0.0001		0.0003		<0.0001
	Spring	3.78		3.96		13.85	
	Summer	3.85		4.19		14.88	
	Autumn	3.8		4.21		14.88	
	Winter	4.48		4.1		12.8	
2015	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	3.79		4.05		14.09	
	≥ 35	6.5		4.91		9.51	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	5.13		4.48		11.06	
	Non-Pearl River Delta region	3.43		3.93		15.12	
	Infant sex		<0.0001		<0.0001		<0.0001
	Boy	4.51		3.68		13.43	
	Girl	3.47		4.63		14.01	
	Season of birth		<0.0001		<0.0001		<0.0001
	Spring	4.02		4.08		13.36	
	Summer	4.03		4.33		14.59	
	Autumn	3.87		4.19		14.24	
	Winter	4.2		3.87		12.53	
2016	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	4.24		3.98		12.4	
	≥ 35	6.87		4.88		8.5	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	5.28		4.25		9.9	
	Non-Pearl River Delta region	3.82		3.92		13.93	
	Infant sex		<0.0001		<0.0001		<0.0001
	Boy	5.02		3.61		11.7	
	Girl	4		4.62		12.23	

	Season of birth		0.0011		<0.0001		<0.0001
	Spring	4.49		4.02		11.76	
	Summer	4.66		4.29		12.37	
	Autumn	4.43		4.08		12.01	
	Winter	4.6		3.93		11.58	
2017	Maternal age (years)		<0.0001		<0.0001		<0.0001
	< 35	3.67		4.11		13.85	
	≥ 35	5.83		4.89		10.05	
	Inhabited city		<0.0001		<0.0001		<0.0001
	Pearl River Delta region	4.27		4.42		12.56	
	Non-Pearl River Delta region	3.82		4.08		13.82	
	Infant sex		<0.0001		<0.0001		0.1572
	Boy	4.53		3.78		13.13	
	Girl	3.5		4.78		13.24	
	Season of birth		<0.0001		<0.0001		<0.0001
	Spring	3.91		4.14		12.57	
	Summer	3.94		4.36		13.91	
	Autumn	3.98		4.46		14.23	
	Winter	4.36		4.04		12.02	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200 miles

Fig 1

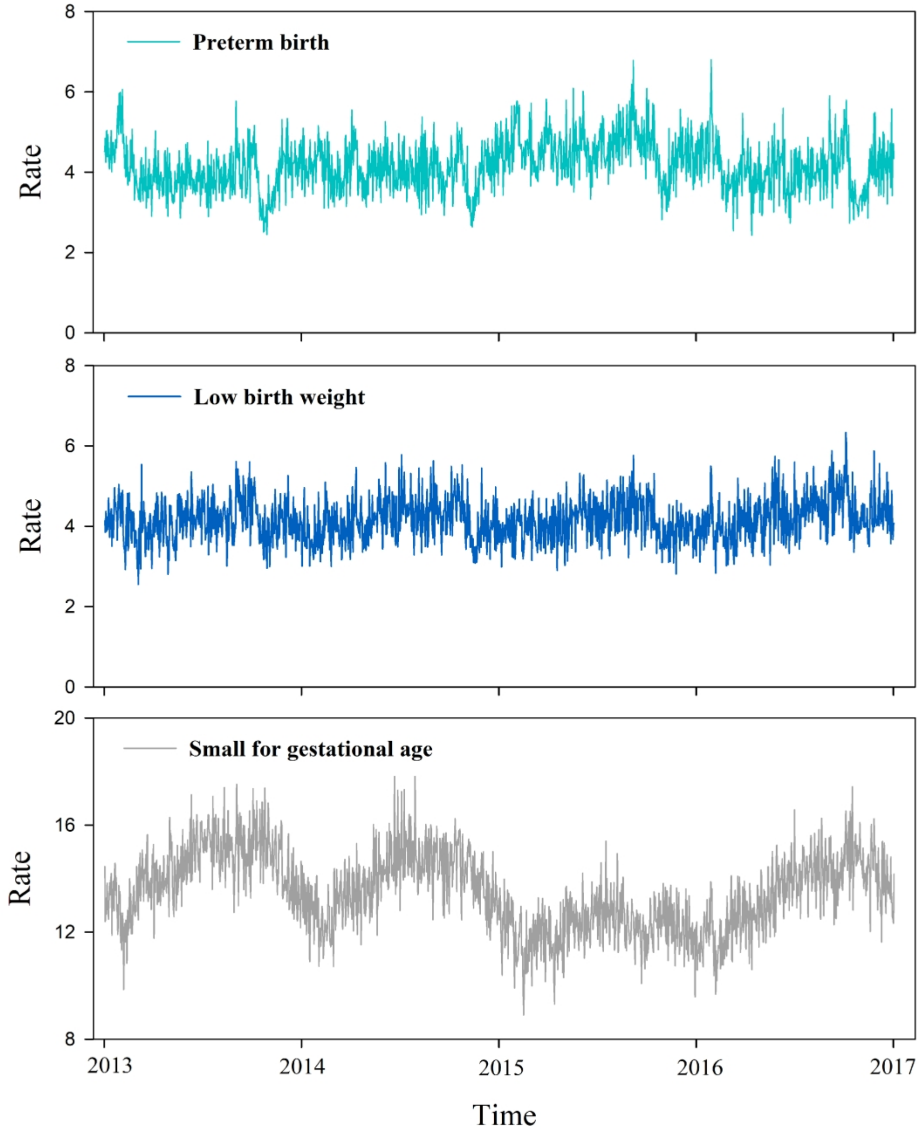
Preterm birth
Rate
Low birth weight
Rate
Small for gestational age
Rate
8
6
4
2
0
20
16
12
8
2013
2014
2015
2016
2017
Time

