Geographic variations in the incidence of congenital hypothyroidism in China: a retrospective study based on 92 million newborns screened in 2013–2018

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Abstract

Background: Although congenital hypothyroidism (CH) has been widely studied in Western countries, CH incidence at different administrative levels in China during the past decade remains unknown. This study aimed to update the incidence and revealed the spatial pattern of CH incidence in the mainland of China, which could be helpful in the planning and implementation of preventative measures.

Methods: The data used in our study were derived from 245 newborns screening centers that cover 30 provinces of the Chinese Newborn Screening Information System. Spatial auto-correlation was analyzed by Global Moran I and Getis-Ord Gi statistics at the provincial level. Kriging interpolation methods were applied to estimate a further detailed spatial distribution of CH incidence at city level throughout the mainland of China, and Kulldorff space scanning statistical methods were used to identify the spatial clusters of CH cases at the city level.

Results: A total of 91,921,334 neonates were screened from 2013 to 2018 and 42,861 cases of primary CH were identified, yielding an incidence of 4.66 per 10,000 newborns screened (95% confidence interval [CI]: 4.62–4.71). Neonates in central (risk ratio [RR] = 0.84, 95% CI: 0.82–0.85) and western districts (RR = 0.71, 95% CI: 0.69–0.73) had lower probability of CH cases compared with the eastern region. The CH incidence indicated a moderate positive global spatial autocorrelation (Global Moran I value = 0.394, $P < 0.05$), and the CH cases were significantly clustered in spatial distribution. A most likely city-cluster (log-likelihood ratio [LLR] = 588.82, RR = 2.36, $P < 0.01$) and 25 secondary city-clusters of high incidence were scanned. The incidence of each province and each city in the mainland of China was estimated by kriging interpolation, revealing the most affected province and city to be Zhejiang Province and Hangzhou city, respectively.

Conclusion: This study offers an insight into the space clustering of CH incidence at provincial and city scales. Future work on environmental factors need to focus on the effects of CH occurrence.

Keywords: Congenital hypothyroidism; Newborn screening; Geographic mapping; Incidence

Introduction

Congenital hypothyroidism (CH) is an endocrine disorder that can cause intellectual disability and serious developmental delay, but with few or no clinical manifestations of thyroid hormone deficiency in neonates.[1] CH occurrence is related to embryo defects in thyroid gland dysgenesis or thyroid hormone synthesis.[2,3] Several mutations in thyroid developmental genes[4] and environmental factors such as iodine deficiency or excess iodine[5] have been associated with a higher risk of CH. However, its etiology remains unclear.

CH incidence is estimated at 1:2000 to 1:4000 newborns worldwide,[6] and varies by geographic location, with higher incidence in Spain,[7] Italy,[8] and Greece,[9] which are adjacent to the ocean, than that in landlocked countries, such as the Czech Republic and Bolivia.[7,10] Geographic variations in CH incidence were also observed within the same country. A US-study showed a higher

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incidence in the southwest, the Great Lakes, and Hawaii.[11] Similar geographic variations exist across China, with a 1.3 times higher incidence in newborns in coastal and inland areas[12,13] than that in remote provinces.[13-15] Further, the difference in CH incidence between cities in the same province can reach 1.5-fold.[16,17] Between-city variations in CH incidence have been ignored when using the rough data, such as provincial or regional level data, as the clustering algorithm is susceptible to the spatial scales. Clustering CH incidence using city-level data may provide new insights into the spatial distribution of CH in China. However, little is known about the high-resolution estimates of CH incidence throughout China or at different administrative levels in contemporary China.

This study describes the spatial distribution of CH cases at the provincial city levels in the mainland of China, to facilitate the cross-sectional comparison of CH disparity and explore the under-recognized association between CH etiology and environmental factors.

Methods

Ethical statements

The study was approved by the Ethics Committee of Sichuan University, China (No. K2017038). All participants signed informed consent before the screening and all procedures were performed in accordance with the *Declaration of Helsinki*, 1964, and its later amendments.

