BMJ Open Phenylketonuria incidence in China between 2013 and 2017 based on data from the Chinese newborn screening information system: a descriptive study

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ABSTRACT

Objective This study examines the incidence and spatial clustering of phenylketonuria (PKU) in China between 2013 and 2017.

Methods Data from the Chinese Newborn Screening Information System were analysed to assess PKU incidence with 95% CIs by province, region and disease severity. Spatial clustering of PKU cases was analysed using global and local spatial autocorrelation analysis in the geographic information system.

Results The database contained 4925 neonates with confirmed PKU during the study period, corresponding to an incidence of 6.28 (95% CI: 6.11 to 6.46) per 100 000 neonates screened. Incidence was highest in the provinces of Gansu, Ningxia and Qinghai, where it ranged from 19.00 to 28.63 per 100 000 neonates screened. Overall incidence was higher in the northern part of the country, where classical disease predominated, than in the southern part, where mild disease predominated. PKU cases clustered spatially (global Moran's $I=0.3603$, $Z=5.3097$, $p<0.001$), and local spatial autocorrelation identified four northern provinces as high-high clusters (Gansu, Qinghai, Ningxia and Shanxi).

Conclusions China shows an intermediate PKU incidence among countries, and incidence differs substantially among Chinese provinces and between northern and southern regions. Our results suggest the need to focus efforts on screening, diagnosing and treating PKU in high-incidence provinces.

INTRODUCTION

Phenylketonuria (PKU; OMIM 261600), an autosomal recessive disease, results mainly from mutations in, or deletion of, the gene encoding phenylalanine hydroxylase (PAH).¹ If left untreated, PKU can irreversibly damage the central nervous system to varying degrees and lead to intellectual disability, mental disorders, behavioural problems and seizures,² which not only reduce quality of neonatal life but also place a severe financial burden on the families.³

Early dietary therapy can effectively reduce damage to the nervous system and

Strengths and limitations of this study

- The study covers the largest, most geographically extensive newborn population in mainland China because it draws on the Chinese Newborn Screening Information System.
- The study provides the most comprehensive view of phenylketonuria (PKU) incidence by province, region and disease severity between 2013 and 2017 across China.
- The study explored spatial clustering of PKU cases using global and local spatial autocorrelation analysis.
- The north-south differences in PKU incidence may be confounded in this study by lower screening rates in some areas than in some provinces showing high incidence.

improve prognosis,^{4 5} highlighting the need for early PKU screening and diagnosis.⁶ Newborn screening programme has been in place in western Europe and North America for decades,^{7 8} but they did not start in China until 1981 and in the ensuing two decades, they expanded to all 31 provinces.⁹ Screening coverage across the country has increased from less than 10% before 2001 to 36.96% by 2007 and to 96.1% in 2016.¹⁰⁻¹² However, there remain strong regional inequities in healthcare infrastructure and access, so screening rates can be lower in some areas, especially in remote western parts.¹²

Despite these advances in screening, recent nation-wide data on PKU incidence are lacking. Data collected by the National Centre for Clinical Laboratories from particular regions indicated an incidence of 8.64 per 100 000 neonates screened for the period 1985–2007,¹³ compared with 8.50 per 100 000 for the period 2000–2007.¹⁴ Data from 193 Chinese neonatal screening laboratories

indicated an incidence of 8.2 per 100 000 neonates in 2013, when the screening coverage was approximately 86%–88%.¹⁵ More recent nation-wide data are needed to gain an accurate picture of PKU in China. At the same time, the geographical distribution of the disease needs to be much better understood because China shows substantial inequalities in healthcare resources and disease epidemiology between urban and rural areas, and between north and south. Such knowledge may help guide rational allocation of resources and efforts aimed at PKU screening and early diagnosis.

To begin to address these gaps, the aim of this present study is to investigate the incidence of PKU in China for the period 2013–2017 using data from the National Newborn Screening Programme, and to analyse the global and local spatial distribution of the disease.

