Meta-Analysis of Observational Studies in Epidemiology

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The association between body lead levels and childhood rickets

A meta-analysis based on Chinese cohort

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Abstract

China has serious lead pollution and a high incidence of childhood rickets. High lead levels have been reported in childhood rickets, but the results were inconsistent.

To evaluate the association between body lead levels and childhood rickets.

After a systematic literature search, we identified 15 studies determining body lead levels between rickets children and healthy controls, and 4 studies focusing on the cases of different disease severity. Standard mean differences (SMD) and the corresponding 95% confidence intervals (CI) were pooled to compare the lead levels between different groups.

Sixteen case-control studies were included with a total of 5082 cases and 6054 controls. Compared with healthy controls, the body lead levels in rickets children were significantly higher (SMD (95%CI): 0.67 (0.41–0.93)), and subgroup analyses showed consistent results. The cases with moderate-to-severe disease activity also had a significantly higher lead level than mild-to-moderate cases (SMD (95%CI): 0.64 (0.31–0.97)).

This meta-analysis suggested an association between body lead levels and childhood rickets, and lead exposure might be a risk factor for rickets.

Abbreviations: AAS = atomic absorption spectrometry, BALP = bone alkaline phosphatase, BMD = bone mineral density, ICP-AES = inductively coupled plasma-atomic emission spectrometry, NOS = Newcastle–Ottawa Scale, SMD = standard mean differences (SMD).

Keywords: body lead, childhood rickets, meta-analysis

1. Introduction

Rickets is a common pediatric disease characterized by skeleton deformity and hypoevolutism. It is prevalent among the Chinese children under 2 years old, with an incidence of 19.7–35.8%.[1] Most cases were caused by vitamin D deficiency, which could lead to abnormal calcium and phosphors metabolism and subsequent osteodysplasty.[2] In addition to inadequate dietary intake, multiple factors were also related with the etiology, especially the pollution of heavy metals.[3–5] Chinese decades of rapid industrialization and urbanization coincided with serious water, food and air pollution, and the children were easily exposed to the environmental heavy metals.[6,7] On the other hand, considering the unique ways to interact with the environment, children are likely to receive larger doses of heavy metals than adults.[8] Thus, Chinese children are at a high risk of the harm from environment heavy metals.[9] As one of the most commonly encountered heavy metals, lead exposure has become a major health hazard for Chinese children.[10]

Lead exposure has been reported in association with the damage in multiple organs. In Reilly et al study, chronic lead exposure was associated with worsening kidney function in both African American male and female residents, as well as male workers in Dallas smelter communities.[11] Blood lead levels was also adversely associated with anthropometric measures among Mexican children.[12] Moreover, recent epidemiological and experimental studies have validated the association between lead exposure and low bone mineral density (BMD), which could eventually lead to osteoporosis, osteopenia and fracture.[13,14] Lead exposure rats showed a decreased in trabecular bone surface and distribution while trabecular thickness and cortical area increased.

As with the rapid industrialization for decades, lead pollution was extremely serious in China. In the Chinese town with serious pollution of heavy metals, blood lead levels in kindergarten children were negatively correlated with both height and weight, but positively correlated with bone resorption biomarkers, indicating the effects of lead exposure in children's skeletal development.[15] Several Chinese studies have reported the association between body lead levels and rickets, but the results were inconsistent.[16–31] Thus, we conducted a meta-analysis to investigate the association between body lead levels and childhood rickets.

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Y-FZ and J-WX contributed equally to this study.

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2. Methods

2.1. Literature search

A comprehensive literature search was conducted in PubMed, China Knowledge Resource Integrated Database (CNKI), China Wanfang Database and China SinoMed Database from inception to October 2018, using the key words including: ("lead" OR "plumbum" OR "trace element" [MeSH Terms]) and ("rickets" OR "rhachitis" OR "rachitis" [MeSH Terms]). Moreover, we also reviewed the references of related studies and reviews for undetected studies. This study was approved by the ethics committee of The Central Hospital of Enshi Autonomous Prefecture.

