Congenital Heart Disease

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REVIEW

The Prevalence of Congenital Heart Disease among School-Age Children in China: A Meta-Analysis and Systematic Review

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ABSTRACT

Objectives: To estimate the prevalence of Congenital Heart Disease (CHD) in school-age children, to identify the extent to which altitude affects the prevalence of the disease, and to examine trends in prevalence over time in China. **Methods:** Seven databases were systematically searched and last retrieved on September 10, 2021 for all studies reporting the prevalence of CHD in children after 1970 in China, which were then divided into high and low altitude regions based on 2500 meters above sea level. The random-effected model was used to combine prevalence data and subgroups analysis. The baseline data of all cases and individuals were used for comparison to calculate the odds ratio (OR) for overall and different altitude prevalence. **Results:** A total of 12,926,083 individuals (aged 3-18 years), with 31,835 cases from 86 studies, were included in the analysis. The pooled CHD prevalence of total children was 4.69 [95% confidence interval (CI): 4.10 to 5.29] per 1000 children. Overall, temporal trends analysis indicated that the prevalence of CHD in children continuously decreased with time, from 6.19 (95% CI: 4.50 to 7.88) per 1000 children in 1976–1985 to 3.30 (95% CI: 2.49; 4.38) per 1000 children in 2016–2021. The OR for the prevalence of CHD in children from high and low altitudes with baseline data was 2.84 (95% CI: 2.48 to 3.27) and 1.31 (95% CI: 1.13 to 1.53) (χ^2 = 53.89, p < 0.01), respectively. The OR of the prevalence of CHD in male children compared to females was 0.60 (95% CI: 0.53 to 0.68) at high altitudes and 0.79 (95% CI: 0.71 to 0.89) at low altitudes. Among the seven most common subtypes, patent ductus arteriosus was the most common at high altitudes, while atrial septal defects were the most common at low altitudes. **Conclusion:** This study provides valuable insights for further disease prevention and etiological exploration. The overall decreasing trend in the prevalence of CHD in children over time may indicate a positive effect of perinatal management and treatment during infancy.

KEYWORDS

Congenital heart disease; prevalence; school-age children; meta-analysis; altitude

1 Introduction

Congenital Heart Disease (CHD) is defined as a functionally significant structural heart or intrathoracic great vessels disease present at birth [1]. This, in fact, is the most common congenital disability accounting for approximately one-third of all major congenital anomalies. The reported prevalence of CHD substantially varies worldwide, ranging from 0.6%–9.4% [2,3]. This discrepancy can be attributed to the age of diagnosis, the definition of the disease (e.g., whether or not patent foramen ovale was classified as CHD), and the diagnostic technique [4,5]. The prevalence of CHD seems to be constantly changing as diagnostic technology evolves and diagnostic criteria are being updated.

China is the country with the highest burden of CHD worldwide. It is also a country with diverse topography, vast area, and uneven economic development [6–8]. Early studies indicated that the prevalence of CHD differs in gender, geographical factors, economic status, and similar [7,9]. In their study, Zhao et al. extended the regime to study the prevalence of CHD at live birth in China [6]. In contrast to studies of CHD live births conducted with large birth registries, sample sizes for studies of school-age children with CHD are usually derived from cross-sectional surveys with relatively modest sizes. Moreover, individual studies of CHD prevalence in children reported widely varying rates, ranging from 0.70% to 13.35% [10,11]. These factors limit the generalizability at the level of the whole country. Previous studies have also shown substantial differences in the prevalence of CHD disease in relation to altitude [12–14]. Therefore, a comprehensive study of the prevalence of CHD in children and exploration of the subgroup heterogeneity is necessary. Accordingly, in the present study, we examined the discrepancy based on the medically significant altitude of 2500 meters above sea level [15]. The altitude level above 2500 m was defined as high altitude and the altitude below 2500 m as low altitude.

The prevalence of CHD among the global school-aged between 1970 and 2017 was reported. This review article pointed common subtypes of unrepaired CHD and conducted subgroup analysis for different economics levels and genders [16]. Nonetheless, CHD prevalence among school-aged children in China hasn't been analyzed separately. A summarized data on the prevalence of CHD among Chinese school-aged is missing. Furthermore, altitude is a factor that has a significant influence on the occurrence of vascular disease, however, the altitude impact to CHD prevalence is unclear. To fill this gap, we perform this study to estimate the prevalence of CHD of school-age children in China, to identify the extent to what altitude affects the prevalence of the disease, and to examine trends of the prevalence over time in China between 1970 and 2021.

2 Methods

2.1 Protocol and Registration

The systematic review and meta-analysis were conducted with the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17,18]. The protocol was preregistered on the International Prospective Registered of Systematic Reviews (PROSPERO: CRD42021277019).

2.2 Search Strategy

We systematically reviewed publications that reported on the prevalence of total CHD among school-age children (3–18 years old). Relevant publications were retrieved by searching PubMed, Web of Science, Embase, China Biology Medicine disc database, Wanfang database, China National Knowledge Infrastructure, and Weipu on August 31, 2021. We used the following search terms (formatted for PubMed search): ("Heart Defect, congenital" [Mesh] OR "Heart Abnormality" [ti/ab] OR "Congenital Heart Disease" [ti/ab] OR "Congenital Heart Defect" [ti/ab] OR "Heart Abnormalities" [ti/ab]) AND ("Prevalence" [Mesh] OR" Period Prevalence" [ti/ab] OR "Point Prevalence" OR "Epidemiology" [Mesh] OR "Social Epidemiology" [ti/ab] OR "Epidemiology, social" [ti/ab] OR "Incidence" [Mesh] OR "Incidence proportions" [ti/ab] OR" Incidence Rate" [ti/ab]) AND ("China" [Mesh] OR "People's

Republic of China"[All Fields] OR "Mainland China"[ti/ab] OR "Chinese" [All Fields]). Studies published before 1970 were excluded from the analysis.

2.3 Selection Criteria

The articles that met the following criteria were included: (a) participants were Chinese school-age children (3–18 years old); (b) the publications were in Chinese or English language; (c) the relevant data on CHD prevalence or its subtypes among school-age children could be extracted; (d) articles were published after 1970; (e) quality assessment JBI-PCAT (Joanna Briggs Institute–Prevalence Critical Appraisal Tool) score $\geqslant$ 4. Studies that reported on CHD prevalence in specific children, such as handicapped children, were excluded.