Data source

The data collected in this study were derived from the Chinese Newborn Screening Information System (CNBSIS) between 2013 and 2018. In 2018, a total of 246 newborn screening centers were authorized by the government to participate in the program and be responsible for the screening and diagnosis of neonatal hypothyroidism [Supplementary Figure 1, http://links.lww.com/CM9/A643; Hong Kong (China), Taiwan (China) and Macao (China) were not included]. The data of only one newborn screening center in Tibet were not used as it would mean considering an extremely small number of screened newborns (the coverage of newborn screening of less than 5% on average from 2013 to 2018) and would not be representative. In China, around 15,000,000 neonates were screened each year, covering approximately 97.5% of live births.[18] Following the technical guidelines for neonatal disease screening issued by the National Health Commission in 2010, a screening pathway that could detect all forms of CH (mild, moderate, and severe), was conducted nationwide; the standard operating procedure is given in Supplementary Figure 2, http://links.lww.com/CM9/A643. More details about the CNBSIS and quality control have been described elsewhere in other research.[12]

Data collection

Newborn screening information on the sample collection, delivery, laboratory testing, clinical diagnosis, and follow-up is routinely collected and reported through the CNBSIS. Three-level (local, provincial, and national) surveillance networks and medical workers groups were established to undertake the data collection. Trained staff in the local newborn screening center fill in the online individual case records of demographic, clinical, and laboratory information as soon as a neonate is diagnosed with CH. The number of neonates diagnosed and screened is gathered and reported to the provincial newborn screening center on a quarterly basis. All the reports are then inspected by the professionals in the provincial newborn screening center (PNBSC) responsible for data quality. Incomplete forms and false information are rejected, sent to the local newborn screening center (LNBSC), and checked. The final records and forms are then reported to the National Office of Maternal and Child Health Surveillance (https://sfyz.mchscn.org) for diagnosis conformation and further data review. The Tibet Autonomous Region was not included in this study due to the data being blank before 2015 and inaccurate afterward.

Statistical analysis

The available data derived from the CNBSIS on dates of birth and maternal real residence of confirmed CH cases were retrospectively analyzed. Cases without accurate address information geo-coded to city level were excluded. The CH incidence at the national, regional, and provincial levels was presented as the numbers of confirmed primary CH cases per 10,000 screened newborns during 2013 to 2018, as we considered the false-negative as zero. However, because the number of screened newborns at the city level was not available, we instead used the number of newborns as the denominator of the incidence in each city. To minimize such systematic error (the higher the screening coverage, the smaller the error), and to obtain more robust estimates of CH incidence in smaller geographic areas, the data from 2013 to 2018 were used to estimate the city-level CH incidence in eastern provinces, where the coverage of newborn screening had reached 95% since 2013, while the data from 2017 to 2018 were used in central and western provinces where the screening coverage did not reach 95% on average until 2017.

In the present study, the north and south were divided along the 35th parallel north. Thirty-one provinces were grouped into the eastern province (Guangdong, Shandong, Liaoning, Jiangsu, Fujian, Shanghai, Zhejiang, Tianjin, and Beijing), central province (Hunan, Hebei, Anhui, Hubei, Jilin, Jiangxi, Shanxi, Heilongjiang, Henan, and Hainan), and western province (Inner Mongolia, Guangxi, Shaanxi, Sichuan, Yunnan, Gansu, Guizhou, Xinjiang, Chongqing, Ningxia, Qinghai, and Tibet). The classification criteria of the eastern, central, and western regions of China were used with reference to National Maternal and Child Health Surveillance considering the factors of geographical location and economic development.[19,20] Region-specific data were aggregated using the "aggregate" function of the "stats" package in the R 3.6.1. The 95% confidence interval (CI) of CH incidence was calculated by Poisson distribution. Except for the overall and regional CH incidence, provincial and city level incidences were standardized by gender using the gender composition of total screened newborns during 2013–2018. All tests of hypotheses were two-tailed with a type 1 error rate fixed at 5%.