2.2. Study selection and exclusion

The studies were included if meeting the following criteria: (i) all patients were diagnosed as childhood rickets according to certain criteria; (ii) assessed serum or hair lead levels in cases and healthy controls or in the cases with different disease severity; (iii) similar age and sex distribution in 2 groups. The exclusion criteria were as follows: animal studies, reviews, or case reports.

2.3. Data extraction and quality assessment

Two authors extracted the data by a standardized collection form. All differences were resolved by discussion. In each study, the following information was extracted: first author, publication year, study area, lead measurement, diagnostic criteria, sample types, age distribution, number of cases and controls, disease severity, and lead levels. The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of included studies.[32]

2.4. Statistical analysis

Standard mean differences (SMD) and the corresponding 95% confidence intervals (CI) were pooled to compare body lead levels between rickets and controls, as well as in the cases with different disease severity. The heterogeneity among studies was estimated by Q test and I^2 statistic.[33] $I^2 > 50\%$ represented substantial heterogeneity, and the summary estimate was analyzed by a random-effects model. Otherwise, a fixed-effects model was applied. Sensitivity analysis was conducted to estimate the stability of the meta-analysis by omitting 1 study at a time during repeated analyses. Publication bias was assessed by using funnel plots and Begg test. All statistical analyses were performed using software STATA version 12.0 (StataCorp LP, College Station, TX).

3. Results

3.1. Characteristics of the included studies

The search strategy identified 596 records: 178 from PubMed, 139 from CNKI, 157 from Wangfan, and 122 from SinoMed (Fig. 1). After excluding duplicated and irrelevant records, 16