2.4 Data Extraction and Quality Assessment

Two authors (Shuqin Zhang and Jin Luo) who independently performed reviewing were responsible for data extraction and quality evaluation. Any disagreements were solved through discussion. The main information extracted from the literature contained title, publication year, investigation time, altitude, geographic region, common subtypes, total subjects, and CHD cases. We used the JBI-PCAT evaluation tool to appraise the methodological quality of the literature, which was specifically developed for systematic reviews of prevalence data [19,20]. The JBI-PCAT contains nine aspects of the problem, which are answered with Yes, No, Unclear, and Not applicable. According to the number of answers "Yes", we classified the studies into three levels, i.e., high quality $\geqslant$6; moderate quality 4–5; low quality $\leqslant$3. Low-quality studies were discarded seen in Supplementary Table 1.

2.5 Statistical Analysis

R (4.1.1) Meta package was used for data analysis. For heterogeneity analysis, we applied the Cochran Q test ($p < 0.1$ indicated significant difference) to make statistical inference and forest plot to perform statistical description; I^2 was further used to quantify the size of heterogeneity. $I^2 > 50\%$, indicated significant heterogeneity, and the random-effect model was selected to combine the effect size with 95% CI. Egger's regression test and the funnel plot were used to analyze publication bias. The odds ratio (OR) for CHD prevalence was calculated for each study using the pooled data from the included studies (containing all cases and individuals) as baseline data. Subtype analysis was conducted based on altitude (altitude > 2500 m or altitude $\leqslant$ 2500 m), gender (male or female), income level (low, lower-middle, upper-middle, high), and geographic region (Central region, North region, Northeast region, Eastern region, South region, Southwest region, Northwest region). The Chi-square test was used to compare the prevalence of total CHD among subgroups in school-age children, using the Bonferroni method to adjust p values. $p < 0.05$ indicated statistically significant difference. Time trends were plotted using the Cubic spline smoothing technique. We divided income groups into low income ($\leqslant$\$1045), lower-middle-income (\$1046 to \$4095), upper-middle income (\$4096 to \$12695), and high income ($\geqslant$\$12,696) according to World Bank Income Groups [21].

3 Results

3.1 Literature Screening and Characteristics

The initial search yielded 8,364 potential eligible publications from seven databases. After excluding duplicates, titles, abstracts, and full-text, 86 studies were finally included in the meta-analysis, involving 31,835 CHD cases and 12,926,083 children. Among these 86 studies, 59 were from low-altitude areas and 24 were from high-altitude areas, and 3 additional studies reported prevalence at both altitudes (Fig. 1). All the included studies were cross-sectional designs with a high JBI-PCAT score of 7.9 ± 1.4 (mean ± SD, rang 4–9). In most studies (93.1%), the main diagnostic tool was echocardiography; the

remaining studies applied combinations of diagnostic tools, such as X-rays, physical examination, and electrocardiographs.

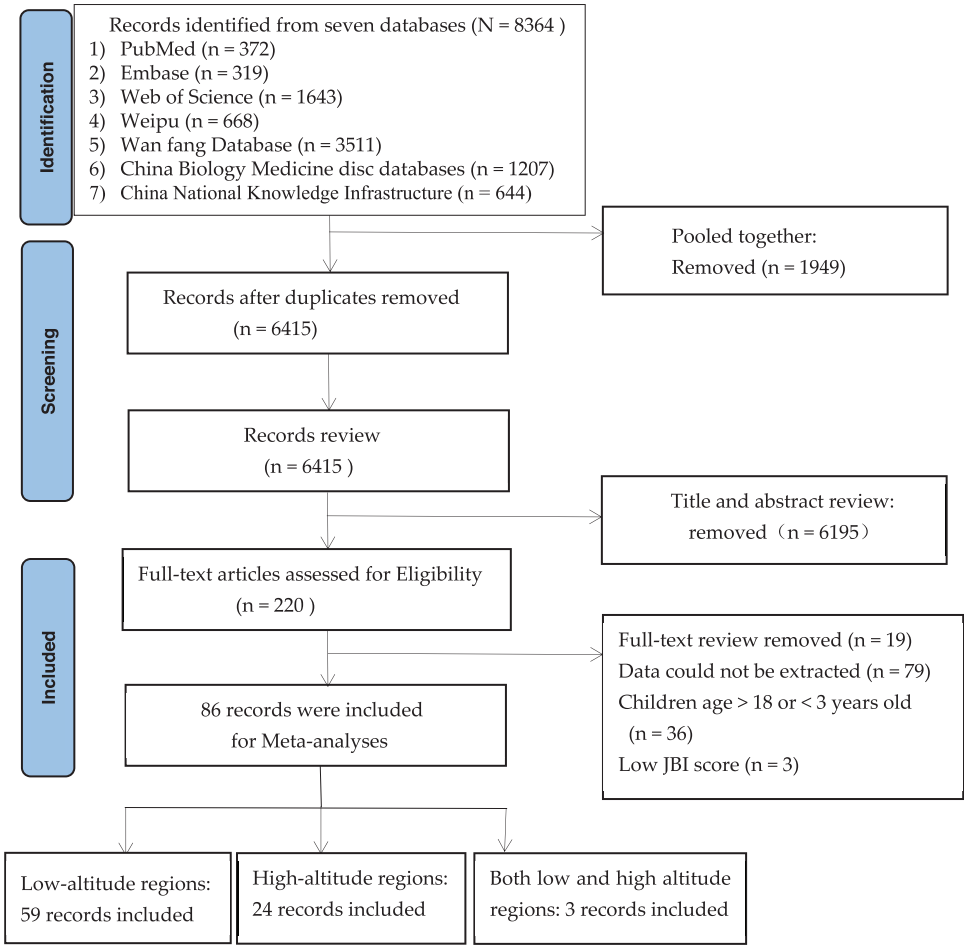

Figure 1: The PRISMA flow chart to identify and screen literature

3.2 Children's CHD Prevalence Overall and Its Altitude Differences

A total of 86 papers were included in the study, of which 27 and 62 reported the prevalence of CHD at high and low altitudes, involving 1,434,399 children (CHD identified in 8,334 individuals) and 11,491,684 children (CHD identified in 23,501 individuals), respectively. The average overall prevalence of CHD in school-age children and that at high and low altitudes (per 1000 children) in China between 1976 and 2021 was 4.69 (95% CI: 4.10 to 5.29), 6.80 (95% CI: 5.65 to 8.05), and 3.20 (95% CI: 2.76 to 3.73), respectively.

