BMJ Open

Prevalence of cleft lip and/or cleft palate in Guangdong province, China, 2015–2018: a spatio-temporal descriptive analysis

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To cite: Zhu Y, Miao H, Zeng Q, *et al*. Prevalence of cleft lip and/or cleft palate in Guangdong province, China, 2015–2018: a spatio-temporal descriptive analysis. *BMJ Open* 2021;**11**:e046430. doi:10.1136/bmjopen-2020-046430

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-046430).

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Received 02 November 2020
Accepted 17 July 2021

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ABSTRACT

Objectives This study aimed to investigate the temporal and spatial characteristics of cleft lip and/or palate based on a large-scale birth defect monitoring database.

Methods Data on perinatal infants and children with cleft lip and/or palate defects from 1 January 2015 to 31 December 2018 in Guangdong province of China were collected. The variables including the demographic data, basic family information (address, education level, etc.), the infant's birth weight, gender and other basic parameters were collected and analysed.

Results During the study period, the prevalence of cleft lip and/or palate was 7.55 per 10 000 perinatal infants. The prevalence of cleft lip, cleft palate and cleft lip and palate were 2.34/10 000, 2.22/10 000 and 2.98/10 000, respectively. The prevalence of cleft lip and/or palate showed a pronounced downward trend, reducing from 8.47/10 000 in 2015 to 6.51/10 000 in 2018. We observed spatial heterogeneity of prevalence of cleft lip and/or palate across the study period in Guangdong. In the Pearl River Delta region, the overall prevalence of cleft lip and/or palate was 7.31/10 000, while the figure (7.86/10 000) was slightly higher in the non-Pearl River Delta region ($p<0.05$). Concerning infant gender, the prevalence was in general higher in boys than girls ($p<0.05$). In addition, the higher prevalence was more common in mothers older than 35 years old. For the birth season, infants born in spring tended to have a higher prevalence than those born in other seasons, regardless of the prevalence of cleft lip and palate calculated separately or jointly ($p<0.05$). The majority of newborns with cleft lip and palate were accompanied by other birth defects.

Conclusion This study contributes a better understanding of the characteristics of spatio-temporal trends for birth defects of cleft lip and/or palate in south China.

Strengths and limitations of this study

- ► This study is a descriptive analysis focused on temporal and spatial characteristics of cleft lip and/or palate and revealed the current situation of adverse birth outcomes in Guangdong, south China.
- ► Multiple adverse pregnancy outcomes including cleft lip, cleft palate and cleft lip and palate have been investigated and compared in terms of their temporal trend and spatial distribution.
- ► This study based on a cohort of nearly 7.1 million live births contributed a better understanding of spatio-temporal distribution characteristics of the birth defects in the study area.
- ► As a descriptive analysis, this study was unable to identify the causal relationship between spatio-temporal factors and adverse pregnancy outcomes.
- ► As we only have 4 years of data that is limited to determine a trend, these trends of birth defect need to be taken with caution.

INTRODUCTION

Cleft lip and/or cleft palate are congenital abnormalities, which caused by the disruption of teratogenic threats in the early stage of embryonic development and the cracking of the lips or palate.[1] Cleft lip and/or cleft palate can occur synchronously or asynchronously and can be mild or severe with or without alveolar clefts. The disease can be divided into non-syndrome and syndrome types.[2] Non-syndromic type accounts for more than 70% of facial congenital malformations.[3] Non-syndromic type can also be divided into cleft lip, cleft palate and cleft lip and palate, which does not include other systemic deformities and syndromes. Syndrome type accounts for less than 30% of the entire facial deformity. In addition to cleft lip and/or palate, syndrome type has deformities of other tissues and organs in the body, which are more than 300 types. Cleft lip and/or palate could bring a huge health burden to patients and families, and have a negative impact on patients' mental health and quality of life.[4] The disease is usually accompanied by various complications, which mainly affect voice and face.[5] A previous study[6] showed that adults with oral–facial clefts have a negative sense of social belonging and adaptation, compared with healthy adults.

As for the international distribution of cleft lip and palate, the prevalence of cleft lip and palate is declining globally.[7] In many other regions, data on cleft lip and palate cases are of poor or incomplete quality, often lacking information on important variables such as gender and severity of morphological abnormalities, the published data on the prevalence of cleft lip and/or cleft palate from different parts of the world are quite different.[8] A previous study revealed that the African population had the lowest incidence of the disease, which is about 0.4/1000; in India, the average prevalence index of this disease was 0.398/1000 from 2007 to 2011.[9] Europe's incidence is about 1/1000; Asia and South Americas have relatively a high incidence of about 2/1000.[10] Cleft lip and/or palate have the highest rates at birth in Asian (especially in China and Japan),[3] and China is one of the regions with high incidence of about 1.663/1000.[9]