Fig 2


PTB
LBW
SGA
Zhuhai
Zhongshan
Zhaoqing
Zhanjian
Yunfu
Yangjiang
Shenzhen
Shaoguan
Shanwei
Shantou
Qingyuan
Meizhou
Maoming
Jieyang
Jiangmen
Huizhou
Heyuan
Guangzhou
Foshan
Dongguan
Chaozhou
2014
2015
2016
2017

Fig 3

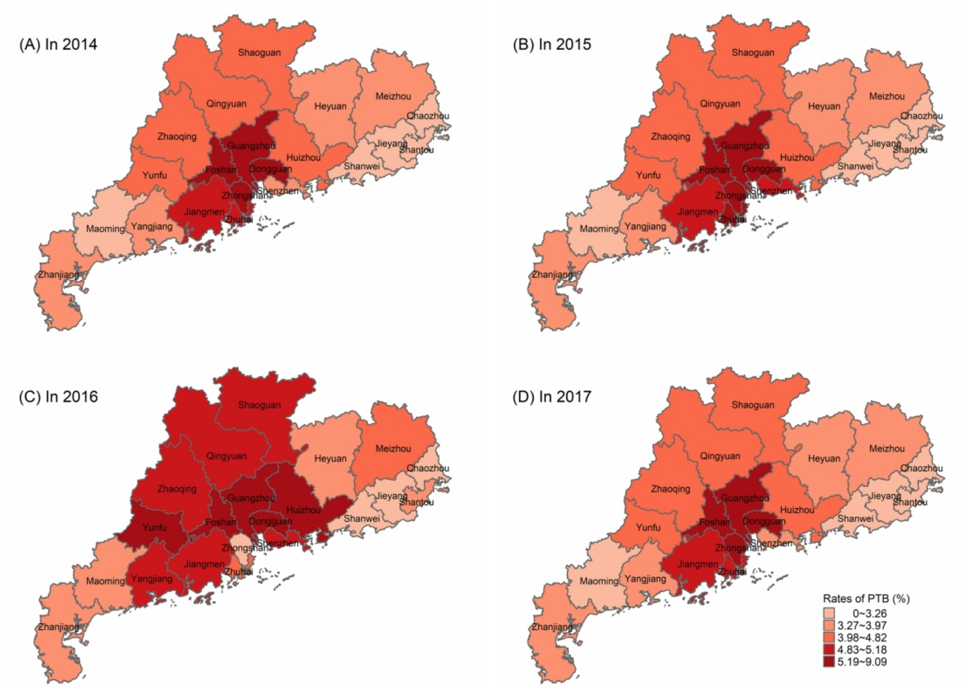
(A) In 2014
(B) In 2015
(C) In 2016
(D) In 2017
Shaoguan
Qingyuan
Heyuan
Meizhou
Chaozhou
Zhaoqing
Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Zhongshan
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
Rates of PTB (%)
0~3.26
3.27~3.97
3.98~4.82
4.83~5.18
5.19~9.09