Compared with the pooled OR [1.67 (95% CI: 1.45 to 1.91)] of 86 studies included, the OR for CHD prevalence in children at high altitude was 2.84 (95% CI: 2.48 to 3.27), and the OR for CHD prevalence in children at low altitude was 1.31 (95% CI: 1.13 to 1.53) ($\chi^2 = 53.89$, $p < 0.01$) (Fig. 2) (Supplementary Table 1).

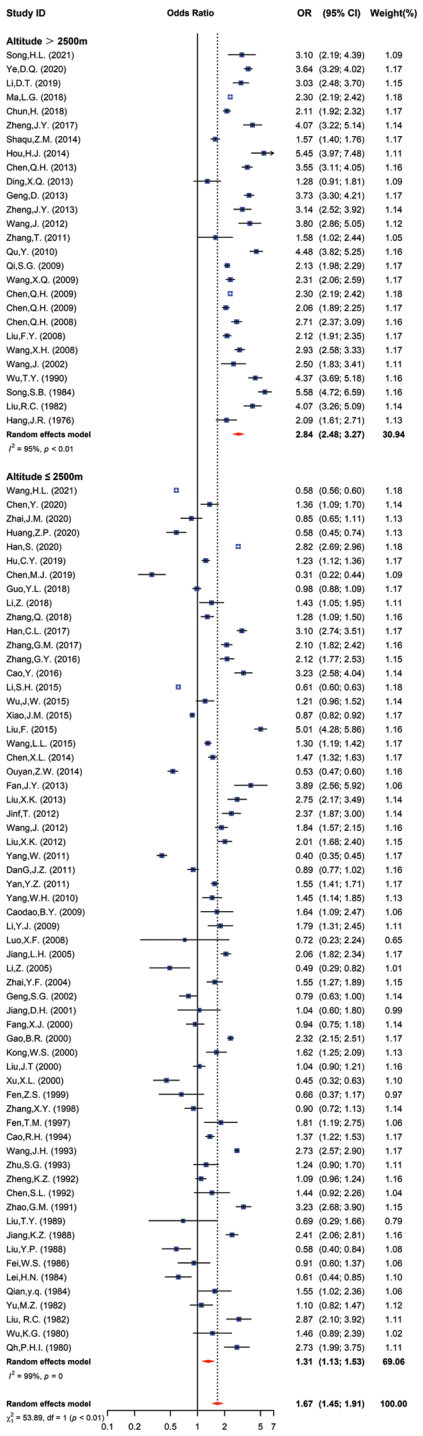

Figure 2: The odds ratio of CHD prevalence in children from different altitudes *vs*. all school children in China

3.3 Prevalence of CHD in Children over Time

As shown by time trend analysis, the overall trend in CHD prevalence in children decreased over time, except for a small rise between 2006 and 2015, from 6.19 per 1000 children in 1976–1985 to 3.30 per

1000 children in 2016–2021 (Fig. 3A). At the same time, a decreasing trend in CHD prevalence in children with was observed at different altitudes. At high altitudes, the prevalence of CHD children decreased from 10.01 per 1000 children in 1976–1985 to 6.25 per 1000 children in 2016–2021, and at low altitudes, the prevalence of CHD children decreased from 4.05 per 1000 children in 1976–1985 to 2.52 per 1000 children in 2016–2021. Of note, a steep decline was observed between 1986 and 1995 and a stable rise in later years in high-altitude regions (Fig. 3B).

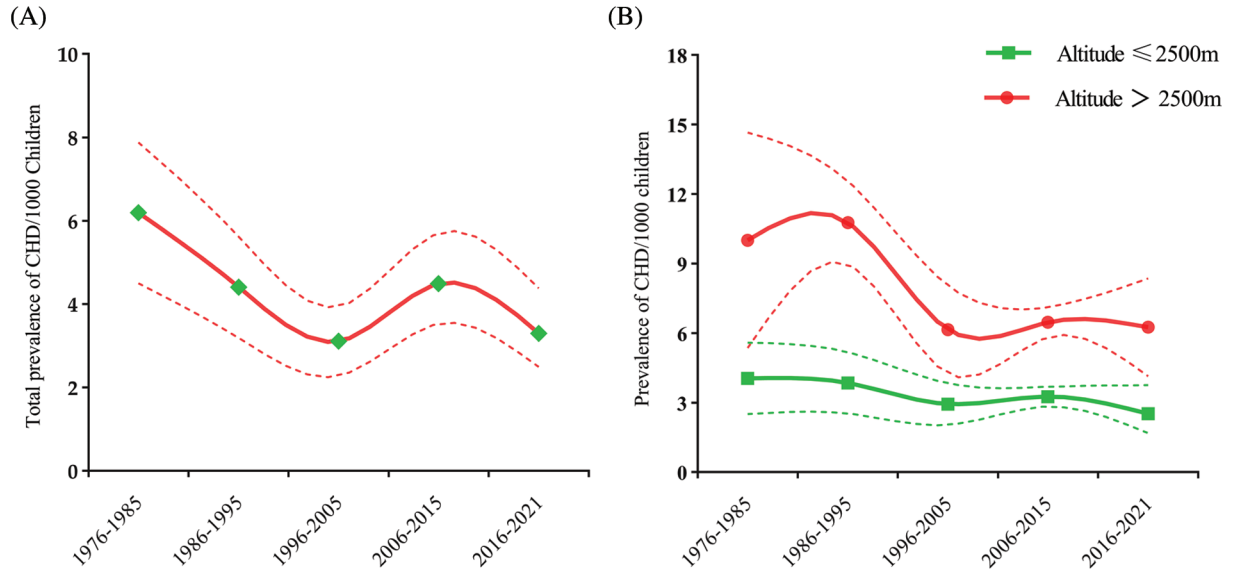

Figure 3: (A). Total CHD prevalence in children over time from 1976 to 2021 in China. The full line is the estimated overall prevalence of CHD; the dotted line represents the 95% CI. (B). The CHD prevalence in children over time at high and low altitude regions in China. The full line is the estimated prevalence of CHD; the dotted line represents the 95% CI

3.4 Total Prevalence of CHD in Children in Relation to Gender

A total of 49 studies reported on the total prevalence of CHD in school-age children in relation to gender, involving 1,755,808 males (CHD identified in 7,078 individuals) and 1,528,686 females (CHD identified in 8,267 individuals). Among these, 20 studies in high-altitude regions included 629,171 males (CHD identified in 2,989 individuals) and 555,253 females (CHD identified in 4,047 individuals), and 29 studies in low-altitude regions, included 1,126,637 males (CHD identified in 4,089 individuals) and 973,433 females (CHD identified in 4,220 individuals).