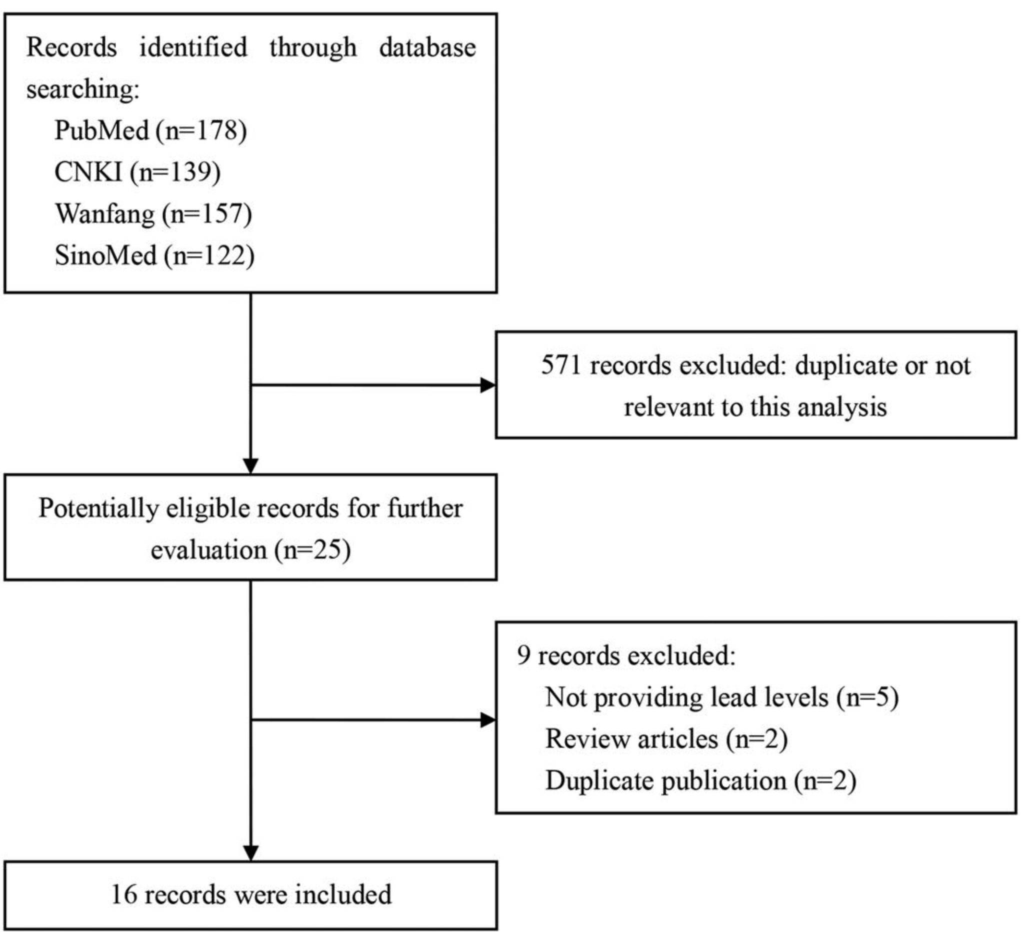

Figure 1. Flowchart of literature search.

Table 1

Characteristics of included studies on the lead levels between childhood rickets and healthy controls.

					Rickets			Healthy controls			
Study	Area	Method	Diagnostic criteria	Sample	Age[§]	Cases	lead levels	Age	Cases	lead levels	Unit
Luo LR 1994	Guangdong	ICP-AES	Disease history, symptom, force line, biochemical examination	Blood	22d–2.5y	71	4.21±1.90	4m–3y	60	2.52±1.61	μmol/l
He SL 1999	Jiangxi	Polarography	The Chinese criteria in 1986	Hair	0–1y	56	15.29±5.14	0–1y	36	11.30±4.20	NA
					1–3y	62	14.40±4.97	1–3y	40	10.76±3.96	
Ye X 2001	Guangdong	ICP-AES	The Chinese criteria in 1986	Hair	0–1y	52	12.81±3.13	0–1y	32	9.75±1.70	NA
					1–3y	58	11.81±2.90	1–3y	36	9.22±2.02	
Pan H 2002	Guangdong	ICP-AES	The Chinese criteria in 1986	Blood	0–3y	103	0.22±0.07	0–3y	103	0.23±0.04	μg/ml
Wang XF 2003	Henan	AAS	The Chinese criteria in 1986	Blood	6m–3y	46	109.28±50.10	6m–3y	68	89.65±28.36	μg/l
Zhu QY 2006	Shandong	AAS	The Chinese criteria in 1986	Blood	3m–3y	312	0.278±0.143	2.3y	297	0.157±0.120	μmol/l
Tan MZ 2006	Guangdong	AAS	The Chinese criteria in 1986	Blood	0–3y	120	65.00±18.25	0–3y	100	31.00±20.21	μg/l
Liu AP 2007	Gansu	AAS	Chinese Textbook of Pediatrics (1979)	Blood	0–3y	30[*]	14.00±5.94	0–3y	80	8.90±1.69	μg/dl
					0–3y	35[†]	14.60±6.51				
					0–3y	21[‡]	7.30±2.14				
Zeng GZ 2007	Fujian	AAS	The Chinese criteria in 1986	Blood	0.5–3y	250	78.52±33.51	0.5–3y	250	49.43±27.72	g/l
Yang ZC 2007	Jiangsu	ICP-AES	The Chinese criteria in 1986	Blood	0–3y	120	0.42±0.14	0–3y	100	0.26±0.14	μmol/l
Hu HD 2007	Jiangxi	AAS	Disease history, symptom, physical examination, BALP	Blood	0–6m	121	48.12±27.90	0–6m	122	47.23±20.96	μg/l
					7–12m	104	68.05±40.35	7–12m	105	65.40±41.87	
					13–18m	86	69.83±26.94	13–18m	86	65.15±36.94	
					19–24m	48	60.39±33.39	19–24m	48	71.83±29.40	
					25–30m	26	74.33±39.46	25–30m	26	68.16±29.38	
					31–36m	35	70.20±35.77	31–36m	35	62.81±24.02	
Gan Y 2011	Guangxi	AAS	The Chinese criteria in 1986	Blood	3m–3y	117	0.268±0.145	3m–3y	108	0.162±0.128	μmol/l
Liao ZG 2011	Jiangxi	AAS	The Chinese criteria in 1986	Blood	3m–3y	216	27.48±15.27	4m–3y	220	19.95±12.98	umol/l
Du WR 2012	Hebei	DPSA	BALP	Blood	0–6y	2897	63.15±26.56	0–6y	4014	61.83±31.00	μg/l
Zhang XP 2014	Hebei	Polarography	BALP	Blood	0–3y	96	200±50	0–3y	88	100±22	μg/l