Fig 4

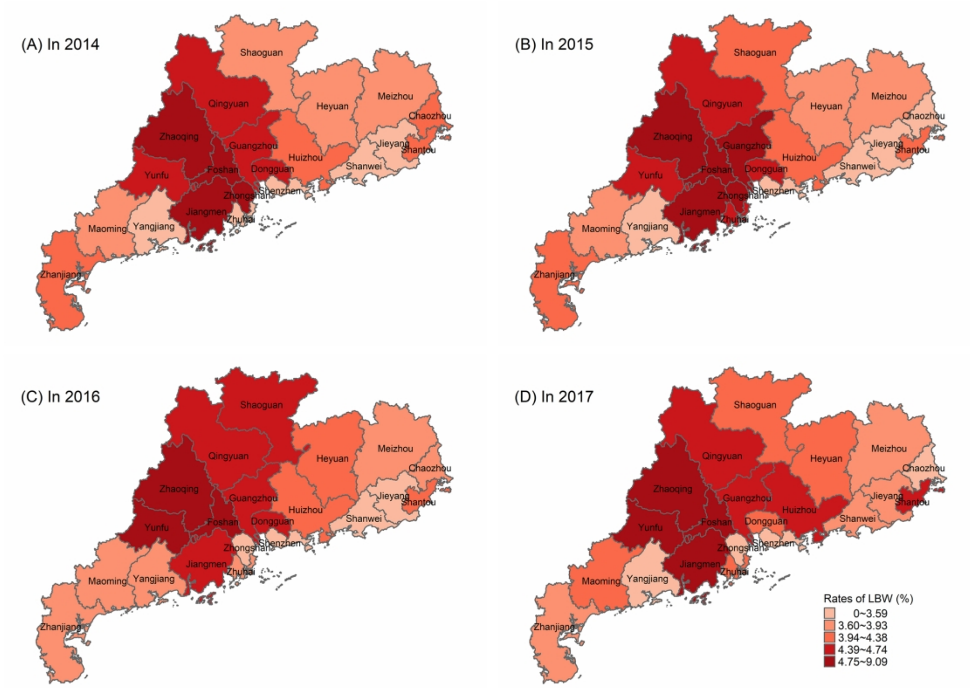
(A) In 2014
Shaoguan
Qingyuan
Heyuan
Meizhou
Chaozhou
Zhaoqing
Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
(B) In 2015
(C) In 2016
(D) In 2017
Rates of LBW (%)
0~3.59
3.60~3.93
3.94~4.38
4.39~4.74
4.75~9.09