Reported total CHD prevalence in school-age children was 3.97 per 1000 children (95% CI: 3.47 to 4.53) among males, and 5.90 per 1000 children (95% CI: 5.08 to 6.87) among females (χ^2 =141.32, $p <$ 0.001). In both high and low-altitude areas, the prevalence of CHD was significantly lower in male children than in females (Fig. 4A). Additionally, the OR for male compared with female CHD children was 0.60 (95% CI: 0.53 to 0.68) at high altitudes (Fig. 4B) and 0.79 (95% CI: 0.71 to 0.89) at low altitudes (Fig. 4C) (Supplementary Table 1).

3.5 Prevalence of Common Subtypes of CHD in Children

The CHD prevalence in children and percentage of the 7 most common subtypes are shown in Table 1, and the cumulative percentages of the 7 most common children CHD subtypes, overall and at high and low altitude are shown in Fig. 5A. Overall, the reported prevalence in CHD subtypes among children (per

1000 children) was as follows: VSD, 1.19 (95% CI: 1.02 to 1.38); ASD, 1.52 (95% CI: 1.24 to 1.83); PDA, 0.96 (95% CI: 0.77 to 1.17); PS, 0.11 (95% CI: 0.08 to 0.14); TOF, 0.10 (95% CI: 0.08 to 0.14); TGA, 0.03 (95% CI: 0.01 to 0.04); COA, 0.11 (95% CI: 0.04 to 0.21). The prevalence (per 1000 children) of 3 commonest CHD subtypes in children were PDA [2.7 (95% CI: 2.09 to 2.37)], ASD [2.32 (95% CI: 2.02 to 2.63)], and VSD [1.13 (95% CI: 0.88 to 1.41)] in high altitude areas, while in low altitude areas they were ASD [2.32 (95% CI: 2.02 to 2.63)], VSD 1.22 (95% CI: 1.01 to 1.45)], and PDA [0.49 (95% CI: 0.39 to 0.61)] (Fig. 5B), respectively.

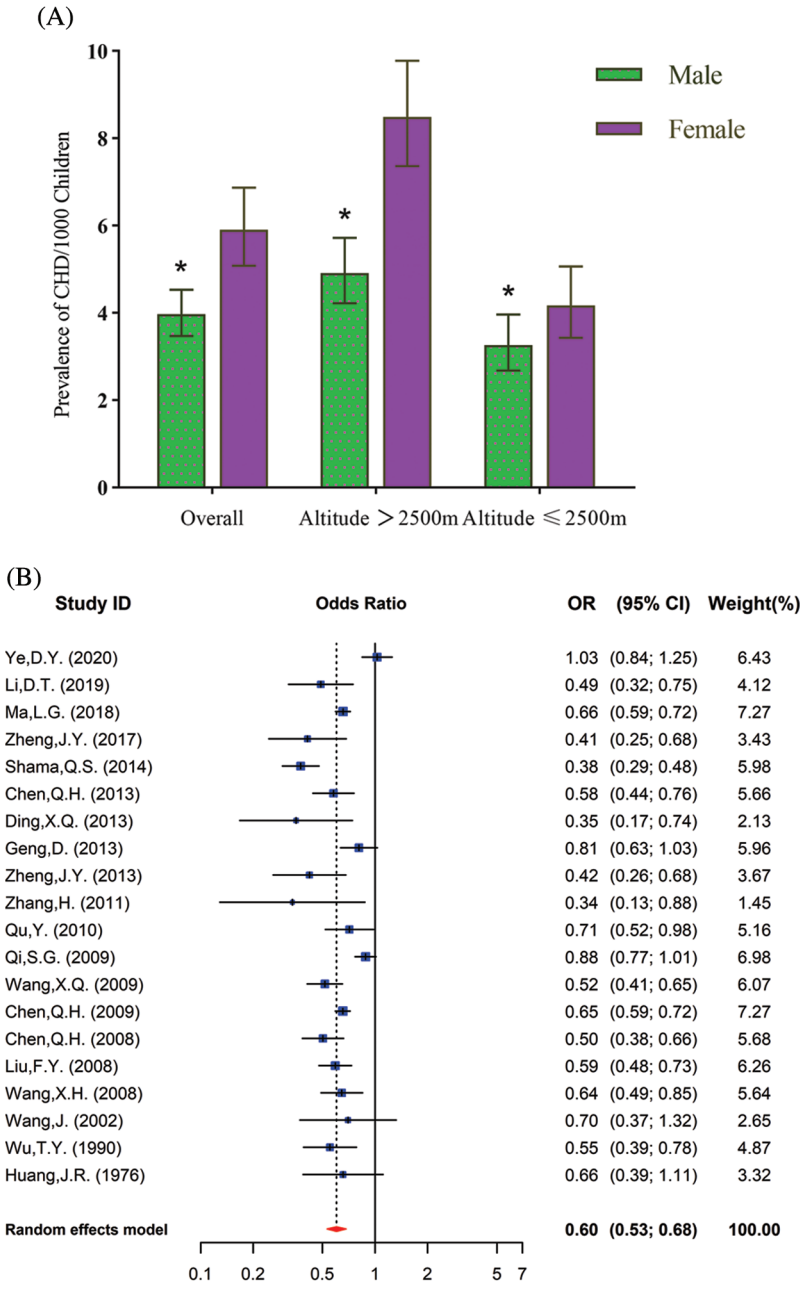

Figure 4: (Continued)