METHODS

Data collection

The data in this study were extracted from the Chinese Newborn Screening Information System (CNBSIS), based at the National Office of Maternal and Child Health Surveillance. The CNBSIS covers >95% of districts/counties in 30 provinces and includes 230 newborn screening centres covering >90% of the newborn population in mainland China.¹⁶ The exception is Tibet, where screening centres did not open until 2015 and are still too sparse to provide accurate data on PKU incidence. Data from blood sampling cards, laboratory test reports and medical records were entered in the CNBSIS by trained staff at local newborn screening centres in each province. The quality and accuracy of data entry were checked at the provincial level by experienced doctors at provincial newborn screening centres. More details about data collection and quality control have been described elsewhere.¹⁶

PKU diagnosis

PKU was diagnosed based on the criteria in the 2010 edition of the 'National Newborn Screening Guidelines'¹⁷ from the Chinese Ministry of Health. Neonates were diagnosed with this disease if phenylalanine concentration in blood exceeded 360 µmol/L and tetrahydrobiopterin-deficient hyperphenylalaninaemia was excluded. In some analyses, PKU cases were stratified based on pretreatment plasma phenylalanine concentration into mild disease (360–1200 µmol/L) or classical disease (>1200 µmol/L).^{18 19}

Statistical analysis

Statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, NC, USA). Incidence of PKU was reported as the number of PKU cases diagnosed (c), divided by the number of newborns screened (b). The corresponding 95% CIs were calculated as follows²⁰:

$$\text{lower limit} = c \times \left(1 - \frac{1}{ac} - \frac{1.96}{3} \sqrt{\frac{1}{c}} \right)^3 / b \times 100000$$

and

$$\text{upper limit} = (c + 1) \times \left(1 - \frac{1}{a(c+1)} + \frac{1.96}{3} \sqrt{\frac{1}{c+1}} \right)^3 / b \times 100000$$

For analyses of the spatial distribution of PKU cases, provinces in mainland China were divided²¹ into a southern region (Jiangsu, Anhui, Hubei, Chongqing, Sichuan, Tibet, Yunnan, Guizhou, Hunan, Jiangxi, Guangxi, Guangdong, Fujian, Zhejiang, Shanghai and Hainan) or northern region (Shandong, Henan, Shanxi, Shaanxi, Gansu, Qinghai, Xinjiang, Hebei, Tianjin, Beijing, Inner Mongolia, Liaoning, Jilin, Heilongjiang and Ningxia). Global and local spatial autocorrelation of PKU incidence for the study period was assessed based on global and local Moran's I values²² as calculated in ArcGIS V.10.2 (ESRI, Redlands, CA, USA). Geographical data to generate maps were taken from the National Geomatics Centre of China (<http://ngcc.sbsm.gov.cn>).

Patient and public involvement

Patients and members of the public were not involved in the design of this study.

RESULTS

PKU incidence in China from 2013 to 2017

During 2013–2017, approximately 83.8 million babies were born in China, of which 78.4 million (93.55%) were screened and registered in the CNBSIS. Over the entire country, PKU incidence was 6.28 (95% CI: 6.11 to 6.46) per 100 000 neonates screened (table 1). Among 30 provinces and municipalities, incidence was highest in Gansu (28.63, 95% CI: 25.98 to 31.48), followed by Ningxia (19.00, 95% CI: 15.34 to 23.28) and Qinghai (17.37, 95% CI: 12.81 to 23.03). Incidence was lowest in Guangdong and Guangxi (<1 per 100 000 neonates screened). The proportion of PKU cases that were classical exceeded 50% in 17 of 30 provinces and municipalities.

To gain insights into larger-scale trends in PKU incidence in China, we collapsed the provinces and municipalities into northern and southern blocs (table 2). The north showed significantly higher incidence of mild and classical PKU than the south. Within the north, classical disease was present at significantly higher incidence than mild disease while the converse was observed in the south.

Spatial clustering of PKU in China from 2013 to 2017

Across the entire country during the study period, moderately positive global spatial autocorrelation was observed, based on global Moran's I (0.3603, Z=5.3097, p<0.001; figure 1). Analysis of local Moran's I on univariate local indicator of spatial association maps identified high–high (HH) and low–low (LL) cluster areas (figure 2). HH clusters encompassed four northern provinces (Gansu, Qinghai, Ningxia and Shanxi), whereas LL clusters included seven southern provinces