A Chinese shapefile (China Administration Map, 2019, https://www.webmap.cn) containing all data was imported, and investigations of space-correlation and space-clustering of the CH incidence in newborns were conducted by running OpenGeoDa2.0 (Center for Spatial Data Science, University of Chicago, IL, USA), ArcMap10.4.1 (Environmental Systems Research Institute, USA), and SaTScan (Harvard Medical School and Harvard Pilgrim Health Care Institute Boston, MA, USA) software. The spatial aggregation was analyzed using the Global Moran's I and local indicators of spatial association (LISA) at the provincial level. The Getis-Ord Gi statistic was used as the LISA statistic to identify the statistically significant hotspot. A purely spatial, discrete Poisson model was adopted and clusters of high incidence were scanned at the city level using the circular window set for this analysis. Additionally, the areal kriging interpolation was adopted to predict a smoother rate map and "none-missing" spatial distribution of CH incidence in the 364 cities of China including seven cities in Tibet, before using the scan statistics at the city level. As the data contained islands (Hainan Province) and the administrative area was uneven, we used the row standardized Delaunay-triangulation as the spatial weights matrix method to identify neighbors in this study. The formulation and parameter setting of spatial statistics mentioned above are available in Supplementary files, http://links.lww.com/CM9/A643.

Results

General geographical distributions of CH incidence

From 2013 to 2018, 91,921,334 neonates were screened, and 42,861 cases were confirmed as having primary CH, yielding an overall CH incidence of 4.66 per 10,000 screened neonates (95% CI: 4.62–4.71). Among these CH newborns, 21,069 (49.16%) were female, 21,780 (50.82%) were male, and 12 (0.02%) were unknown gender or ambiguous genitalia. The CH incidence by geographical location over the study period is shown in Table 1. The CH incidences in the central and western districts were 0.84-fold (95% CI: 0.82–0.85) and 0.71-fold (95% CI: 0.69–0.73) than that in the eastern district with gender-adjusted, respectively. However, the incidences between the northern and southern regions did not differ significantly (RR = 0.99, 95% CI: 0.97–1.01).

Spatial distribution of CH incidence at the provincial level

Table 2 presents the gender-standardized CH incidence of 30 provinces between 2013 and 2018. The CH incidence ranged from 2.29 to 7.71 per 10,000 newborns screened and obviously varied across provinces. The highest incidence was in Zhejiang (7.71 per 10,000 newborns screened, 95% CI: 7.18–8.27), followed by Fujian (7.02 per 10,000 newborns screened, 95% CI: 6.51–7.56), and Jiangxi (6.90 per 10,000 newborns screened, 95% CI: 6.39–7.43). The lowest incidences were in Xinjiang (2.29 per 10,000 newborns screened, 95% CI: 2.00–2.61) and Qinghai (2.54, 95% CI: 2.24–2.87). A moderate global clustering of CH cases occurred (Global Moran I value = 0.394, $P < 0.05$). Supplementary Figure 3, http://links.lww.com/CM9/A643 shows the LISA map in China. One high–high local cluster (high numbers of cases in an area with high numbers of cases in surrounding areas), which included 11 provinces (Anhui, Fujian, Guangdong, Henan, Hubei, Hunan, Jiangxi, Jiangsu, Shandong, Shanghai, and Zhejiang), was detected.

Spatial distribution of CH incidence at the city level

Figure 1 displays the spatial distribution of CH incidence at the city level in China between 2013 and 2018. We observed an evident gradient distribution of CH incidence, increasing gradually from the northwest to southeast areas. The locations of the highest predicted incidence were in the east and southeast parts of China. The CH incidence in Hangzhou, Zhejiang (18.72 per 10,000 newborns screened) was 17 times as high as that of Aksu Prefecture, Xinjiang (1.10 per 10,000 newborns screened). Figure 1 also illustrates the geographical concentration of the occurrence of CH varying within the same provinces; for instance, the incidence in the northern part of Zhejiang was higher than that in the southern part.

Figure 2 shows the spatial clustering of CH incidence at the city level in China over the entire study period, following the purely spatial Poisson discrete scan analysis. Overall, there was one most likely cluster and 25 secondary clusters

Table 1: Incidence rates of CH by geographical location in China, 2013–2018.