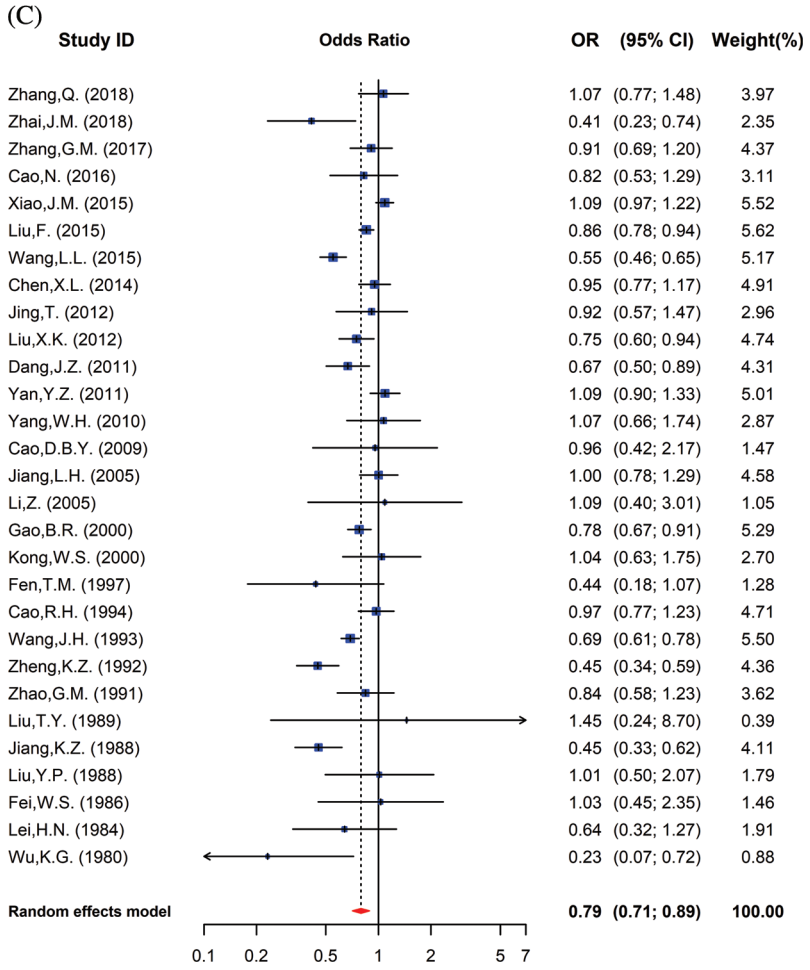

Figure 4: (A). The CHD prevalence in children from the overall high-altitude and low-altitude regions in China in relation to gender. Data are presented as Mean ± SE. *, $p < 0.05$, compared with different genders. (B). Meta-analysis of risk of CHD prevalence in male and female school children in high altitudes. Values <1 reflect the lower proportion of males. (C) Meta-analysis of risk of CHD prevalence among male and female school children in low altitudes. Values <1 reflect the lower proportion of males

3.6 Prevalence of CHD in Children in Relation to Different Geographical Regions

Significant regional differences were detected. The highest reported prevalence of total CHD among school-age children was in the Northwest region [5.97 per 1000 children (95% CI: 4.93 to 7.11)], while the lowest was in the Central region [1.32 per 1000 children (95% CI: 1.15 to 1.50)]. The reported total prevalence of CHD among children in the Northwest region was significantly higher compared with all other regions (all, $p < 0.05$). The Southwestern region was the second highest reporting total CHD prevalence in children [4.33 per 1000 children (95% CI: 3.38 to 5.40)] (Fig. 6).

3.7 Prevalence of CHD in Children in Relation to Different Income Regions

Only lower-middle and upper-middle regions data were available. The significant difference between two income groups were found: the reported prevalence of total CHD among school-age children in lower-middle regions 4.61 (95% CI: 3.93 to 5.35) per 1000 and upper-middle regions 2.53 (95% CI: 1.97 to 3.26) per 1000 ($\chi^2 = 9048.08$, $p < 0.001$) (Fig. 7).

Table 1: The school-age children's prevalence and percentage of the most common CHD subtypes

Common subtypes	Number of studies			Total (Event)			School-age children prevalence, % (95% CI)			Percentage, % (95% CI)		
	Overall	Altitude ≥2500 m	Altitude <2500 m	Overall	Altitude ≥2500 m	Altitude <2500 m	Overall	Altitude ≥2500 m	Altitude <2500 m	Overall	Altitude ≥2500 m	Altitude <2500 m
Ventricular Septal Defect (VSD)	58	17	41	9,471,313 (8550)	712,358 (944)	8,758,955 (7606)	1.19 (1.02, 1.38)	1.13 (0.88, 1.41)	1.22 (1.01, 1.45)	40.78 (40.12, 41.45)	24.00 (22.67, 25.34)	44.66 (43.91, 45.40)
Atrial Septal Defect (ASD)	58	17	41	9,471,31 (7531)	712,358 (1554)	8,758,955 (5977)	1.52 (1.24, 1.83)	2.32 (2.02, 2.63)	1.23 (0.95, 1.53)	35.92 (35.27, 36.57)	39.51 (37.98, 41.04)	35.09 (34.38, 35.81)
Patent Ductus Arteriosus (PDA)	58	17	41	9,471,31 (4044)	712,358 (1408)	8,758,955 (2636)	0.96 (0.77, 1.17)	2.70 (2.09, 3.37)	0.49 (0.39, 0.61)	19.29 (18.76, 19.82)	35.80 (34.30,37.30)	15.48 (14.93, 16.02)
Pulmonary Stenosis (PS)	35	7	28	8,472,10 (608)	133,664 (14)	8,338,444 (594)	0.11 (0.08, 0.14)	0.10 (0.05, 0.16)	0.11 (0.08, 0.14)	2.90 (2.67, 3.13)	0.36 (0.17, 0.54)	3.49 (3.21, 3.76)
Tetralogy of Fallot (TOF)	29	5	24	1,781,694 (162)	119,669 (10)	1,662,025 (152)	0.10 (0.08, 0.14)	0.09 (0.03, 0.18)	0.11 (0.07, 0.14)	0.77 (0.65, 0.89)	0.25 (0.10, 0.41)	0.89 (0.75, 1.03)
Transposition of the Great Arteries (TOG)	6	0	6	516,61 (13)	_	516,671 (13)	0.03 (0.01, 0.04)	_	0.03 (0.01, 0.05)	0.06 (0.03, 0.10)	_	0.08 (0.03, 0.12)
Coarctation of the Aorta (COA)	12	3	9	518,173 (57)	34,072 (3)	484,101 (54)	0.11 (0.04, 0.21)	0.09 (0.02, 0.22)	0.12 (0.04, 0.24)	0.27 (0.20, 0.34)	0.08 (0.00, 0.16)	0.32 (0.23, 0.40)

Note: CHD: Congenital Heart Disease; CI: confidence interval.

