

Incidence of Newly Diagnosed Type 1 Diabetes Mellitus in Children and Adolescents in Henan Province of China from 2017 to 2020: A Retrospective Multicenter Study Based on Hospitalization Data

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What is already known on this topic?

The incidence of type 1 diabetes mellitus (T1DM) is rapidly increasing worldwide. A national study including 13 cities reported that the incidence per 100,000 person years in China was 1.93 (0.83-3.03) for the 0-14 years age group from 2010 to 2013. The incidence of T1DM varied between regions.

What this study adds?

Henan province was defined as a less developed region in China. However, the incidence in Henan Province of China has been unknown for more than two decades. Our study investigated the incidence of newly diagnosed T1DM cases between 2017 and 2020 in Henan province of China.

Abstract

Objective: The incidence of type 1 diabetes mellitus (T1DM) is rapidly increasing worldwide. However, the incidence in Henan Province of China has been unknown for more than two decades. This study aimed to estimate the incidence of T1DM in the 0.5-14.9 years age group in Henan Province of China from 2017 to 2020.

Methods: A retrospective analysis of hospital registration data from 18 cities in Henan Province, China, identified 1726 patients (843 males, 883 females) between 0.5-14.9 years of age with newly diagnosed T1DM in Henan Province from January 1st, 2017, to December 31st, 2020, covering more than 19 million children years at risk.



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Results: The crude incidence of T1DM per 100 000 person years for the 0.5-14.9 years age group in the Henan Province of China was 2.19 [95% confidence interval (CI): 1.99, 2.40], with a peak in the 10-14.9 years age group. The rate ratio of females to males was 1.32 (95% CI: 1.20, 1.45) in the 0.5-14.9 years age group. The incidence rate was higher in females than males in the 5-9.9 years age group ($p < 0.01$) and the 10-14.9 years age group ($p < 0.01$). The seasonality of the incidence was different from that in previous reports, with the lowest incidence in the spring.

Conclusion: The incidence of T1DM in the 0.5-14.9 years age group in Henan Province was still among the lowest reported globally, but was in line with other incidence rates reported from China.

Keywords: Incidence, type 1 diabetes mellitus, children, China, new onset

Introduction

The incidence of type 1 diabetes mellitus (T1DM) in children has been rapidly increasing worldwide. According to the DiaMond (Diabetes Mondiale) Project, the incidence of T1DM in Chinese children was 0.51 per 100,000 person years from 1988 to 1996, which was one of the lowest in the world (1). A national study including 13 cities reported that the incidence per 100,000 person years in China was 1.93 (0.83-3.03) for the 0-14 years age group from 2010 to 2013 (2). However, the population of the national study did not include residents of Henan Province. Henan Province is in the center of China, located at latitude $31^{\circ}23'-36^{\circ}22'$ North and longitude $110^{\circ}21'-116^{\circ}39'$ East, with an average altitude of 100 m above sea level.

Based on the gross domestic product for each province, Henan was defined as a less developed region in China. The DiaMond Project reported that from 1989 to 1994, the incidence of T1DM in 0-14 year old children was 0.5/100,000 in Zhengzhou, the capital city of Henan Province (1). The incidence of T1DM in Henan Province has thus been unknown for more than two decades. There is no nationwide registry for T1DM in Henan province of China, and both patients and their parents are reluctant to publicly disclose their disease because of traditional cultural values. Because of this, the capture-recapture method, which is thought to be the standard method of T1DM incidence survey, is not feasible in Henan Province. Instead, we chose a hospital data-based survey to estimate the incidence of T1DM, as in a previous study (3). In this study, we analyzed the incidence of childhood T1DM in Henan Province based on newly diagnosed and hospitalized T1DM cases from January 1st, 2017, to December 31st, 2020. This T1DM study may help advance the understanding of geographic and economic factors to the development of T1DM.

Methods

The study design was approved by the ethics review board of Children's Hospital Affiliated to Zhengzhou University. We reviewed T1DM cases using hospital registration data from 137 hospitals located in 18 cities in Henan Province.

Records were audited by senior pediatric endocrinologists in each hospital to rule out non-T1DM cases. Patients were eligible for study inclusion if they: 1) were 6 months to 14 years old; 2) were admitted to any of the selected hospitals from January 1st, 2017, to December 31st, 2020; and 3) were newly diagnosed with T1DM based on the 2009 International Society for Pediatric and Adolescent Diabetes guidelines and recommendations made by the World Health Organization Expert Committee. The age of T1DM onset was divided into three groups for consistency with previous studies (2): 0.5-4.9; 5-9.9; and 10-14.9 years. Data including sex, date of birth, race, and diabetes diagnosis date were collected from 1726 patients.