Location	No. of primary CH	No. of newborns screened	Incidence per 10,000 newborns screened (95% CI)	ARR* (95% CI)
Total	42,861	91,921,334	4.66 (4.62, 4.71)	
Region type 1				
East	18,637	34,537,711	5.40 (5.33, 5.48)	Ref.
Central	14,850	32,905,813	4.50 (4.43, 4.57)	0.84 (0.82, 0.85)
West	9374	24,477,810	3.83 (3.76, 3.91)	0.71 (0.69, 0.73)
Region type 2				
North	12,348	26,312,540	4.69 (4.61, 4.78)	Ref.
South	30,513	65,608,794	4.65 (4.60, 4.70)	0.99 (0.97, 1.01)

ARR: Adjusted odds ratio; CH: Congenital hypothyroidism; CI: Confidence interval; Ref.: Reference group. *ARR was adjusted by gender.

Table 2: Incidence rates of primary CH by province in China, 2013–2018.

Provinces	No. of primary CH	Crude CH incidence (95% CI)	Gender-standardized CH incidence (95% CI)
Anhui	2312	5.35 (5.14, 5.58)	5.37 (4.93, 5.84)
Beijing	801	5.80 (5.41, 6.22)	5.80 (5.34, 6.29)
Chongqing	982	6.09 (5.72, 6.49)	6.08 (5.61, 6.58)
Fujian	2453	7.02 (6.75, 7.30)	7.02 (6.51, 7.56)
Gansu	636	3.78 (3.49, 4.08)	3.76 (3.39, 4.16)
Guangdong	3094	5.37 (5.19, 5.57)	5.38 (5.23, 5.53)
Guangxi	2434	5.18 (4.98, 5.39)	5.18 (4.74, 5.65)
Guizhou	806	2.97 (2.77, 3.18)	2.98 (2.65, 3.33)
Hainan	208	2.75 (2.39, 3.15)	2.77 (2.45, 3.12)
Hebei	2654	4.93 (4.75, 5.12)	4.93 (4.50, 5.39)
Heilongjiang	237	3.11 (2.73, 3.54)	3.08 (2.71, 3.51)
Henan	2970	4.04 (3.90, 4.19)	4.04 (3.66, 4.45)
Hubei	1471	4.17 (3.96, 4.39)	4.17 (3.78, 4.59)
Hunan	2077	4.59 (4.40, 4.80)	4.59 (4.18, 5.03)
Inner Mongolia	234	3.32 (2.91, 3.77)	3.32 (2.97, 3.70)
Jiangsu	2429	4.75 (4.57, 4.95)	4.75 (4.33, 5.20)
Jiangxi	1997	6.80 (6.51, 7.11)	6.90 (6.39, 7.43)
Jilin	296	2.90 (2.58, 3.25)	2.89 (2.57, 3.24)
Liaoning	585	3.15 (2.90, 3.41)	3.13 (2.79, 3.50)
Ningxia	190	3.25 (2.81, 3.75)	3.25 (2.91, 3.62)
Qinghai	87	2.53 (2.03, 3.12)	2.54 (2.24, 2.87)
Shandong	5186	6.46 (6.29, 6.64)	6.46 (5.97, 6.98)
Shanghai	764	6.22 (5.79, 6.68)	6.22 (5.74, 6.73)
Shaanxi	1028	3.90 (3.67, 4.15)	3.90 (3.52, 4.31)
Shanxi	628	3.21 (2.97, 3.47)	3.21 (2.87, 3.58)
Sichuan	1718	3.77 (3.60, 3.96)	3.77 (3.40, 4.17)
Tianjin	313	4.60 (4.10, 5.14)	4.58 (4.17, 5.02)
Xinjiang	391	2.31 (2.09, 2.55)	2.29 (2.00, 2.61)
Yunnan	868	2.66 (2.49, 2.85)	2.66 (2.35, 3.00)
Zhejiang	3012	7.71 (7.43, 7.99)	7.71 (7.18, 8.27)

CH: congenital hypothyroidism; CI: Confidence interval.

encompassing 38 cities. The most likely cluster was a circular area centered on Jiaxing, Zhejiang (30.84 N, 120.93 E, with a radius of 75.38 km). The area included 5 cities (Shanghai, Hangzhou, Suzhou, Huzhou, and Jiaxing), with 2181 total CH cases and 966 expected cases under the null hypothesis of no clusters (RR = 2.36, the log-likelihood ratio [LLR] = 588.82, $P < 0.01$). The 25 secondary significant clusters were mainly located in Shandong (7/25 clusters), followed by Zhejiang (3/25 clusters). Additionally, one cluster that involved the two cities of Xuzhou and Linyi and crossing the provincial border was also detected (Secondary cluster 7, Figure 2). This cluster was centered in 34.34 N, 118.02 E, and had a radius of 44.56 km, which covered part of two provinces (Shandong and Jiangsu).