Guangdong province is located in southern China, with 21 cities and a large population. Its Gross Domestic Product (GDP) ranks first in the country, however, the economic development is quite unbalanced among cities in the province. In Guangdong province, the Pearl River Delta regions are economically developed regions with a GDP accounting for 80% of the province, and hence have a better distribution of health resources. However, the non-Pearl River Delta regions are mainly economically undeveloped areas, and so as the distribution of health resources. In order to improve the quality of the birth health, understand the status and tendency of birth defects during perinatal period, and then provide scientific basic evidence for further intervention, Guangdong province has launched a birth defects surveillance programme based on hospitals since the end of 1980s by government, and then the monitoring hospitals had been expanded to all hospitals with midwifery services cross over province since October 2014.[11] Guangdong province stipulates that perinatal infants born in medical institutions must routinely monitor 23 types of congenital defects including cleft lip and palate. A 'Registration Card for Birth Defect' should be reported through the Guangdong Province Maternal and Child Health Information Platform when a birth defect of perinatal infant is diagnosed in any monitoring hospital. Based on the monitoring data of perinatal and birth defects in Guangdong, this study intended to investigate the epidemiological status and characteristics of temporal and spatial distribution for cleft lip and palate in Guangdong. The results of this study could provide a relevant basis for the ongoing prevention and control strategy of cleft lip and palate.

MATERIALS AND METHODS

Patient and public involvement

A total of 7 134 693 perinatal infants in all midwifery institutions in Guangdong province from 1 January 2015 to 31 December 2018 were reported and included. Among them, we identified a total of 9353 children with cleft lip and/or palate defects, including live births, stillbirths and early neonatal deaths. We excluded newborns whose gestational age less than 28 weeks and more than 1 week after delivery (n=3892) and 77 cases absence of gestational weeks. After that, there were 5384 perinatal infants with defects of cleft lip and/or palate included as the study subjects. There were some missing value in the variables, including maternal gestational age (n=41), race (n=20), residential areas (n=285), infants sex (n=24), multiple births (n=23), birth weight (n=400), time of diagnosis (n=489), pregnancy outcome (n=187), per capita income of household (n=572), parity (n=177) and maternal education level (n=964).

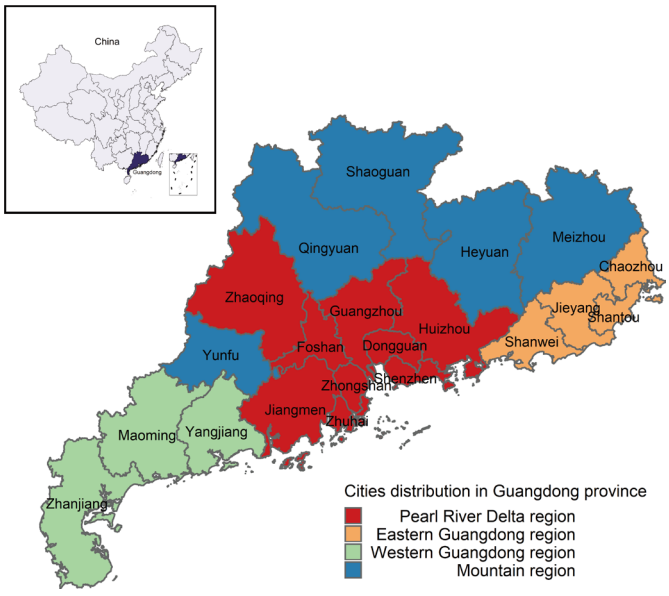

Figure 1 Geographical locations of the study area. Guangdong province is located in south China. This study included all 21 cities in Guangdong province, which are Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Zhaoqing, Huizhou, Jiangmen, Chaozhou, Shantou, Jieyang, Meizhou, Shanwei, Shaoguan, Heyuan, Qingyuan, Yunfu, Yangjiang, Maoming and Zhanjiang.

Study site

Figure 1 shows the location of Guangdong province and the regional distribution of 21 cities. Guangdong province, which located in south China, is the most economically developed province in the region. The 21 cities can be divided into four regions, namely the Pearl River Delta region, the East Guangdong region, the West Guangdong region and the Mountainous region. There are nine cities in the Pearl River Delta region, including Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Jiangmen, Huizhou and Zhaoqing. The East Guangdong region contains four cities, including Shantou, Chaozhou, Jieyang and Shanwei. The West Guangdong region includes Yangjiang and Maoming, Zhanjiang and other three cities. And the cities of Shaoguan, Qingyuan, Heyuan, Meizhou and Yunfu are considered as the Mountainous region. The Pearl River Delta region is the largest plain area in Guangdong province, and also the most

densely populated and economically developed area. Compared with the Pearl River Delta region, the other three regions are economically underdeveloped areas in the province. In particular, there are insufficient medical and health resources and uneven distribution in the Mountainous region of Guangdong province.[12 13]

Data sources

We extracted data from the Guangdong Province Maternal and Child Health Information Platform, which including registration cards and quarterly reports for infants with birth defects uploaded by more than 1900 midwifery institutions. The content of the Registration Card for Birth Defects includes basic prenatal conditions (age, education, date of last menstrual period, gestational week, pregnancy, parity, etc.) and postpartum conditions (delivery methods, infant gender, weight, height, etc.). The contents of the quarterly report include the number of perinatal babies per month, the number of perinatal babies by gender, the number of birth defects and deaths, age of pregnant mothers and the area of residence. To ensure the quality of monitoring data, the registration card and the quarterly report need to go through multi-level review by institutional, county, district, city and provincial levels. Once the data are rejected at any level, the medical workers of the institution must verify and correct the data based on clinical information.