Statistical Analysis

Crude incidence rates were calculated as the number of cases per 100,000 person-years, and the population of the sixth Chinese census conducted by the National Bureau of Statistics of China as the denominator. We estimated the incidence separately for three age groups at diagnosis (0.5-4.9, 5-9.9, and 10-14.9 years), and according to sex and season. The 95% confidence intervals (CIs) were calculated by inverting the score test for a binomial proportion. The incidence differences according to sex in the three age groups were evaluated using the χ^2 test. Multivariate Poisson regression models were used to assess the effects of age group and sex on the incidence of diabetes. The incidence rate ratios (IRRs) and their 95% CIs were calculated from the regression coefficients and corresponding standard errors in the Poisson regression models. Statistical analyses were performed using the R4.0.5 analytical software (<https://cran.r-project.org/>). Statistical significance was set at $p < 0.05$.

Results

Based on registration data from the selected hospitals, 1726 children (843 males, 883 females) with newly diagnosed T1DM were eligible for inclusion in the analysis. Incidence calculations for this patient population were derived from national census demographic statistics for 2010, in which 36.0%, 32.8%, and 31.2% of children in Henan Province

were 0.5-4.9 years, 5-9.9 years, and 10-14.9 years of age, respectively. The Han ethnicity accounts for 98.84% of the population in Henan province. In our study, 1714 children were from the Han ethnicity group, accounting for 99% of the total.

The incidence per 100,000 person years for the 0.5-14.9 years age group in the 18 cities of Henan province was 2.19 (95% CI: 1.99, 2.40) (Table 1). The incidence per 100,000 person years in the 0.5-4.9 years age group was 1.42 (95% CI: 1.16, 1.73), 1.39 (95% CI: 1.05, 1.81) among males, and 1.46 (95% CI: 1.07, 1.94) among females. The incidence per 100,000 person years in the 5-9.9 years age group was 1.82 (95% CI: 1.51, 2.18), 1.50 (95% CI: 1.13, 1.96) among males, and 1.82 (95% CI: 1.51, 2.18) among females. The incidence per 100,000 person years in the 10-14.9 years age group was 3.46 (95% CI: 3.01, 3.95), 2.96 (95% CI: 2.41, 3.59) among males, and 3.46 (95% CI: 3.01, 3.95) among females. Table 1 summarizes the incidence of T1DM in the different age groups and sexes.

The incidence rate was different between males and females. The female-to-male IRR was 1.32 (95% CI: 1.20, 1.45) in the 0.5-14.9 years age group. The incidence rates between males and females among different age groups are shown in Table 1. The incidence rate in females was higher than males in the 5-9.9 years age group ($p < 0.01$) and the 10-14.9 years age group ($p < 0.01$). There was no significant difference between males and females in the 0.5-4.9 years age group ($p = 0.5763$). The rate ratios were 1.29 (95% CI: 1.13-1.47) and 2.44 (95% CI: 2.16-2.74) in the 5-9.9 and 10-14.9 years age groups, respectively (Table 2).

People in Henan Province experience four distinct seasons a year: spring (March-May), summer (June-August), autumn (September-November), and winter (December-February). In Spring, the incidence rate was 1.92 (95% CI: 1.73, 2.12) per 100,000, lower than that in the other seasons (Table 3). The significant differences were found among spring, summer, and autumn ($p < 0.01$). The incidence rates between males and females in different seasons are also shown in Table 3.

Discussion

The incidence of T1DM in the 0.5-14.9 years age group in Henan Province of China from 2017 to 2020, which has been unknown for more than two decades, was estimated in our study. Based on the data from 2019 International Diabetes Federation, T1DM incidence remains the highest in Finland (60/100,000/year), and the lowest across East and South-East Asia (4). According to our study, the incidence rate in Henan province is one of the lowest compared to global rates, but similar to the overall incidence of China (2). China remains one of the countries with the lowest incidence of T1DM worldwide. The mechanism of low incidence in China is largely attributed to genetic, environmental, and behavioral factors. Our study population was Han people who have a low susceptibility to T1DM (1). Previous studies in China showed that the incidence of T1DM among children aged 0-14 years was strongly correlated with latitude (2). Moreover, less developed regions in China had lower prevalence compared to well developed regions (5). Henan Province is situated between 31°23' to 36°22' North, in the