The space scanning map was consistent with the kriging interpolation map. In all of the eastern provinces except for Liaoning, there was at least one statistically significant cluster area for CH cases. Among all the city clusters, the cities located in the Yangtze river delta region accounted for 31.58% (12 cities), while those located in Shandong province accounted for 26.32% (10 cities).

Discussion

This study updated the incidence of primary CH among Chinese newborns using the data from the CNBSIS between 2013–2018, with an overall incidence of 4.66 per 10,000 newborns screened, which is consistent with estimates from previous studies in China.[12,13] We found that the incidence of primary CH varied significantly between provinces and that the eastern region was higher in incidence. By analyzing the spatial auto-correlation and scan-statistic significant clustering, we added new evidence to the geographical variations in primary CH incidence, namely that (1) the CH incidence indicated a moderate positive global spatial auto-correlation and a high–high cluster was identified; (2) the spatial distribution of the CH incidence revealed a clear gradient distribution of the northwest-southeastern part of China; and (3) CH cases are significantly clustered and most of the city-clusters were located in the Shandong Province and Yangtze River Delta region.

In terms of the CH incidence in different countries reported in the literature, the overall primary CH incidence observed in our study was close to the incidence in other Asian countries, such as Iran (4.50 cases per 10,000 births) and Bangladesh,[21,22] but higher than that in France (2.88 cases per 10,000 births) and New Zealand (3.1 cases per 10,000 births).[23,24] The higher incidence of CH in the Asian population could be partially explained by genetic and hereditary factors. According to published studies,[25,26] there was a high prevalence of *DUOX* mutations in Japan