Table 1 Incidence of PKU in China by province and severity, 2013–2017

Province or municipality	Cases	Incidence (95% CI) per 100 000 neonates screened	PKU severity, n (% of all PKU cases)	
			Mild	Classical
Gansu	428	28.63 (25.98 to 31.48)	168 (39.25)	260 (60.75)
Ningxia	93	19.00 (15.34 to 23.28)	42 (45.16)	51 (54.84)
Qinghai	48	17.37 (12.81 to 23.03)	17 (35.42)	31 (64.58)
Shanxi	243	15.17 (13.32 to 17.20)	92 (37.86)	151 (62.14)
Xinjiang	184	13.22 (11.38 to 15.27)	113 (61.41)	71 (38.59)
Liaoning	197	12.23 (10.58 to 14.06)	81 (41.12)	116 (58.88)
Inner Mongolia	58	10.87 (8.25 to 14.05)	25 (43.10)	33 (56.90)
Hebei	520	10.78 (9.88 to 11.75)	231 (44.42)	289 (55.58)
Beijing	124	10.58 (8.80 to 12.62)	40 (32.26)	84 (67.74)
Jilin	94	10.58 (8.55 to 12.95)	47 (50.00)	47 (50.00)
Shaanxi	232	10.46 (9.16 to 11.90)	107 (46.12)	125 (53.88)
Heilongjiang	98	9.89 (8.03 to 12.05)	44 (44.90)	54 (55.10)
Tianjin	57	9.79 (7.42 to 12.69)	20 (35.09)	37 (64.91)
Shandong	629	9.31 (8.59 to 10.06)	269 (42.77)	360 (57.23)
Jiangsu	365	8.28 (7.45 to 9.17)	215 (58.90)	150 (41.10)
Anhui	292	7.94 (7.05 to 8.90)	139 (47.60)	153 (52.40)
Henan	475	7.80 (7.12 to 8.54)	224 (47.16)	251 (52.84)
Shanghai	56	5.25 (3.97 to 6.82)	36 (64.29)	20 (35.71)
Yunnan	133	5.04 (4.22 to 5.97)	67 (50.38)	66 (49.62)
Zhejiang	135	4.01 (3.37 to 4.75)	92 (68.15)	43 (31.85)
Hubei	118	3.96 (3.28 to 4.74)	75 (63.56)	43 (36.44)
Hunan	78	2.01 (1.59 to 2.51)	34 (43.59)	44 (56.41)
Sichuan	75	1.98 (1.55 to 2.48)	50 (66.67)	25 (33.33)
Chongqing	24	1.77 (1.13 to 2.63)	11 (45.83)	13 (54.17)
Guizhou	37	1.74 (1.23 to 2.41)	22 (59.46)	15 (40.54)
Fujian	44	1.47 (1.07 to 1.97)	37 (84.09)	7 (15.91)
Jiangxi	32	1.29 (0.88 to 1.82)	16 (50.00)	16 (50.00)
Hainan	7	1.11 (0.45 to 2.29)	0 (0.00)	7 (100.00)
Guangdong	43	0.53 (0.39 to 0.72)	24 (55.81)	19 (44.19)
Guangxi	6	0.15 (0.05 to 0.32)	6 (100.00)	0 (0.00)
Total	4925	6.28 (6.11 to 6.46)	2344 (47.59)	2581 (52.41)

CI, Confidence Interval; PKU, phenylketonuria.

(Guizhou, Hunan, Jiangxi, Guangxi, Guangdong, Fujian and Hainan).

DISCUSSION

Our comprehensive analysis of CNBSIS data for 2013–2017 suggests a nation-wide PKU incidence of 6.28 per

100 000 neonates screened in China. Incidence differed significantly between the north and south of the country, with high-incidence provinces being Gansu, Ningxia, and Qinghai, and low-incidence provinces being Guangdong and Guangxi. The provinces of Gansu, Ningxia, Qinghai and Shanxi appear to be HH cluster type. These

Table 2 Incidence of PKU in China by north/south region and severity, 2013–2017

Region	Mild PKU		Classical PKU	
	Cases, n (95% CI)	Incidence (95% CI) per 100 000 neonates screened	Cases, n (95% CI)	Incidence (95% CI) per 100 000 neonates screened
South	824 (768 to 880)	1.73 (1.62 to 1.86)	621 (572 to 670)	1.31 (1.21 to 1.41)
North	1520 (1444 to 1596)	4.92 (4.67 to 5.17)	1960 (1873 to 2047)	6.34 (6.06 to 6.63)
Total	2344 (2249 to 2439)	2.99 (2.87 to 3.11)	2581 (2481 to 2681)	3.29 (3.16 to 3.42)

CI, Confidence Interval; PKU, phenylketonuria.