Diagnosis of cleft lip and palate

Cases of cleft lip and palate were diagnosed by medical workers of midwifery institutions in accordance with a unified standard of the 'China Birth Defect Programme', and relevant information was filled in the registration card for birth defects. Medical workers can choose methods of auxiliary examinations including ultrasound and autopsy based on symptoms, signs and medical history to detect the cases of cleft lip and palate. Medical workers must indicate the diagnosis method when they fill out the Registration Card for Birth Defects. The diagnostic criteria meet the following conditions: (1) cleft lip (ICD 10: Q35.0–Q35.9): partial or complete split of one or both sides of the upper lip at birth, including recessive split; (2) cleft palate (ICD 10: Q36.0–Q36.9): at birth, partially or completely split of the uvula and soft palate include or exclude one or both sides of the hard palate; (3) cleft lip and palate (ICD 10: Q37.0–Q37.9): both cleft lip and/or cleft palate at birth.

Statistical analysis

The prevalence of different disease types of cleft lip and/or palate was calculated according to the urban and rural areas, the Pearl River Delta areas and the non-Pearl River Delta areas, different age groups of pregnant mothers and different birth seasons. Descriptive statistics were used to show the basic characteristics of cleft lip and/or palate children and their pregnant mothers. The characteristics including the mother's ethnicity, parity, conception season, income level, education level and the birth weight, gender, single or multiple births, whether there are other birth defects and prognosis were investigated. After we calculated the prevalence of cleft lip and/or palate based on the characteristics of the newborn and their mother, we used the χ^2 test to compare the prevalence, if necessary, the cohran-Armitage test was used in search of trends, for example, a trend in the years. Also, we compared each age category to the 25–29 age category, and obtained a separate adjusted p value for each category (<24, 30–34 and ≥35) versus 25–29 using the adjustment method of Benjamini and Hochberg. The similar analysis approach was conducted to compare each season of birth category to the spring category and obtained a separate adjusted p value for each category (summer, autumn and winter) versus spring. According to whether other birth defects were combined, we analysed the prognosis of children with different types of cleft lip and palate, including live birth, stillbirth and death within 7 days after birth. The p values derived from all statistical analyses were then compared with the adopted significance level of 0.05. A map was used to depict the location of Guangdong province in China and the geographical distribution of the four regions in Guangdong province (the Pearl River Delta regions, the East Guangdong, the West Guangdong and the Mountain regions). We used a dot-line diagram to demonstrate the annual prevalence trend of cleft lip and/or palate in Guangdong. Finally, we used maps to demonstrate the annual prevalence trend of cleft lip and/or palate in all cities of Guangdong. All statistical analyses were performed within the R V.3.62 software.

RESULTS

Figure 2 shows that the prevalence of cleft lip and/or palate was 7.55/10 000 (95% CI=7.35/10 000 to 7.75/10 000). During the study period, the prevalence of cleft lip and/or palate showed a pronounced downward trend based on the cohran-Armitage test, reducing from 8.47/10 000 (95% CI=8.04/10 000 to 8.93/10 000) in 2015 to 6.51/10 000 (95% CI=6.13/10 000 to 6.91/10 000) in 2018 (p<0.05, cohran-Armitage test). The annual prevalence of cleft lip (2.68/10 000, 95% CI=2.43/10 000 to 2.94/10 000), cleft palate (2.45/10 000, 95% CI=2.22/10

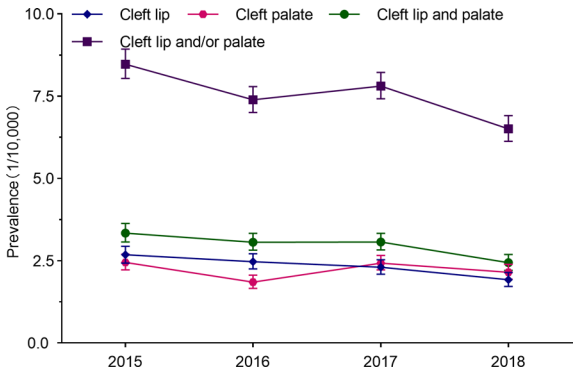

Figure 2 Prevalence of cleft lip and/or palate (per 10 000 perinatal infants) in Guangdong province, China, 2015–2018.