AAS=atomic absorption spectrometry, BALP=bone alkaline phosphatase, DPAS=differential potentiometric stripping analysis, ICP-AES=inductively coupled plasma-atomic emission spectrometry, NA=not available.

[§] d=day, m=month, y=year.

[*] mild disease.

[†] moderate disease.

[‡] severe disease.

case-control studies were included into this meta-analysis.[16–31] All studies were based on Chinese children, and most studies diagnosed the rickets cases according to the Chinese criteria (1986) for the prevention and treatment of rickets in childhood. Fifteen studies compared the lead levels between rickets and healthy controls (a total of 5082 cases and 6054 controls) (Table 1). Four studies investigated the difference of lead levels in the cases with different disease severity (a total of 287 mild-to-moderate cases and 145 moderated-to-severe cases) (Table 2). Most studies focused on the children aging from 0 to 3 years, and only one focused on 0 to 6 years. Fourteen studies measured the lead levels in blood, while 2 in hair. Atomic absorption spectrometry (AAS) and inductively coupled plasma-atomic emission spectrometry (ICP-AES) were the most common methods to measure lead levels. In quality assessment, all included studies had an NOS score of 6.

Table 2

Characteristics of included studies on the association between body lead levels and rickets severity in children.

Study	Area	Measurement	Diagnostic criteria	Sample	Disease severity	Age	Cases	lead levels	Unit
He SL 1999	Jiangxi	Polarography	The Chinese criteria in 1986	Hair	Mild	0–1y	34	13.65±5.62	NA
						1–3y	35	13.76±5.23	
					Moderate	0–1y	22	17.82±2.93	
						1–3y	27	15.23±4.57	
Ye X 2001	Guangdong	ICP-AES	The Chinese criteria in 1986	Hair	Mild	0–1y	40	12.29±2.51	NA
						1–3y	42	10.90±2.06	
					Moderate	0–1y	12	14.55±4.43	
						1–3y	16	14.17±3.47	
Lin L 2004	Guangdong	ICP-AES	The Chinese criteria in 1986	Blood	Mild to moderate	>1y	106	135.70±71.24	μg/ml
					Moderate to severe	>1y	33	185.45±68.83	
Liu AP 2007	Gansu	AAS	Chinese Textbook of Pediatrics (1979)	Blood	Mild	0–3y	30	14.00±5.94	μg/dl
					Moderate	0–3y	35	14.60±6.51	

AAS=atomic absorption spectrometry, ICP-AES=inductively coupled plasma-atomic emission spectrometry, NA=not available, y=year.