Fig 5

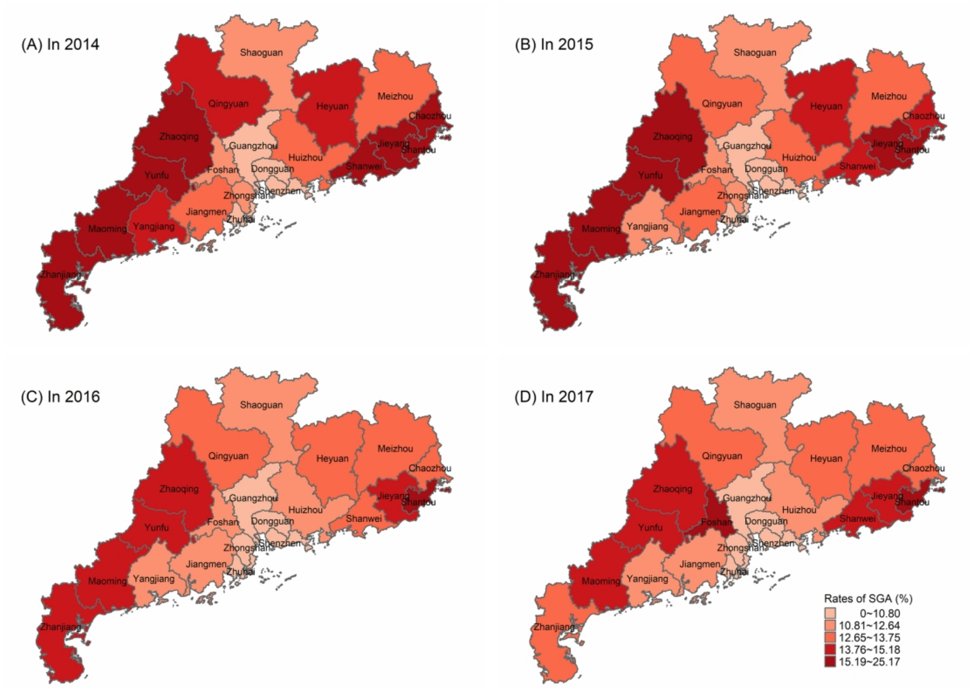
(A) In 2014
(B) In 2015
(C) In 2016
(D) In 2017
Shaoguan
Qingyuan
Heyuan
Meizhou
Chaozhou
Zhaoqing
Guangzhou
Huizhou
Jieyang
Shantou
Yunfu
Foshan
Dongguan
Shanwei
Zhongshan
Shenzhen
Jiangmen
Zhuhai
Maoming
Yangjiang
Zhanjiang
Rates of SGA (%)
0~10.80
10.81~12.64
12.65~13.75
13.76~15.18
15.19~25.17

Fig 6

Supplementary File

Figure S1. The results of purely spatial clustering of preterm births according to the Kulldorff's spatial scan statistic. The most likely cluster identified was marked with red.