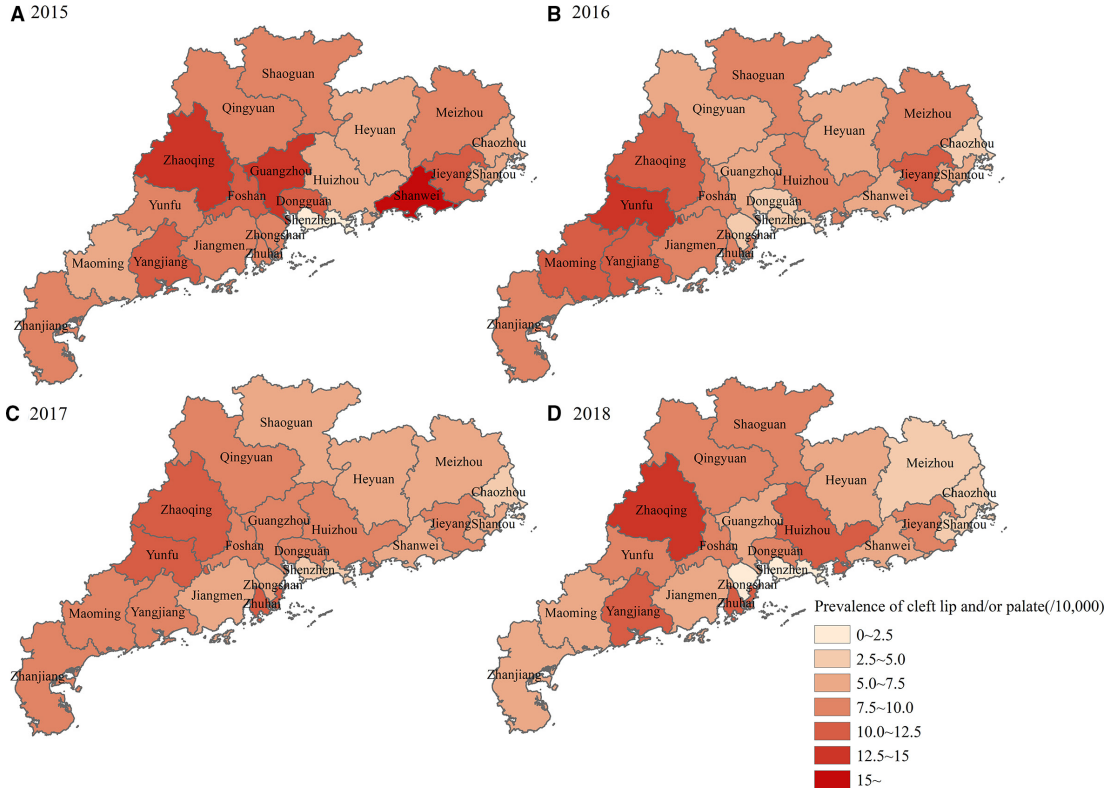

Figure 3 Spatial distributions of the prevalence of cleft lip and/or palate in Guangdong Province, China, 2015–2018. Spatial distributions of cleft lip and/or palate prevalence in (A) 2015, (B) 2016, (C) 2017 and (D) 2018.

000 to 2.70/10 000) and cleft lip and palate (3.34/10 000, 95% CI=3.07/10 000 to 3.63/10 000) were highest in 2015. From 2015 to 2018, the annual prevalence was relatively stable for cleft lip or cleft palate alone, with a slight decline across the years. When considering the infants born with cleft lip and palate, the annual prevalence decreased from 3.34/10 000 (95% CI=3.07/10 000 to 3.63/10 000) in 2015 to 2.44/10 000 (95% CI=2.21/10 000 to 2.69/10 000) in 2018 (p<0.05, cohran-Armitage test).

Figure 3 shows the spatial distribution characteristics of the prevalence of cleft lip and/or palate in all 21 cities in Guangdong province, China, from 2015 to 2018. In 2015, Shanwei city had the highest prevalence (21.68/10 000) of cleft lip and/or palate, while Shenzhen city had the lowest figure (0.65/10 000). In 2016, the highest prevalence (12.92/10 000) occurred in Yunfu city, while the prevalence (2.64/10 000) was lowest in Dongguan city. In the last 2 years of 2017 and 2018, Zhaoqing city had the highest prevalence of cleft lip and/or palate, with the figure of 12.06/10 000 and 13.30/10 000, respectively. However, in 2017 and 2018, the lowest prevalence occurred in Shenzhen (2.92/10 000) and Zhongshan city (1.64/10 000), respectively. Spatial heterogeneity of prevalence of cleft lip and/or palate across the study period in Guangdong province was observed.

Table 1 shows the prevalence of cleft lip and/or palate in different subgroups. When considering the strata of residential areas of infants, the prevalence of cleft palate alone for urban residents was in general higher than that for rural residents (2.80/10 000 vs 1.59/10 000, p<0.05). However, the prevalence of cleft lip and palate for rural infants was higher than that for urban infants (3.25/10 000 vs 2.32/10 000). In the Pearl River Delta region, the overall prevalence of cleft lip and/or palate was 7.31/10 000, while the figure (7.86/10 000) was slightly higher in the non-Pearl River Delta region (p<0.05). Similarly, the prevalence (2.45/10 000) of cleft lip and palate in the non-Pearl River Delta region was higher than that (2.26/10 000) in the Pearl River Delta region (p<0.05). On the contrary, as for cleft palate alone, the prevalence (2.63/10 000) in the Pearl River Delta region was slightly higher than that (1.68/10 000) in the non-Pearl River Delta region (p<0.05). In general, our results indicated an increased risk in young women and in older women (p<0.05). Furthermore, based on the comparison of each age category to the 25–29 age category, the prevalence was much higher among babies born by mothers older than 35 years of age in cleft lip and/or palate newborns (adjusted p<0.05). Besides, except for cleft palate, the prevalence of cleft lip and/or palate in newborns born by mothers under 24 years old was significantly higher than reference category of mothers aged 25–29 age old (adjusted p<0.05). For birth season, we observed that infants born in spring tended to have an increased risk of these defects than those born in other seasons, regardless of the prevalence of cleft lip and palate calculated separately or jointly (p<0.05), and found that the prevalence of cleft lip and palate and the prevalence of cleft lip and/or palate were significantly associated with the birth in