Figure 1 Spatial distribution of phenylketonuria incidence in China, 2013–2017.

results place China near the middle of countries and populations for which PKU incidence has been reported (figure 3).^{2 23–25} The large variation in incidence around the world may reflect ethnic and geographical differences in polymorphisms of the PAH gene.^{26–28} For example, incidence is higher among Caucasians than other populations.^{29 30} Studies to identify genetic risk factors for PKU, and particularly the more severe classical disease,

Figure 2 Univariate local indicator of spatial association cluster map of phenylketonuria incidence in China, 2013–2017.

Figure 3 Phenylketonuria incidence by country.

are urgently needed. They may lead to reliable genetic screening of newborns.

We measured slightly lower nation-wide PKU incidence than previous studies in China.^{13–15} Our results are likely to be more reliable because we included only neonates diagnosed with PKU, not those diagnosed with tetrahydrobiopterin deficiency, in contrast to two of those studies.^{14 15} In addition, neonatal screening coverage was higher during our study period of 2007–2013 than during the earlier periods in two of those studies.^{13 14}

The five high-incidence provinces in our study (Gansu, Ningxia, Qinghai, Shanxi and Xinjiang) have incidences similar to those of several high-incidence areas such as Ireland, Scotland, Israel (Yemenite Jews) and Czech Republic. The high proportion of Hui, Uyghur and other minority populations in these five Chinese provinces may help explain the higher PKU incidence. For example, in Ningxia, incidence is much higher among Hui than among the Han majority,³¹ and Uyghurs share consanguinity with Caucasians,³² suggesting that they may also show higher incidence than other populations. Future studies should examine these possibilities in greater detail. Our observation that all five high-incidence provinces lie in northern China is likely no coincidence, consistent with a previous study.⁹ The northern region is generally less developed than the southern, with lower per-capita income (with the notable exception of Beijing and Shanghai) and less access to medical facilities and public health infrastructure such as screening. In addition, neonatal screening coverage is substantially lower in inland areas than in coastal areas.¹² Our data suggest that efforts at PKU screening and diagnosis need to be improved in the north, not only because overall PKU

incidence is higher there but also because the incidence of classical disease exceeds that of mild disease.

Our analysis suggests that PKU cases in China show positive global spatial autocorrelation, which may reflect that the disease is an autosomal recessive, monogenic disorder, so its incidence is determined primarily by the presence of the disease allele in both parents rather than by environmental factors. The clustering revealed HH clusters in the northern provinces of Gansu, Ningxia, Qinghai and Shanxi, whereas LL clusters were identified in the south (Guizhou, Hunan, Jiangxi, Guangxi, Guangdong, Fujian and Hainan). These results further emphasise the need for greater screening and early diagnosis measures in the north, together with greater support interventions for families of affected children.

Although our analysis provides the most comprehensive insights so far into PKU incidence and severity across China, the data have some limitations. Differences in neonatal screening coverage may bias our findings and, because coverage correlates with access to healthcare resources, it may confound our analyses of north–south differences. Another potential confounder are differences in how often neonates were recalled for definitive diagnosis of PKU following a positive result on initial screening. Nevertheless, we consider such confounding to be minimal, given that the recall rate exceeded 85% in most provinces during the study period. Since CNBSIS does not record the nationality of each parent individually, we could not perform more detailed analyses of ethnicity on PKU incidence or severity.

CONCLUSION

PKU incidence in China during the period 2013–2017 is intermediate on the global level, and it is substantially higher in the north than in the south of the country. The provinces with the highest incidence are Gansu, Ningxia and Qinghai. The disease shows positive spatial autocorrelation, with Gansu, Ningxia, Qinghai and Shanxi appearing as HH cluster areas. Health authorities should strengthen screening, early diagnosis and family support measures in high-incidence provinces.

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Contributors HML and JZ contributed to study design. LCX, JT, KD, XHL, QL, XLY, JL, ELY, HQW, HML and JZ contributed to data acquisition. LCX, JT and MXW analysed the data. LCX wrote the first draft of the manuscript, which all authors revised and approved for publication.

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This article was previously published with error in Figure 3.

The unit of incidence (horizontal ordinate) in figure 3 has been corrected to 100 000.

The revised figure is below:

Figure 3 Phenylketonuria incidence by country.

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