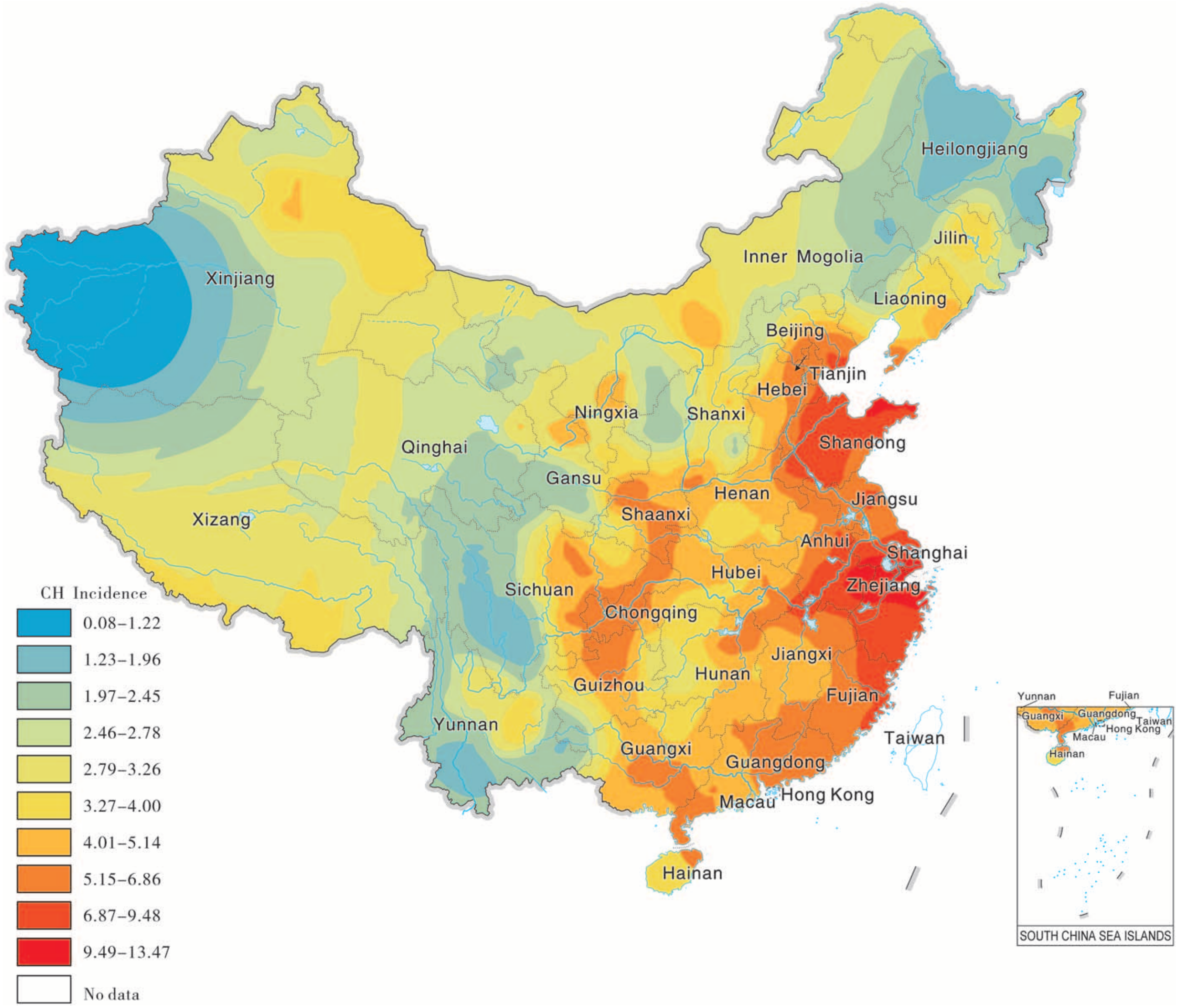

Figure 1: The spatial distribution of CH incidence at the city level in China, 2013–2018. The CH incidence in Tibet was estimated as 2.69 per 10,000 newborns screened (areal kriging interpolation was used to create the map, and the RMSE, standardized-RMSE, and mean square error values of this method were 0.0002, 0.961, and 0.043, respectively. The incidence interval was created by the geometric spacing method). CH: Congenital hypothyroidism; RMSE: Root mean squared error.

and China, which was the instigator of the hydrogen peroxide requirement for thyroid hormone synthesis. Additionally, the variation in reported CH incidence among countries may also be affected by other potential factors that result in incomparability, including different study methods (such as whether or not population-based and different population characteristics) and screening methods (TSH CO cut-off value and screening pathway).[27,28]

There was a large geographical variation in CH incidence across regions and between provinces in China. We found that the CH incidence was higher in the east, but lower in the west. Several factors could have contributed to these differences. First, changes in assay methodology accounted in part for the difference in CH incidence. Due to more sensitive testing methods and lower TSH CO for neonatal CH screening in the east than those in the west, neonates with transient CH had more chance of being detected, resulting in higher CH incidence in the east. For example, the laboratory of Shaanxi Province set the TSH CO level as 10 μU/mL for the level while Shandong Province was set at 8.5 μU/mL.[29,30] Further, because of differences in the staff investment, instrument detection system, sample processing, and socioeconomic status among newborn screening centers (the east is known to often be better off than the mid-west),[31] children with suspected cases had a higher probability of recall for diagnosis in the east. For instance, by adopting the phone app of "Newborn Screening Management Network System," Xiamen city had greatly improved the recall and follow-up rates.[32] Studies revealed that Zhejiang's recall rate reached 93.80% 15 years ago, although the recall rate in Sichuan and Xinjiang ranged from 78.54% to 38.75% in the last 5 years.[33-35]

Furthermore, we detected hot spot areas in the same eastern district; these findings may be explained by