Table 1 Prevalence of cleft lips and/or palate (per 10 000 perinatal infants) in Guangdong province, China, 2015–2018

Variables*	Numbers of perinatal infants	Cleft lip (n=1671)				Cleft palate (n=1585)				Cleft lip and palate (n=2128)				Cleft lip and/or palate (n=5384)			
		N†	Prevalence	95% CI	P value	*N*†	Prevalence	95% CI	P value	*N*†	Prevalence	95% CI	P value	*N*†	Prevalence	95% CI	P value
Years					<0.05				<0.05				<0.05				<0.05
2015	1 654 337	443	2.68	2.43 to 2.94		406	2.45	2.22 to 2.70		553	3.34	3.07 to 3.63		1402	8.47	8.04 to 8.93	
2016	1 854 660	458	2.47	2.25 to 2.71		344	1.85	1.66 to 2.06		568	3.06	2.82 to 3.33		1370	7.39	7.00 to 7.79	
2017	1 931 797	445	2.3	2.09 to 2.53		470	2.43	2.22 to 2.66		594	3.07	2.83 to 3.33		1509	7.81	7.42 to 8.22	
2018	1 693 899	325	1.92	1.72 to 2.14		365	2.15	1.94 to 2.39		413	2.44	2.21 to 2.69		1103	6.51	6.13 to 6.91	
2015–2018	7 134 693	1671	2.34	2.23 to 2.46		1585	2.22	2.11 to 2.33		2128	2.98	2.86 to 3.11		5384	7.55	7.35 to 7.75	
Residential areas					0.67				<0.05				<0.05				0.27
Urban	3 309 392	712	2.15	2.00 to 2.32		926	2.8	2.62 to 2.98		767	2.32	2.16 to 2.49		2405	7.27	6.98 to 7.56	
Rural	3 825 301	842	2.2	2.05 to 2.35		609	1.59	1.47 to 1.72		1243	3.25	3.07 to 3.44		2694	7.04	6.78 to 7.31	
Region‡					0.10				<0.05				<0.05				<0.05
PRD	4 070 443	920	2.26	2.12 to 2.41		1071	2.63	2.48 to 2.79		985	2.42	2.27 to 2.58		2976	7.31	7.05 to 7.58	
Non-PRD	3 064 250	751	2.45	2.28 to 2.63		514	1.68	1.54 to 1.83		1143	3.73	3.52 to 3.95		2408	7.86	7.55 to 8.18	
Mother's age					<0.05				<0.05				<0.05				<0.05
<24	1 706 681	457	2.68	2.44 to 2.93	<0.05§	323	1.89	1.69 to 2.11	0.06§	708	4.15	3.85 to 4.47	<0.05§	1488	8.72	8.28 to 9.17	<0.05§
25–29	2 757 631	578	2.1	1.93 to 2.27		598	2.17	2.00 to 2.35		707	2.56	2.38 to 2.76		1883	6.83	6.52 to 7.14	
30–34	1 783 859	371	2.08	1.87 to 2.30	0.93§	400	2.24	2.03 to 2.47	0.63§	412	2.31	2.09 to 2.54	0.10§	1183	6.63	6.26 to 7.02	0.53§
≥35	886 522	249	2.81	2.47 to 3.18	<0.05§	259	2.92	2.58 to 3.30	<0.05§	281	3.17	2.81 to 3.56	<0.05§	789	8.9	8.29 to 9.54	<0.05§
Season of birth¶					<0.05				<0.05				<0.05				<0.05
Spring	1 606 602	403	2.51	2.27 to 2.77		404	2.51	2.28 to 2.77		549	3.42	3.14 to 3.72		1356	8.44	8.00 to 8.90	
Summer	1 762 310	450	2.55	2.32 to 2.80	0.82**	415	2.35	2.13 to 2.59	0.44**	502	2.85	2.60 to 3.11	<0.05**	1367	7.76	7.35 to 8.18	<0.05**
Autumn	2 017 256	402	1.99	1.80 to 2.20	<0.05**	411	2.04	1.85 to 2.24	<0.05**	583	2.89	2.66 to 3.13	<0.05**	1396	6.92	6.56 to 7.29	<0.05**
Winter	1 748 525	416	2.38	2.16 to 2.62	0.56**	355	2.03	1.82 to 2.25	<0.05**	494	2.83	2.58 to 3.09	<0.05**	1265	7.23	6.84 to 7.64	<0.05**
Infants sex					<0.05				<0.05				<0.05				<0.05
Male	3 790 783	1023	2.7	2.54 to 2.87		673	1.78	1.64 to 1.91		1309	3.45	3.27 to 3.65		3005	7.93	7.65 to 8.22	
Female	3 343 910	642	1.92	1.77 to 2.07		908	2.72	2.54 to 2.90		805	2.41	2.24 to 2.58		2355	7.04	6.76 to 7.33	

Subjects with missing values were excluded from this analysis.
*Chi-square tests were used to compare prevalence for all of these variables and obtained the p value. Besides, the mother's age and season of birth of each category were compared with the reference category to obtain the adjusted p values, which were estimated by the Benjamini and Hochberg method.
†The number of cleft lip and/or palate.
‡Two regions, the Pearl River Delta (PRD) region and the non-Pearl River Delta (non-PRD) region, are considered. The PRD region includes the cities of Guangzhou, Shenzhen, Foshan, Dongguan, Zhuhai, Zhongshan, Jiangmen, Huizhou, Zhaoqing and the other cities in Guangdong province are located in the non-PRD region, respectively.
§Adjusted p values were obtained by comparing to the reference category (mothers aged 25–29 years).
¶Spring includes March, April and May. Summer includes June, July, and August. Autumn includes September, October and November. Winter includes December, January and February.
**Adjusted p values were obtained by comparing to the reference category (spring).

spring (adjusted p<0.05) by comparing each season of birth category to the spring category. Concerning infant gender, the prevalence of the disease was in general higher in boys than girls. For example, the overall prevalence of cleft lip and/or palate in boys was 7.93/10 000, while the figure in girls was 7.04/10 000 (p<0.05).