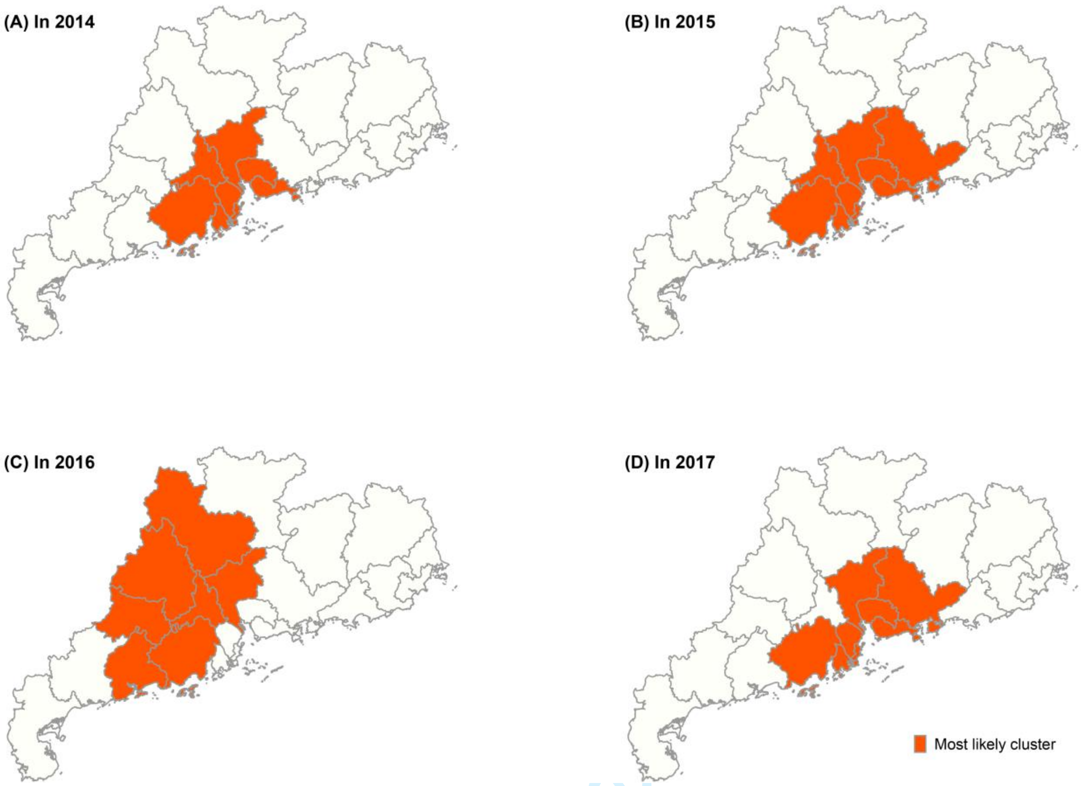

Figure S2. The results of purely spatial clustering of low birth weight infants according to the Kulldorff's spatial scan statistic. The most likely cluster identified was marked with red.

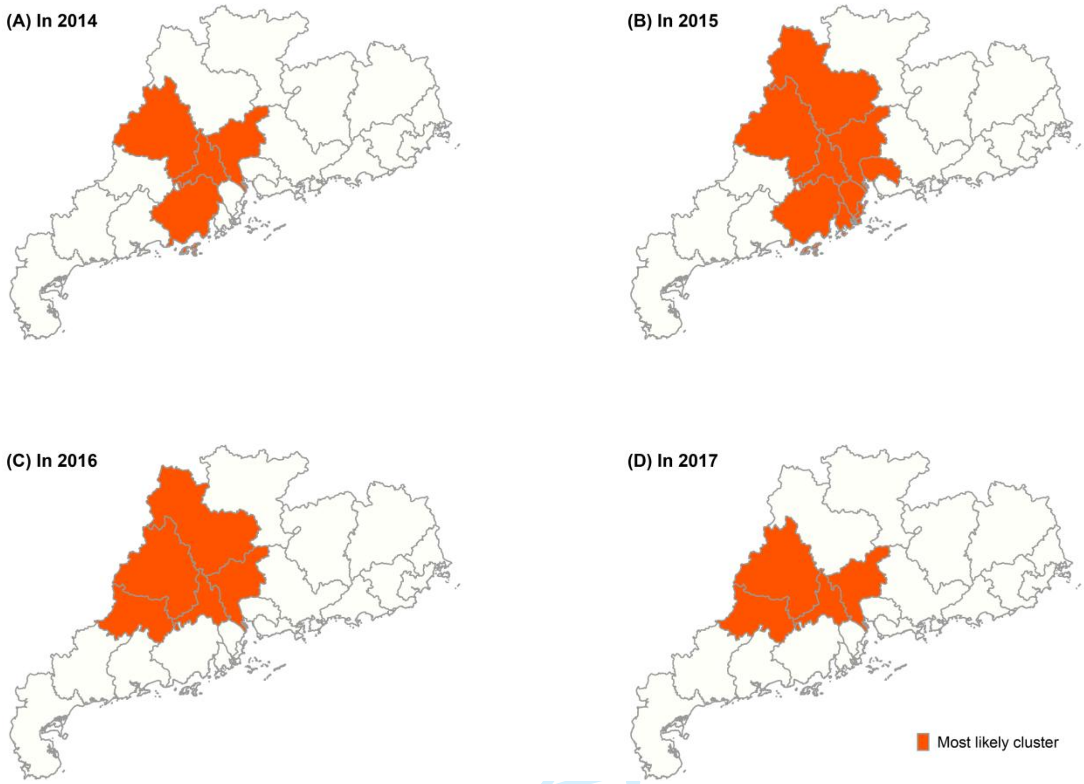

Figure S3. The results of purely spatial clustering of small-for-gestational-age infants according to the Kulldorff's spatial scan statistic. The most likely cluster identified was marked with red.