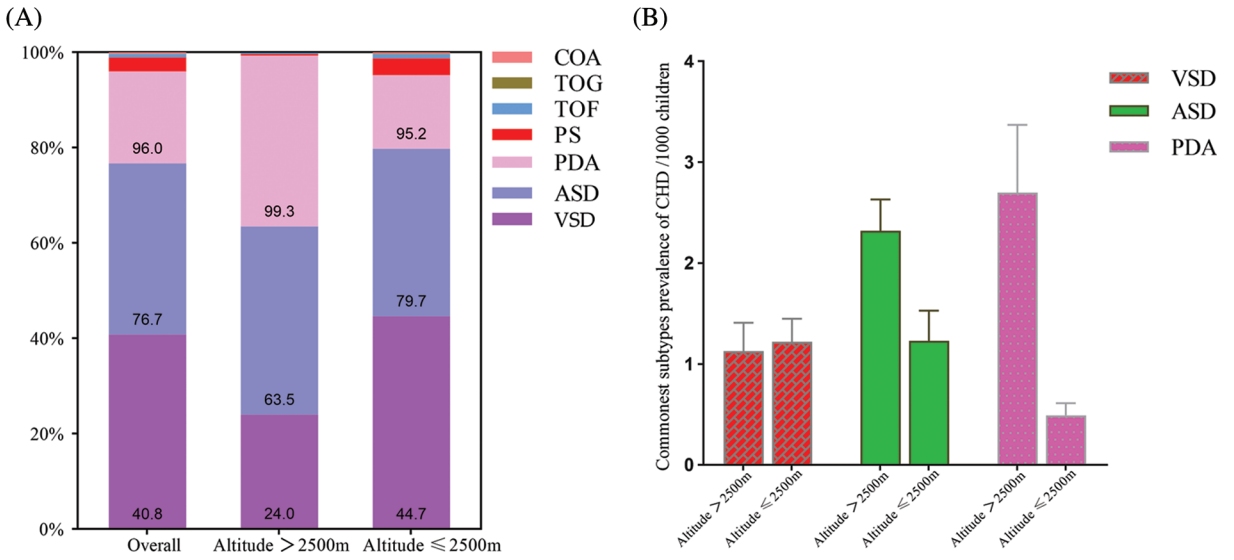

Figure 5: (A) Seven specific subtypes cumulative percentage of CHD children in China. (B) The prevalence of 3 most common subtypes of CHD in children in China

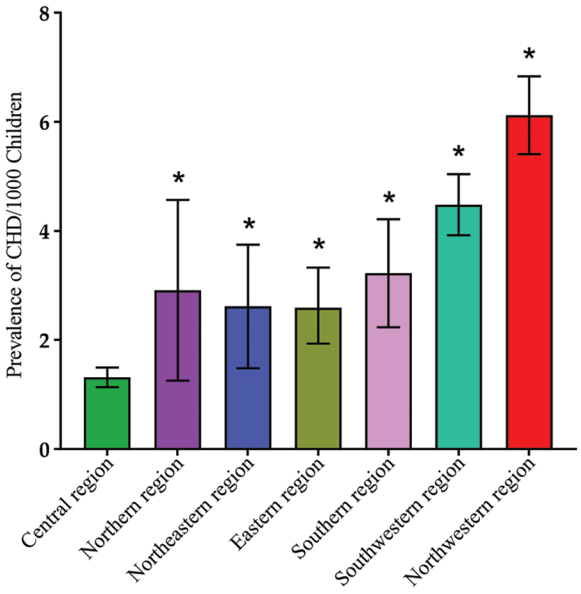

Figure 6: CHD prevalence in different geographic regions in China. Data are presented as Mean ± SE. *, $p <$ 0.05, compared with central region

3.8 Heterogeneity, Subgroup Analyses, and Publication Bias

Heterogeneity in subgroups by altitude, gender, and income levels was explored in pooled estimates, revealing statistical significance (I^2 rang 84.0%–99.4%; Q statistic, all $p < 0.001$) (Table 2). Estimates of prevalence in school-age children did not significantly change after excluding any of the individual studies. However, egger's regression test ($t = 7.06$, $p < 0.001$) and the funnel plot showed publication bias seen in Supplementary Fig. 1.

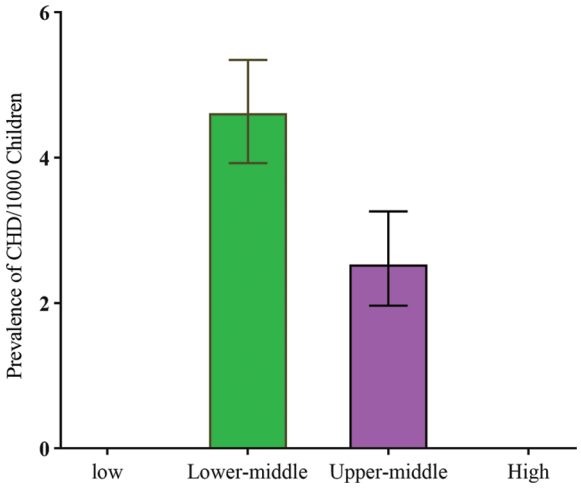

Figure 7: CHD prevalence and income level in China

Table 2: Subgroup analyses for total CHD children prevalence in China

Subgroup variables	Number of studies	Event	Total	School-age Children prevalence, % (95% CI)
Altitude (χ^2 = 7341.72, p < 0.001)				
Low altitude regions	62	23,501	11,491,684	3.20 (2.76, 3.73)
				Q = 9131.5, p < 0.001; I^2 = 99.3%
High altitude regions	27	8334	1,434,399	6.80 (5.65, 8.05)
				Q = 883.78, p < 0.001; I^2 = 97.1%
Gender (χ^2 = 141.32, p < 0.001)				
Male	49	7078	1,755,808	3.97 (3.47, 4.53)
				Q = 1142.86, p < 0.001; I^2 = 95.8%
Female	49	8267	1,528,686	5.90 (5.08, 6.87)
				Q = 1708.84, p < 0.001; I^2 = 96.7%
Income levels (χ^2 = 101.02, p < 0.001)				
Upper-middle-income	20	2819	1,368,356	2.53 (1.97, 3.26)
				Q = 601.63, p < 0.001; I^2 = 96.8%
Lower-middle-income	70	29,016	11,557,727	4.61 (3.93, 5.35)
				Q = 11917.94, p < 0.0001; I^2 = 99.4%
Area (χ^2 = 9048.08, p < 0.001)				
Southwestern region	32	8994	3,477,724	4.33 (3.38, 5.40)
				Q = 3795.86, p < 0.001; I^2 = 99.2%
Northwest region	27	8697	1,546,043	5.97 (4.93, 7.11)
				Q = 359.17, p < 0.001; I^2 = 96.7%

(Continued)

Table 2 (continued)

Subgroup variables	Number of studies	Event	Total	School-age Children prevalence, % (95% CI)
Eastern region	13	10,194	6,520,562	2.64 (1.83, 3.61)
				$Q = 727.97$, $p < 0.001$; $I^2 = 99.2\%$
Northern region	7	2030	505,014	2.60 (1.33, 4.29)
				$Q = 4823.63$, $p < 0.001$; $I^2 = 99.4\%$
Southern region	5	1569	659,975	3.175 (1.855, 4.846)
				$Q = 113.26$, $p < 0.001$; $I^2 = 96.5\%$
Northeastern region	4	140	56,774	2.59 (1.61, 3.81)
				$Q = 18.79$, $p = 0.0003$; $I^2 = 84.0\%$
Central region	2	211	159,991	1.32 (1.15, 1.50)
				$Q = 0.22$, $p = 0.6364$; $I^2 = 0.0\%$

Note: CHD: Congenital Heart Disease; CI: confidence interval.