Table 2 shows the percentage of cleft lip and/or palate across different subgroups stratified by characteristics of mothers and infants. The percentage of cleft lip and/or cleft palate was larger among women who have given birth before (54.1%) than women who have not given birth before (45.9%). In particular, we observed that the percentage of cleft lip and/or palate perinatal from high-income families (per capita income of household each year greater than or equal to 8000¥) was in general larger than in low-income families (per capita income of household each year less than 4000¥ or between 40 000 and 8000¥). We also found that infants born by mothers with an education level of middle school or less accounted for the majority of cleft lip and/or palate perinatal (63.3%). Also, the relatively large number of cleft lip and/or palate cases was observed in perinatal infants born by mothers with gestational age less than 28 weeks compared with the other two groups of gestational age. Among cleft lip and/or palate perinatal, infants with a birth weight of 2500–4000 g were the majority. Among perinatal infants with cleft lip and palate, boy infants (61.6%) were in general more common than girls (37.9%). The percentage of cleft lip and palate was higher in mothers with multiple births than those with single birth. Also, cleft lip and palate infants were often accompanied by other defective diseases. During the study period, most of the cleft lip and palate infants were live births (75.4%).

Table 3 shows the pregnancy outcome of cleft lip and/or palate perinatal infants with other defective diseases or not. For example, most of the live births with cleft lip and/or palate were accompanied by other defective diseases, accounting for 78.2%. Similar results were observed among stillbirths or infants dead within 7 days, suggesting that the majority of newborns with cleft lip and palate were accompanied by other birth defects.

DISCUSSION

In some countries, accurate demographic data and related cases are difficult to obtain partly due to the fact that the quality of the data was often poor.[14] Most of the previous relevant studies mainly focused on the comparison of the prevalence of the disease. However, we found that there is a lack of relevant studies describing the spatio-temporal characteristics of the disease. We used a reliable data platform for birth defects surveillance that offers accurate and high-quality data to investigate the issue. Our research focused on the perinatal infants who were delivered in all midwifery institutions in the region from 1 January 2015 to 31 December 2018, and described the spatio-temporal and epidemiological characteristics of cleft lip and/or palate in Guangdong province.

Cleft lip with or without cleft palate is the most prevalent congenital craniofacial defect, it is caused by the embryonic developmental disorder of the soft and hard tissues around the cavity and face.[15] It is a heterogeneous group of disorders affecting the structure of the face and oral cavity that has been divided into three general categories: cleft lip, cleft lip and palate and cleft palate.[16–18] Cleft lip and palate may be the result of Mendelian syndrome, it may be a phenotype caused by chromosomal abnormalities or it may be the result of prenatal exposure to certain teratogens.[19] The patient's ability to swallow and speak will be severely restricted, as well as insufficient oral space, breathing difficulties and self-esteem problems due to facial appearance.[20] Besides, the prevalence of cleft lip and/or palate was 7.55/10 000. Some previous studies[14] revealed that the prevalence of cleft lip and/or palate was approximately one patient per 1700 newborns, with East Asia and the Pacific considered having the highest prevalence. The prevalence of the disease in newborns in South Asia and North Africa was 12.8/10 000 and 12.2/10 000, respectively.[8 21] A recent report published by the International Clearinghouse for Birth Defects Surveillance and Research revealed that the average prevalence of the disease was 21.67/10 000 in Japan from 2007 to 2011.[9] In 2016, the prevalence (20.2/10 000) of the disease had declined slightly in Japan.[22] The prevalence of the disease in South Korea was 11.09/10 000.[22] From 2008 to 2012, the Netherlands had 330 cases of the disease, with a prevalence of 15/10 000.[23] An investigation analysed the cases of cleft lip and palate from 45 hospitals in Bogata and Cali from 2001 to 2015, and revealed that the prevalence was 11.8/10 000.[24] The prevalence of the disease in the regions mentioned above was in general higher than that of our present study. Since our study only focused on the perinatal infants, this may result in relatively low estimates of the prevalence of these defects. However, we also need to note that the prevalence in some areas was much lower than the figure of our local prevalence. For example, an analysis of cleft lip and palate in Colombia showed that the prevalence was 3.27 per 10 000 inhabitants from 2009 to 2017.[25] Also, the prevalence of the disease in Brazil was about 5.2/10 000.[26] Compared with some cities in our country, we found that the prevalence of cleft lip and/or palate in Guangdong province was lower than that in Beijing (18.9/10 000)[9] and Gansu province (13.48/10 000).[27]