Table 1. Population and incidence of type 1 diabetes children aged 0.5-14.9 years in Henan Province of China

Age (years)	Number of cases	Population	Mean annual incidence rate (95% CI) per 100,000
Males			
0.5-4.9	55	3951617	1.39 (1.05, 1.81)
5-9.9	55	3655027	1.50 (1.13, 1.96)
10-14.9	101	3414352	2.96 (2.41, 3.59)
0.5-14.9	211	11020996	1.91 (1.66, 2.19)
Females			
0.5-4.9	46	3155452	1.46 (1.07, 1.94)
5-9.9	63	2824983	2.23 (1.71, 2.85)
10-14.9	112	2745887	4.08 (3.36, 4.91)
0.5-14.9	221	8726322	2.53 (2.21, 2.89)
Total			
0.5-4.9	101	7107069	1.42 (1.16, 1.73)
5-9.9	118	6480010	1.82 (1.51, 2.18)
10-14.9	213	6160239	3.46 (3.01, 3.95)
0.5-14.9	432	19747318	2.19 (1.99, 2.40)

CI: confidence interval

center of China, and is also considered a less developed region in China (Table 4) (2,6,7), which may partially explain these incidence levels.

The incidence of T1DM in the 0.5-14.9 years age group in 2017-2020 in our study suggests a 4.38-fold increase over that reported by the DiaMond study in Henan from 1989 to 1994, which is an approximately 6.63% annual increase. The annual increase is similar to that reported in previous studies in other cities of China (2). Compared with EURODIAB (3.3%) (8), the increase seems to be rapid. However, the reasons remain unclear. Westernized lifestyle (9), changes in the immune system (10), and vitamin D deficiency (11) may be associated with this increase. In addition, the increasing rate calculation is based on the data from the DiaMond study, which may be underestimated as some of the participating centers reported very small case numbers.

In addition, our study found that the incidence increased with age and the peak of incidence was within the 10-14.9 years age group, which is consistent with previous studies

(12,13). The incidence of T1DM in children aged 10-14.9 years is 2.44 times as high as that in children aged 0.5-4.9 years. This high level of incidence may be related to the higher level of growth hormone, which may reduce insulin sensitivity and contribute to insulin deficiency (14). In our study, the incidence of T1DM in 0.5-4.9 age group was 1.47 per 100,000 from 2017 to 2020. Previous studies have shown that the incidence of diabetes in children aged 0-5 years increased significantly, reaching 5-35% in different studies in China (6,7). However, the rate of increase was not compared in this study.

Previous studies suggested that the incidence in males exceeds that in females in most countries where incidence is high (populations of European origin), but lower than that in females in low incidence countries (Asia and Africa) (2,15,16). In China, studies in Zhejiang, Harbin, and Hong Kong also reported a higher incidence in females than in males (6,17,18). In our study, the rate ratio of females was 1.32 (95% CI: 1.20, 1.93) in the 0-14 years age group. The higher incidence of females than males in Henan Province was consistent with previous studies.

Among the four seasons, newly diagnosed T1DM has long been described more commonly in winter, early spring, and late autumn months in Western countries (19). In a Japanese study, the peak periods of disease onset were spring and winter, which is similar to Hong Kong and southern China (16,18). However, a lack of seasonality was observed in a study from Shanghai (20). In our study, the incidence was lowest in spring, which was significantly different from that reported in previous studies. This difference may be due to many factors. A multicenter study in China showed that 4.17% cases of T1DM were diagnosed during routine physical examinations, and 11.44% of cases were diagnosed when seeking medical attention for illness symptoms, such as fever and cough (21). This suggests a lack of recognition for T1DM in public and this will lead to a delayed diagnosis and may also account for the lower incidence in China. The different degrees of delayed diagnosis may result in inaccurate statistics on the onset date of diabetes. Moreover, social stigma in China may lower the number of children presenting to hospital or change the seasonality (22). Besides, environmental factors, such as viral infections, may also affect the seasonal variation. During the COVID-19 pandemic in China, infectious diseases such as influenza, bronchiolitis, and acute upper respiratory infections were obviously lower than previously reported (23). Changes in the disease spectrum in China may also change the seasonality of T1DM.