4 Discussion

To the best of our knowledge, this is the first meta-analysis of the prevalence of CHD in school-age children in China. This review study included 31,835 CHD cases and 12,926,083 individuals from 86 published literature.

The prevalence of total CHD in school-age children was 4.69 per 1000 children, and overall prevalence decreased over time from 1976 to 2021, except for a rise during the period 2006–2015. The reported average CHD prevalence in school-age children in China was higher than birth prevalence (2.50 per 1000 birth) [9]. The birth prevalence increased from 0.21 per 1000 children to 4.91 per 1000 children from 1980–2015, revealing a 24-fold increase, while the prevalence rate decreased from 6.19 per 1000 children to 3.30 per 1000 children from 1976–2021, reaching a roughly two-fold decrease. Therefore, the total average prevalence of CHD at birth was higher than the prevalence of CHD in school-age children, which may not represent the true situation.

In the comparison of time trend analysis, the prevalence trend among school-age children was opposite to birth prevalence [2,3,9]. The following reasons might explain this phenomenon: (1) with the development of interventions, surgeries, and medications, many mild lesions of CHD may be cured in infancy [22–25]. Consequently, these children can normally go to school; (2) as socioeconomic level, sonographer skills, and diagnostic equipment evolve, prenatal screening has become increasingly important [26–29], especially for expectant mothers with offspring at high risk of CHD, such as habitual abortion and CHD family history. Once critical Congenital Heart Disease (CCHD) is detected by obstetric examinations, termination of pregnancy may be preferred [30]. (3) According to the research result of Boris Groisman et al., the perinatal mortality rate of CCHD is about 25% [31], which might explain why critical lesions only accounted for 9.7% among CHD school-age children. We also found the opposite time trend compared to the previous meta-analysis by Liu et al. [16]. This might be due to the limited sample size in the previous study, which involved 46 studies from around the world, thus failing to report the prevalence and time trend of CHD among school-age children in China. Therefore, it might not truly reflect the condition of CHD prevalence in school-age children in China.

Another notable finding was that the CHD prevalence in school-age children was 2-fold higher in higher altitude regions than in lower altitude regions. These findings confirm the results of previous studies,

reporting a higher prevalence of CHD in high altitudes [13,32–34]. This huge difference could be attributed to the geographical environment, socio-economical level, and ethnic diversity. Atmospheric oxygen levels decrease as altitude increases, and low oxygen tension results in restricted vasoconstriction, which is thought to be the mechanism of PDA. Meanwhile, high pulmonary vascular resistance and right heart pressure persist at high altitudes, thus inhibiting early closure of the foramen ovale [35–38]. In addition, affected by altitude and cold, the incidence of various cardiovascular diseases also tends to increase [39]. High-altitude areas are economically underdeveloped regions, which could cause social problems, especially in women's and children's health care. Due to the special geographical environment, inconvenient transportation, and lack of medical and health professionals, it is difficult for pregnant women to receive regular obstetric examinations and screening for common neonatal diseases [40,41]. Consequently, many mild diseases in newborns are not timely treated or even discovered until school age. The high-altitude areas are dominated by ethnic minorities, especially Tibetans; however, it remains unknown whether CHD is more common in the Tibetan population, which future studies should address.

Meantime, CHD prevalence in males was significantly lower than in female school children, both in high altitude or low altitude areas. This was consistent with the result of Yoo et al. [42], who reported the total CHD prevalence over time was higher in females in adult and pediatric populations. Additionally, specific CHD prevalence varies according to gender, with males being more prone to severe and complex lesions and females to simple lesions, which corresponds to higher mortality rates in males than females [43,44]. So far, the mechanism underlying gender differences in prevalence has not yet been clarified and should be addressed by further studies.

The present study also revealed a geographical discrepancy in CHD prevalence in children. The Northwest district reported the highest total prevalence of CHD in children in China. However, in a previous meta-analysis of CHD prevalence at birth, the prevalence was relatively low in the Northwest. This result could be partly attributed to inadequate maternal antenatal and postnatal screening systems, which might make some diseases of perinatal infant diseases difficult to detect (e.g., Congenital Heart Disease) [34,40]. Furthermore, most of the Northwest Territories are located at high altitudes and are economically underdeveloped, which may be one of the important reasons for the high CHD prevalence.

Heterogeneity tests revealed high levels of heterogeneity in altitude, gender, geographic regions, and income level in our study. Some factors may contribute to heterogeneity, including the research design of the original papers, socioeconomic situation, study population selection, prenatal care service, ethnic background, and diagnostic tools used. However, the present study included very large sample sizes, which made point estimates very precise and SEs very small. Therefore, heterogeneity was expected and inevitable in cross-sectional studies.

This study has several limitations. First, the study design and diagnostic skills of each original paper varied, which could result in a bias in the reported prevalence and may be present in our estimates. Second, in addition to reporting the total number of cases and participants, not each study reported subgroups in detail, which may affect the stability of subgroup analysis outcome. Finally, whilst studying the CHD prevalence in children at different altitudes, due to the limitation of sample size, we simply defined 2500 m as the segmentation point between high and low altitudes, without further division of altitude, which makes it impossible to determine the prevalence of CHD with increasing altitude.