The results of our present study revealed the epidemiological characteristics and spatio-temporal trends of cleft lip and/or palate in Guangdong, the most economically developed province in South China. The time trends in the prevalence of cleft lip and/or palate may reflect the changes in risk factors and pathogenesis related to the disease. Our research shows that the prevalence of cleft lip only and cleft lip and palate shows a downward trend from 2015 to 2018, while the prevalence of cleft palate is relatively stable. Over time, the prevalence of all types of clefts seems to be decreasing.[28 29] In a study focused on the time trend of cleft lip and/or palate, the

Table 2 Percentage of cleft lip and/or palate across different groups stratified by characteristics of mothers and infants

Characteristics	Cleft lip (n=1671)		Cleft palate (n=1585)		Cleft lip and palate (n=2128)		Cleft lip and/or palate (n=5384)	
	*N**	Percentage	*N**	Percentage	*N**	Percentage	*N**	Percentage
Maternal ethnicity								
Han	1620	97.3	1548	97.9	2043	96.5	5211	97.2
Minorities	45	2.7	34	2.2	74	3.5	153	2.9
Parity								
Nulliparous	702	43.2	744	48.1	943	46.4	2389	45.9
Parous	922	56.8	804	51.9	1088	53.6	2814	54.1
Season of conception								
Spring	403	24.1	404	25.5	549	25.8	1356	25.2
Summer	450	26.9	415	26.2	502	23.6	1367	25.4
Autumn	402	24.1	411	25.9	583	27.4	1396	25.9
Winter	416	24.9	355	22.4	494	23.2	1265	23.5
Income level								
<4000¥	512	35.8	368	25.6	768	39.5	1648	34.3
4000–8000¥	399	27.9	407	28.3	528	27.2	1334	27.7
≥8000¥	521	36.4	662	46.1	647	33.3	1830	38.0
Education level								
Middle school or less	871	64.3	597	49.8	1331	71.3	2799	63.3
High school	313	23.1	330	27.6	347	18.6	990	22.4
College or above	171	12.6	271	22.6	189	10.1	631	14.3
Gestational age								
<28	835	50.5	684	43.3	1137	53.9	2656	49.7
28–36	626	37.8	711	45.0	749	35.5	2086	39.0
≥37	194	11.7	185	11.7	222	10.5	601	11.3
Birth weight, grams								
<2500	265	17.5	217	15.4	602	29.2	1084	21.8
2500–4000	1220	80.6	1158	82.3	1430	69.3	3808	76.4
≥4000	29	1.9	32	2.3	31	1.5	92	1.9
Infants sex								
Male	1023	61.3	673	42.5	1309	61.6	3005	55.9
Female	642	38.5	908	57.3	805	37.9	2355	43.8
Multiple births								
Yes	1590	95.4	1532	97.2	2027	95.8	5149	96.1

Continued

Table 2 Continued

Characteristics	Cleft lip (n=1671)		Cleft palate (n=1585)		Cleft lip and palate (n=2128)		Cleft lip and/or palate (n=5384)	
	*N**	Percentage	*N**	Percentage	*N**	Percentage	*N**	Percentage
No	77	4.6	45	2.9	90	4.3	212	4.0
Time of diagnosis								
During pregnancy	408	27.6	54	3.9	820	40.3	1282	26.2
Within 7 days after delivery	1068	72.4	1323	96.1	1213	59.7	3604	73.8
With other defects								
Yes	1311	78.5	1201	75.8	1425	67.0	3937	73.1
No	360	21.5	384	24.2	703	33.0	1447	26.9
Pregnancy outcome								
Live birth	1466	87.7	1457	91.9	1605	75.4	4528	84.1
Stillbirth	122	7.3	20	1.3	444	20.9	586	10.9
Dead within 7 days	8	0.5	30	1.9	26	1.2	64	1.2

Subjects with missing values were excluded from this analysis.
*N: the number of cleft lip and/or cleft palate.
†Han nationality is the most populous ethnic group in China.
‡Spring includes March, April and May. Summer includes June, July and August. Autumn includes September, October and November. Winter includes December, January and February.

Table 3 Pregnancy outcome of cleft lip and/or palate infants with or without other defects

Pregnancy outcome	Cleft lip (n=1671)		Cleft palate (n=1585)		Cleft lip and palate (n=2128)		Cleft lip and/or palate (n=5384)	
	With, *N* (%)	Without, *N* (%)	With, *N* (%)	Without, *N* (%)	With, *N* (%)	Without, *N* (%)	With, *N* (%)	Without, *N* (%)
Live birth	1147 (78.2)	319 (21.8)	1081 (78.2)	376 (21.8)	1055 (65.7)	550 (34.3)	3283 (72.5)	1245 (27.5)
Stillbirth	89 (71.3)	36 (28.7)	19 (71.2)	2 (28.8)	320 (70.3)	139 (29.7)	428 (71.2)	177 (28.9)
Dead within 7 days	8 (100)	0 (0)	25 (83.3)	5 (16.7)	18 (69.2)	8 (30.8)	51 (79.7)	13 (20.3)

Subjects with missing values were excluded from this analysis.