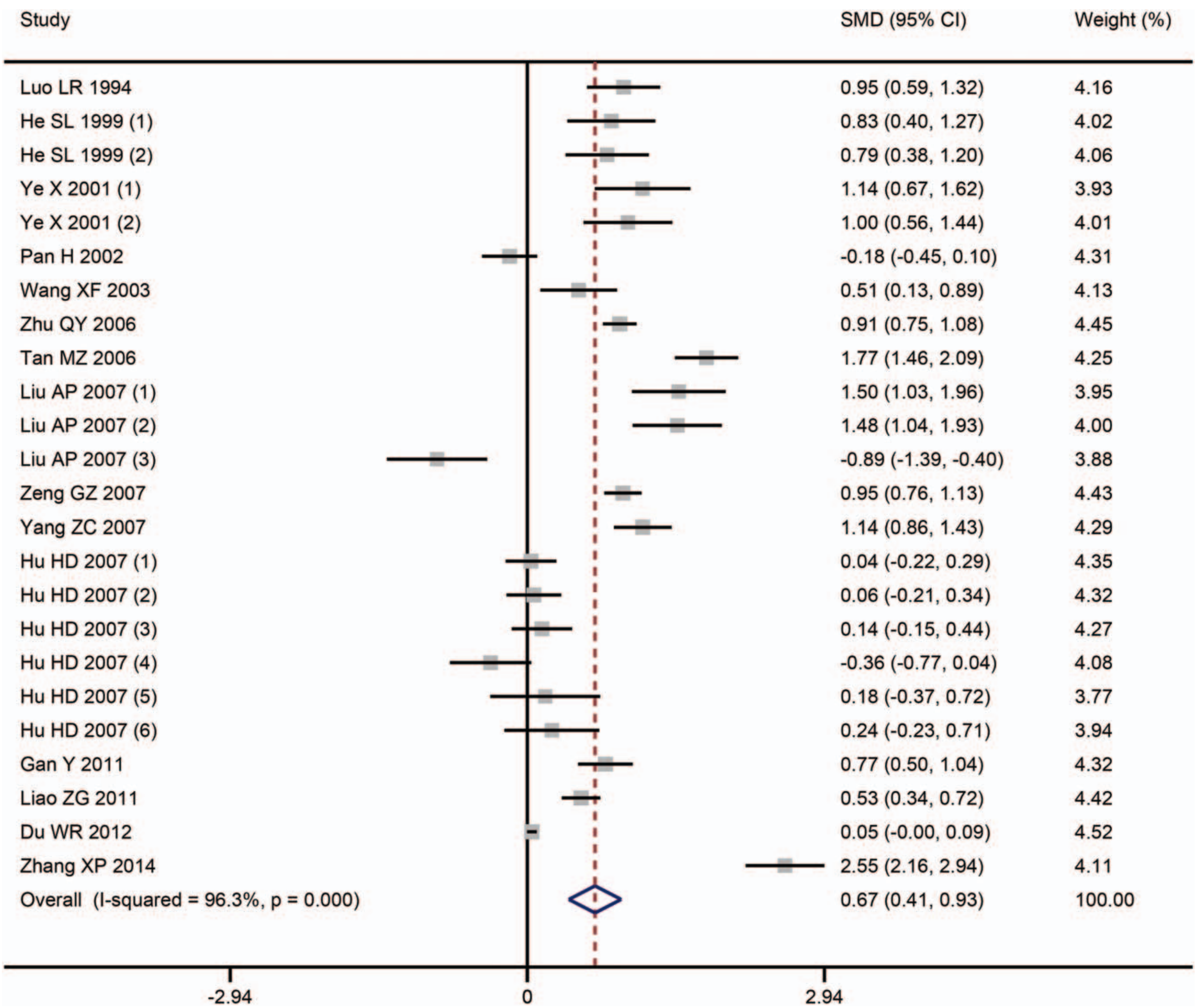

Figure 2. Forest plot of meta-analysis on body lead levels and childhood rickets.

3.2. Body lead levels and rickets

Fifteen studies investigated the difference of body lead levels between rickets and controls, which were expanded into 24 studies in the meta-analysis according to age distribution. It was found that body lead levels in rickets cases were significantly higher than in controls (SMD (95%CI): 0.67 (0.41–0.93); $I^2=96.3\%$, $P_{heterogeneity}<0.001$) (Fig. 2). Sensitivity analysis showed the result was robust (Fig. S1). Begg test detected significant publication bias ($P=.170$) (Fig. S2, http://links.lww.com/MD/C845).

Subgroup analysis was conducted on area, measurement, type of samples, age distribution, diagnosis criteria, and developed area. No substantial changes of the primary result were found between subgroups (Table 3).