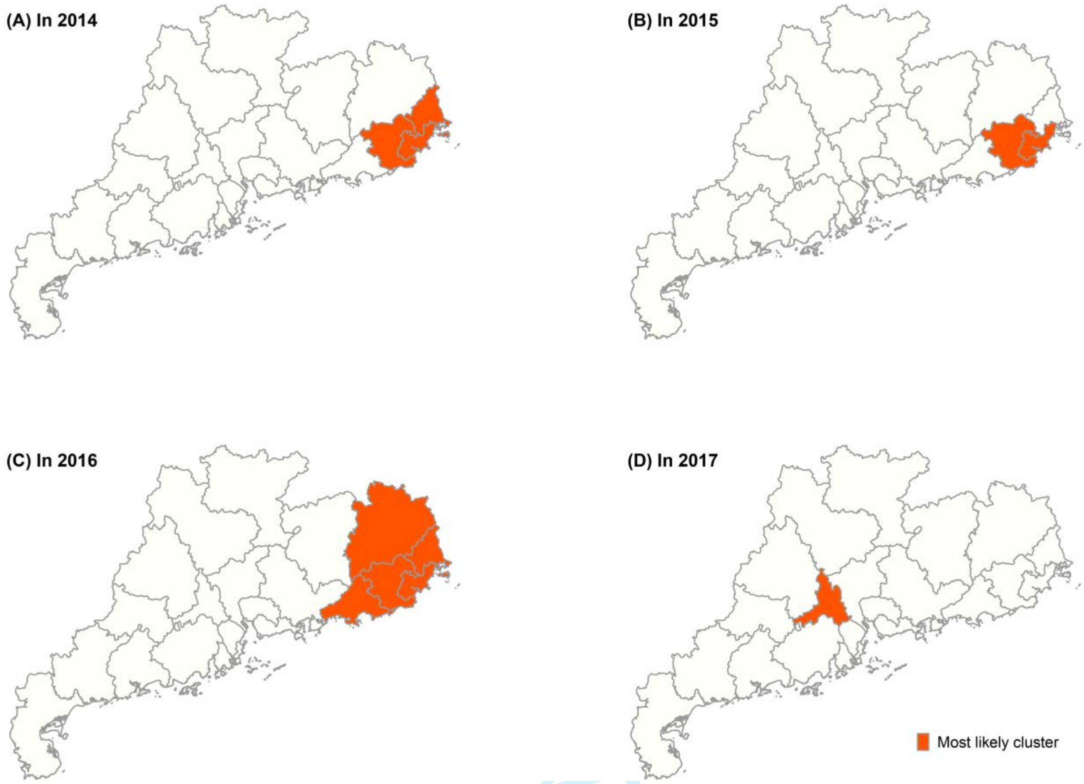

Table S1. The results of purely spatial clustering according to the Kulldorff's spatial scan statistic. The results of the most likely cluster by adverse birth outcome are shown.

Outcome	Year	Coordinates	Observed cases	Expected cases	LLR	*P*-value
PTB	2014	22.5160N, 113.3926E	9439	8669.02	560.61	0.00
	2015	22.5603N, 113.1110E	10716	9995.57	456.72	0.00
	2016	23.0710N, 112.0032E	11809	10390.57	320.46	0.00
	2017	22.5533N, 113.8831E	8892	8530.58	780.61	0.00
LBW	2014	22.9003N, 112.8926E	8037	6820.77	133.05	0.00
	2015	22.9003N, 112.8926E	12099	10424.63	135.78	0.00
	2016	23.1582N, 112.5671E	9840	8510.90	162.32	0.00
	2017	23.1582N, 112.5671E	7792	6677.31	73.06	0.00
SGA	2014	23.4624N, 116.6781E	5943	6331.37	404.23	0.00
	2015	23.2503N, 116.4331E	5013	5357.05	430.82	0.00
	2016	23.4624N, 116.6781E	9158	10061.89	691.66	0.00
	2017	22.9203N, 112.8926E	1824	1464.99	3260.36	0.00

PTB: Preterm birth; LBW: Low birth weight; SGA: small for gestational age; LLR: Log likelihood ratio.

Coordinates: The coordinates of the most likely cluster.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.