prevalence of cleft lip only and cleft lip and palate showed a decreasing trend,[30] which was consistent with our result. But a study in Brazil from 2000 to 2013 showed that the prevalence of cleft lip and/or palate in the region showed an upward trend, especially in poor areas, this may be the result of imbalanced health resources.[31] In China, an epidemiological study revealed that the birth defects had a clear increasing trend, based on 2011–2015 birth defect monitoring data in Guangxi province, China.[32] Research showed that the prevalence had a rising trend in recent years in Gansu province.[27] We speculate that the differences between these studies and our results may be due to the imbalance of public health resources and that these research sites are located in economically underdeveloped areas.[31]

For spatial distributions of the prevalence, we observed spatial heterogeneity of prevalence of cleft lip and/or palate across the study period in Guangdong province. For the prevalence of the disease in the world, previous studies showed that the figure was quite different,[8] which indicated that the distribution of the disease was unbalanced and there existed spatial heterogeneity globally.[28] For example, the prevalence was relatively high in East Asia and the pacific compared with other regions in the world.[25] In addition, the prevalence of the disease was unevenly distributed in different regions and/or ethnic groups in a single country, such as the heterogeneity of different regions in Georgia.[28] According to the WHO, the prevalence of birth defects in the Netherlands varied greatly.[23] Similarly, a study revealed that there were differences in the time trend of the prevalence among 31 different geographic regions in Brazil from 1975 to 1994.[31] In our study, the prevalence of cleft lip and palate in urban areas is higher than that in rural areas. During 2005–2014, the prevalence in urban areas in Hunan province of China was higher than that in rural areas,[33] which was consistent with our findings on spatial heterogeneity in the prevalence of these defects. Furthermore, it is necessary to investigate whether there are no clusters with a defect frequency atypical for the analysed area. Then, we can compare these regions with those of lower frequency in terms of age, income, education, and other factors.

We observed a higher prevalence of cleft lip and/or palate in perinatal infants for older mothers. As the parents get older, their offspring with cleft lip and palate were at a higher risk of more severe disease.[34] Moreover, according to our research results, we observed that the prevalence of male infants with cleft lip alone or cleft lip and palate was higher than that of female infants ($p<0.05$), while the prevalence of female infants with cleft palate alone was higher than that of male infants ($p<0.05$). According to a previous study, gender differences in the incidence among cleft subgroups were observed, with the higher incidence of cleft palate, cleft lip and palate, as well as cleft lip and/or palate occurred in male infants except for cleft palate,[35] which are similar to the results of our study. This similar result supports our findings.

Overall, the higher prevalence of the disease occurred in male infants.[19 36 37] The higher prevalence among boy infants may be partly due to higher sensitivity to environmental pressure as well as gene mutations.[35] For gender disparity, our results were also supported by some epidemiological and genetic studies. For example, several studies showed that cleft lip and cleft lip and palate were more common in male infants, and cleft palate was more common in female infants.[38–40] Our results indicate that male infants with older parents were at a higher risk of cleft lip and palate. In this study, the majority of perinatal infants with cleft lip and palate were complicated by other defects, which may affect the survival rate of the infant, and further research is needed.

This study does have some limitations. First, this study is only a descriptive analysis that exploring the spatio-temporal distribution of cleft lip and/or palate in the region. It does not provide a clear causal relationship between the disease and those spatio-temporal factors. Thus, an in-depth analysis to identify the subgroups at a higher risk of the cleft lip only and cleft lip and palate based on a multivariate approach should be performed in subsequent studies. Second, although our study revealed the spatial distributions and temporal trends in the prevalence of cleft lip and/or palate, we did not consider some potential factors in our study, because these factors may have an impact on the spatio-temporal distribution of the disease. Third, as we only have 4 years of data that is limited to determine a trend, these trends of defect need to be taken with caution. Fourth, cleft lip with or without cleft palate can present as an isolated malformation or a syndromic form of malformation. The discovery of corresponding etiologic factors is important. However, this present study did not differentiate isolated from syndromic forms due to the limitation of data. When more detailed data are available, this issue should be examined in our future studies. Furthermore, the different methods of data collection may have a potential impact on the research results.[8]

This present study is one of a few studies including a large number of perinatal infants to describe the spatio-temporal characteristics of cleft lip and/or palate in south China. The findings of this study could help to understand the epidemiological characteristics of the diseases and provide reliable descriptive material for the subsequent research of the disease.

CONCLUSION

Overall, in Guangdong province, the prevalence of cleft lip and/or palate gradually decreased during the study period from 2015 to 2018. The spatial heterogeneity in the prevalence of cleft lip and palate was observed. Our results indicated that male infants are a risk group, and separately the babies born by mothers with older age have an increased risk of the disease. Most perinatal babies with cleft lip and palate tended to have other defects.

Contributors YZ, HM, QZ, BL, PG and FL conceived the study. YZ, HM, QZ, DW, PG and FL conducted the initial literature searches. YZ, HM, and QZ completed the initial drafts of the manuscript. YZ, HM, QZ, PG and FL revised the manuscript. YZ, HM, QZ, BL, PG and FL reviewed the statistical methods. HM, QZ, XY, HW and YC performed the statistical analysis. All authors read and approved the final manuscript.

Funding This work was supported by the major research plan of National Natural Science Foundation of China (no. 2018YFC1002604). The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by the Human Ethics Committee of Guangdong Women and Children Hospital (no. 201801023), and in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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