Table 2. Incidence rate ratios and 95% CI of children in Henan Province of China

	RR	95% CI
Male	1	
Female	1.32	1.20, 1.45
Age (year)		
0.5-4.9	1	
5-9.9	1.29	1.13, 1.47
10-14.9	2.44	2.16, 2.74

CI: confidence interval

Table 3. Incidence rate of type 1 diabetes children aged 0.5-14.9 years among different seasons in Henan Province of China

Season	Incidence rate (95% CI) per 100,000
Spring	1.92 (1.73, 2.12)
Males	1.68 (1.45, 1.94)
Females	2.22 (1.92, 2.56)
Summer	2.39 (2.17, 2.61)
Males	2.11 (1.85, 2.40)
Females	2.73 (2.39, 3.10)
Autumn	2.35 (2.15, 2.58)
Males	2.15 (1.89, 2.44)
Females	2.61 (2.28, 2.97)
Winter	2.08 (1.88, 2.29)
Males	1.71 (1.47, 1.97)
Females	2.56 (2.23, 2.91)

CI: confidence interval

Table 4. Crude incidence rates per 100 000 person years in various regions in mainland of China

Regions	Years	Age (y)	Crude incidence per 100 000 person years	Latitude (°N)	GDP status
Harbin	2010-2013	0-14	3.59	45.8	Less development
Shenyang	2010-2013	0-14	2.48	41.8	Less development
Beijing	2010-2013	0-14	2.46	39.9	Well development
Yinchuan	2010-2013	0-14	2.43	38.5	Less development
Lanzhou	2010-2013	0-14	2.22	36.0	Less development
Jinan	2010-2013	0-14	2.18	36.7	Less development
Xi'an	2010-2013	0-14	1.82	34.3	Less development
Nanjing	2010-2013	0-14	2.23	32.1	Well development
Shanghai	1997-2011	0-14	3.1	31.1	Well development
Zhejiang	2007-2013	0-18	2.0	27.0-31.1	Well development
Chengdu	2010-2013	0-14	1.14	30.7	Less development
Wuhan	2010-2013	0-14	1.61	30.5	Well development
Changsha	2010-2013	0-14	1.29	28.2	Less development
Guangzhou	2010-2013	0-14	1.55	23.2	Well development

GDP: gross domestic product

Study Limitations

This study has several limitations. First, type 1 and type 2 diabetes in children and adolescents may be misclassified in local hospitals. Second, the limited number of hospitals and cases might cause some missing data and affect the accuracy of incidence. We included the patients in endocrinology department of Children's hospitals and pediatric endocrinology department in general hospitals. However, the missing cases might come from the patients who visited the endocrinology department for adults in local hospitals. We believe the missing cases are limited because of the legal requirements imposed on practicing physician in China. Medical Practitioners Act in China stipulates only pediatricians can treat children between 0-14 years of age. Third, we didn't collect the clinical characteristics of the patients. According to an earlier survey including patients in Henan province, the majority of patients with T1DM in China have typical symptoms coinciding with the other countries (21).

Conclusion

In conclusion, this survey was conducted in Henan Province, China, with a total population of nearly 100 million, and covered more than 19 million children years at risk. The incidence rate in Henan Province was 2.19 per 100,000 from 2017 to 2020, with the highest in the 10-14.9 years age group. Additionally, the incidence rate was higher in females than in males, and there were significant differences in the 5-9.9 and 10-14.9 years age groups. The seasonality of the incidence was different from that in previous reports, with the lowest incidence in spring. Finally, the incidence of T1DM

in children from Henan Province is still among the lowest reported in the World, according to these results. However, ascertainment is unknown. Therefore, these are minimum estimates and the true incidence may be higher. In future, it would be necessary to promote the establishment of a diabetes registration system to better assess the incidence of diabetes in Henan province.

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Ethics

Ethics Committee Approval: The study design was approved by the Ethics Review Board of Children's Hospital Affiliated to Zhengzhou University (protocol no: 2022-K-002, date: 10.01.2017).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: Haiyan Wei, Data Collection or Processing: Qiong Chen, Na Xu, Yongxing Chen, Fengyan Tian, Wei Yang, Yan Cui, Ai Huang, Yangshiyu Li, He Zhang, Zhihong Jiang, Ruizhi Zheng, Yuan Ji, Dongming Zhang, Qiao Ren, Li Ding, Haiyan Wei, Analysis or Interpretation: Mingming Yan, Literature Search: Haiyan Wei, Writing: Qiong Chen, Haiyan Wei.

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