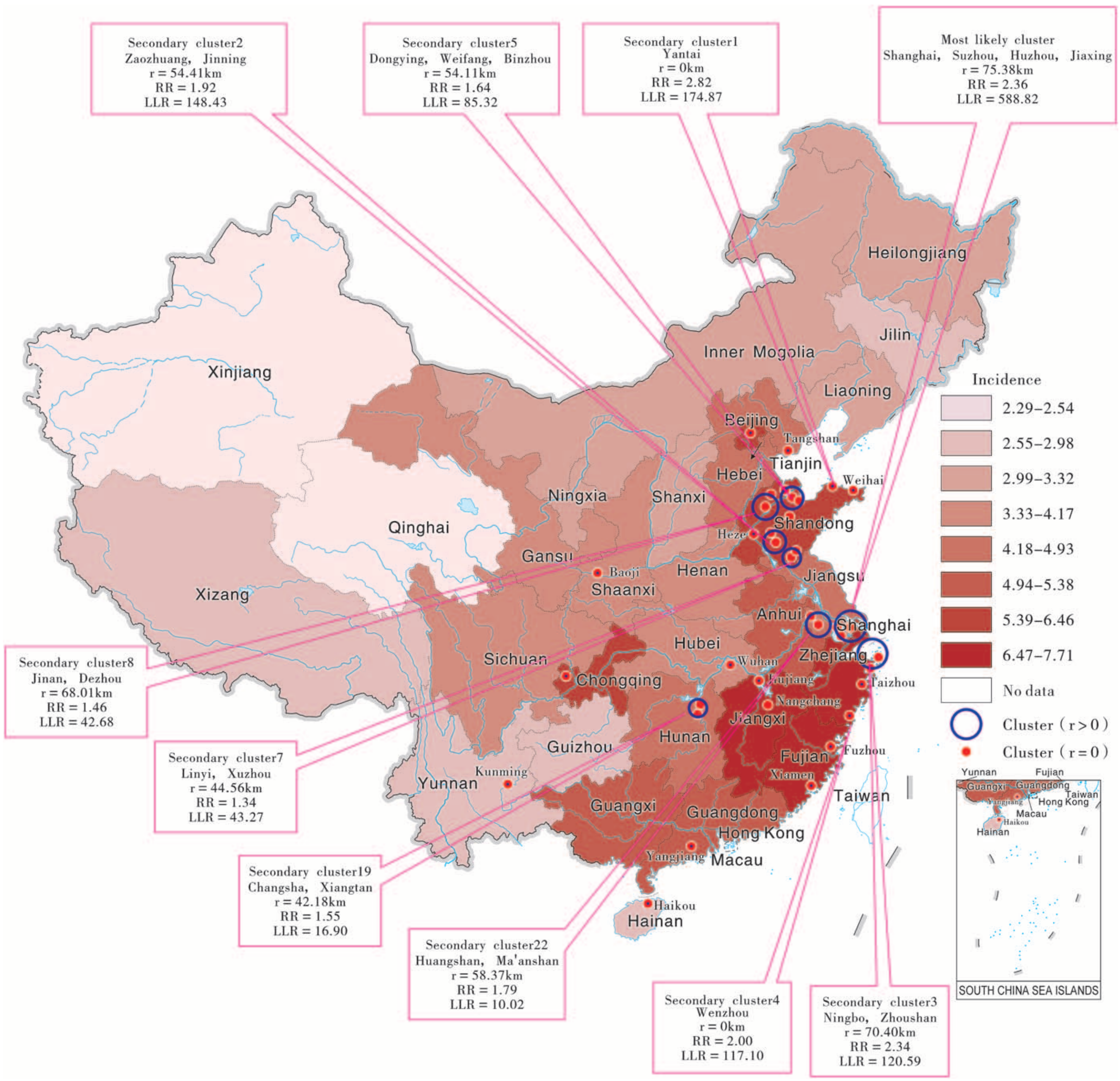

Figure 2: The spatial clustering of CH incidence at the city level in China, 2013–2018 (the maximum circular spatial window for space scan was 80 km). CH: Congenital hypothyroidism.