5 Conclusions

The overall CHD prevalence in school-age children decreased over time, and the prevalence in high altitude areas was more than twice as high as in low altitude areas, thus representing a serious disease burden at high altitudes. The prevalence of CHD was significantly lower in male than in female children, and the difference was more pronounced, especially at high altitudes. We also found that the prevalence of different subtypes of CHD was correlated with altitude. The prevalence of CHD in different regions

remains uncertain, as it is not confirmed whether the differences are real or just methodological. Based on our results, we suggest that the Chinese government pay more attention to high-altitude and economically underdeveloped areas in allocating medical resources and the health care of women and children.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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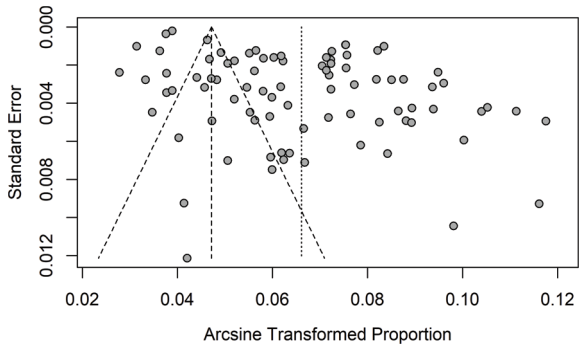
Supplementary File



Supplementary Figure 1: Analysis of publication bias with the funnel plot

Supplementary Table 1: Risk of bias of the selected studies by JBI-PCAT [1,2]

Author	Publish Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Yes Score (_/8) Methodological quality [3]
Wu et al. [4]	1980	Y	Y	Y	Y	N	Y	N	Y	6/8 high
Qh [5]	1980	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Huang et al. [6]	1976	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Yu [7]	1982	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Liu et al. [8]	1982	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Qian et al. [9]	1984	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Le et al. [10]	1984	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Song et al. [11].	1984	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Fei [12]	1986	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Liu [13]	1988	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Jiang et al. [14]	1988	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Liu et al. [15]	1989	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Wu et al. [16]	1990	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhao et al. [17]	1991	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhen et al. [18]	1992	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Chen et al. [19]	1992	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhu et al. [20]	1993	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Wang et al. [21]	1993	Y	Y	N	Y	N	N	N	Y	4/8 moderate
Cao et al. [22]	1994	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Fen et al. [23]	1997	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Zhang et al. [24]	1998	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Kuang et al. [25]	1999	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high

(Continued)

Supplementary Table 1 (continued)

Author	Publish Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Yes Score (_/8) Methodological quality [3]
Fang et al. [26]	2000	N	Y	Y	Y	N	Y	Y	Y	6/8 high
Gao et al. [27]	2000	Y	N	Y	N	Y	Y	Y	Y	6/8 high
Liu et al. [28]	2000	Y	N	Y	Y	N	Y	Y	Y	6/8 high
Kong et al. [29]	2000	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Xu et al. [30]	2000	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Jiang [31]	2001	Y	N	Y	Y	N	Y	Y	Y	8/8 high
Wang et al. [32]	2002	Y	Y	Y	Y	Y	Y	N	Y	7/8 high
Geng et al. [33]	2002	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhai et al. [34]	2004	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Jiang et al. [35]	2005	N	N	Y	Y	N	N	Y	Y	4/8 moderate
Li et al. [36]	2005	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Chen et al. [37]	2008	Y	Y	Y	N	N	Y	Y	N	4/8 moderate
Luo [38]	2008	Y	Y	Y	Y	Y	N	N	Y	6/8 high
Liu et al. [39]	2008	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Wang et al. [40]	2008	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Chen et al. [41]	2009	Y	Y	N	Y	Y	Y	Y	Y	5/8 moderate
Caodao et al. [42]	2009	Y	Y	Y	Y	N	Y	N	Y	6/8 high
Qi et al. [43]	2009	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Li et al. [44]	2009	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Chen et al. [45]	2009	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Wang et al. [46]	2009	Y	N	N	N	N	Y	Y	Y	4/8 moderate
Yang et al. [47]	2010	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Qu et al. [48]	2010	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Dang et al. [49]	2011	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhang et al. [50]	2011	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Yan et al. [51]	2011	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Liu et al. [52]	2012	Y	N	Y	Y	N	Y	Y	Y	6/8 high
Yang et al. [53]	2012	Y	N	Y	Y	N	Y	Y	Y	6/8 high
Wang [54]	2012	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Jing et al. [55]	2012	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zheng et al. [56]	2013	Y	N	Y	Y	Y	Y	Y	Y	7/8 high
Chen et al. [57]	2013	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Liu et al. [58]	2013	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Geng et al. [59]	2013	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high

(Continued)

Supplementary Table 1 (continued)

Author	Publish Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Yes Score (_/8) Methodological quality [3]
Pan et al. [60]	2013	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Ding et al. [61]	2013	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Hou [62]	2014	Y	Y	Y	N	N	Y	N	Y	5/8 moderate
Chen et al. [63]	2014	Y	Y	Y	Y	Y	Y	Y	N	7/8 high
Shaqu et al. [64]	2014	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Ouyang et al. [65]	2014	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Liu et al. [66]	2015	Y	N	Y	Y	N	Y	Y	N	5/8 moderate
Li et al. [67]	2015	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Wu [68]	2015	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Xiao et al. [69]	2015	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Wang [70]	2015	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhang et al. [71]	2016	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Cao [72]	2016	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhang et al. [73]	2017	Y	N	Y	Y	N	Y	Y	Y	6/8 high
Zheng et al. [74]	2017	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Han et al. [75]	2017	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Chen [76]	2018	Y	N	Y	N	Y	Y	N	N	4/8 moderate
Chun et al. [77]	2018	Y	Y	Y	N	N	Y	Y	Y	6/8 high
Ma et al. [78]	2018	Y	Y	Y	Y	N	Y	N	Y	6/8 high
Zhang et al. [79]	2018	Y	N	Y	Y	Y	Y	Y	Y	7/8 high
Li et al. [80]	2018	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Guo et al. [81]	2018	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Li et al. [82]	2019	N	N	Y	Y	N	Y	Y	Y	5/8 moderate
Hu et al. [83]	2019	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Ye et al. [84]	2020	Y	Y	Y	Y	Y	N	N	Y	6/8 high
Chen et al. [85]	2020	Y	Y	Y	Y	N	Y	Y	Y	7/8 high
Han et al. [86]	2020	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Zhai et al. [87]	2020	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Huang et al. [88]	2020	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high
Song et al. [89]	2021	Y	Y	Y	Y	Y	Y	Y	Y	8/8 high

Note: This tool considers (Q1—Were the criteria for inclusion in the sample clearly defined? Q2—Were the study subjects and the setting described in detail? Q3—Was the exposure measured in a valid and reliable way? Q4—Were objective standard criteria used for measurement of the condition? Q5—Were confounding factors identified? Q6-Were strategies to deal with confounding factors stated? Q7—Were the outcomes measured in a valid and reliable way? Q8—Was appropriate statistical analysis used?). We assessed the risk of bias by using the JBI-PCAT. Articles that scored less than or equal to 3 were classified as low methodological quality, articles with scores between 4 and 5 were classified as moderate quality, and those with scores ≥6 were classified as high quality. N, no; NA, not applicable; U, unclear; Y, yes.

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