environmental factors. First, regarding pollutant factors, some studies on maternal exposure to fine particulate matter (PM) found that an increase of PM 2.5 exposure during gestation could increase the risk of CH in China.[36] The Yangtze river delta region, particularly its northern part, has been acknowledged as a high-risk area due to urban expansion, haze, population aggregation, demand for energy, topography, and climate factors. The city with the highest CH incidence, Hangzhou city, is also an important economic core area of the eastern coastal region where the respirable PM has become the primary air pollutant.[37] Second, deficiency or excess of iodine intake and the U-shaped curvilinear relationship between transient CH and iodine have been emphasized by clinicians.[38] Located on the southeast coast of China where seafood is abundant, there is a great possibility of excessive iodine intake with consumption of iodized salt. A previous study in Binzhou city of Shandong province, which happened to be a high cluster area in our study, verified a positive correlation between urine iodine and CH.[39] Higher incidence of CH was similarly found in Taiwan (China), a Pacific island to the southeast of the mainland of China, as well as in fluviomarine areas of the USA.[11,40] China issued the water iodine map in 2019, which indicated that Shandong Province had 14 waterborne high iodine counties. Although local governments advocated non-iodized salt in some high iodine zones,[41] our result indicates that further prevention and control strategies should be considered in relation to the clustered areas in these zones.

An important strength of this study was that diverse methods were used and mutually verified to demonstrate the spatial heterogeneity in CH incidence. First, we adopted both the spatial auto-correlation method and Kulldorff space scanning statistical method to provide a comprehensive description of CH spatial distribution in China in 2013–2018. While the Global Moran I statistics grasp the spatial data on the whole, the Getis-Ord Gi statistics further detect the relationship between each space unit, providing qualitative judgment of the aggregation mode. Spatial scanning statistics can quantitatively calculate the RR and LLR center position. In particular, in the selection of the sensitive parameter in the space scan, we ran spatial scanning several times with different maximum circular spatial windows instead of running the model with the default setting. We started from the maximum cluster size of 50% of the total population and by decrements of 10 km each time until there were fewer overlaps between the clusters defined by radius, the numbers of clusters were no more than 75% of the total amounts of cities, and the larger cluster covered less than 15% of all cities.[42,43] The results showed that clustering areas identified by the Kulldorff statistics were consistently located in the significant provinces identified with the Local Moran's method.

Our study had several limitations. First, we used the number of newborns, rather than the number of screened newborns, for the initial estimation of CH incidence at city level. Even if we chose data years with the high coverage of screening (≥95%) for each region, doing so led to a systematic bias whereby the incidence might be underestimated by an average of 5% maximally. Nevertheless, there is one western province, Qinghai, with relatively lower coverage of newborn screening in 2017 (93.50%) and 2018 (79.90%), although the average coverage has reached ≥95% in the western province since 2017. Therefore, the city-level CH incidences in Qinghai might also be underestimated by approximately 13% on average. Second, to obtain robust estimates of CH incidence at the city level, the data on the number of confirmed CH cases during 2013 to 2018 were used in the eastern region and the data during 2017 to 2018 were used in the central and western regions. However, a slight upward trend in CH incidence (2.30% per year) was observed in the eastern provinces during 2013–2018. The pooled estimates to some extent reflected the incidence of the midpoint year rather than the years of 2017 and 2018, which might underestimate the incidence variations between the eastern cities and central/western cities. Third, there is no way to distinguish infants with dyshormonogenesis or thyroid dysgenesis, mild transient hypothyroidism, or true permanent hypothyroidism through the CNBSIS. The effect of geographical variations on the different CH types and etiological categories was not analyzed. Fourth, although the National Health Commission of China promulgated the Technical Guideline of Newborn Diseases Screening in 2010, there may also be a difference in disease screening ability among different regions in China, which is related to the factors of staff skill, laboratory hardware and software, and screening quality. However, due to the lack of information about the staff training, screening method, test kit, and adopted TSH CO for each newborn screening center in the CNBSIS, it is very difficult to estimate their potential impact on the results of this study.

Our work provided a broad overview of CH incidence in the mainland of China, drawing up an interpolated incidence level distribution map and analyzing spatial clusters at different administrative scales from 2013 to 2018. The CH incidence varies greatly across regions and between provinces. It is higher in the east of the country and clustered in some hotspot areas. With more meteorological and hydrogeological data, future work on associations between environmental factors and CH incidence is needed. Catering to the concept of precision public health,[44] this study's results may serve as suggestions for decision-makers at the regional, provincial, and city levels in terms of medical requirements, preventive and control strategies, and health resource allocation.

Statement

The maps in the manuscript have been reviewed by the Ministry of Natural Resources of the People's Republic of China, the approval number is No. GS(2021)2315.

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Conflicts of interest

None.

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