3.3. Body lead levels and rickets severity

Four studies investigated the difference of body lead levels between mild-to-moderate cases and moderate-to-severe cases, which were expanded into 6 studies in the meta-analysis according to age distribution. The disease severity was classified into mild, moderate and severe according to clinical symptoms (e.g., apositia, night terror, hidrosis, dysphoria), skeletal change and blood levels of calcium, phosphorus and bone alkaline phosphatase (BALP).[15,16,19,22] It was found that body lead levels in moderate-to-severe cases were significantly higher than in mild-to-moderate cases (SMD (95%CI): 0.64 (0.31–0.97); $I^2=57.1\%$, $P_{heterogeneity}=.040$) (Fig. 3). Sensitivity analysis showed the result was robust (Fig. S3, http://links.lww.com/MD/C845). Begg's test detected significant publication bias ($P=.750$) (Fig. S4, http://links.lww.com/MD/C845).

4. Discussion

As a heavy metal, lead and its compounds are widely used, like ethyl petrol, paint and storage battery. It is non-degradable in the environment, and excessive lead could enter the human body by polluted food, water and air. As with the rapid industrialization for decades, lead pollution was extremely serious in China, and the average lead level among urban children was up to 7.02 μg/dl in blood.[34] Different from adults, children had a higher absorption rate and lower excretion rate for lead, and thus the lead load was heavier than adults.[35] Furthermore, most of the

Table 3

Subgroup analysis of body lead levels and childhood rickets.

Variable	Studies	SMD (95%CI)	I^2 (%)
Area			
Developed	8	0.96 (0.60–1.31)	92.5
Developing	16	0.52 (0.22–0.82)	95.2
Measurement			
AAS	15	0.53 (0.24–0.83)	93.5
ICP-AES	5	0.80 (0.22–1.39)	92.8
Polarography	3	1.39 0.23–2.56)	95.8
DPSA	1	0.05 (0.00–0.09)	NA
Sample			
Blood	20	0.62 (0.33–0.90)	96.8
Hair	4	0.93 (0.71–1.15)	0.0
Age (years)			
0–1	2	0.97 (0.65–1.29)	0.0
0–3	19	0.65 (0.35–0.95)	95.0
1–3	2	0.89 (0.59–1.19)	0.0
Diagnosis criteria			
Comprehensive	22	0.62 (0.38–0.86)	91.4
Only based on BALP	2	0.08 (0.03–0.13)	64.4
Developed area			
Yes	8	0.96 (0.60–1.31)	33.8
No	16	0.52 (0.23–0.82)	66.2

AAS = atomic absorption spectrometry, BALP = bone alkaline phosphatase, DPAS = differential potentiometric stripping analysis, ICP-AES = inductively coupled plasma-atomic emission spectrometry, NA = not available.

residual lead deposited in the bone, and it was easily transferred into blood and soft tissues. As a result, high lead levels could cause systemic lesions in children, and the most common was cognitive impairment.[36]

High lead levels also made an influence on skeletal development. The mechanism was multi-aspect. Firstly, high blood lead levels could decrease children's appetite, and contribute to inadequate dietary intake of calcium.[37] Secondly, lead could reduce intestinal absorption of calcium by competitive inhibition. Thirdly, high blood lead levels were related with low blood calcium and 1, 25-dihydroxy-vitamin D levels, which lead to the decrease of active vitamin D.[38] Forthly, most body lead deposited in bone, and high lead levels could induce the apoptosis of osteoblasts.[8]

Thus, lead might get involved in the pathogenesis of childhood rickets. In the study of Huang et al, the incidence of rickets was 28.8% (15/52) in the lead poisoning cases under 3 years, while it was 20.8% (25/120) in the cases aging from 3 to 12 years.[39] In our study, we also found a higher lead level in rickets than in healthy controls, and the levels were also associated with the disease severity. In the recent study, lead-related lesions could also occur in low concentrations of less than 10 μg/dl, indicating the great harm for children.[40] Thus, it was necessary to take some interventions to prevent lead exposure in children.[41]

This study had several strengths. Firstly, to the best of our knowledge, this is the first meta-analysis to evaluate the association between body lead levels and childhood rickets. Secondly, we also evaluated the association between body lead levels and rickets severity. However, several limitations in this study should be considered. First, the number of cases in the meta-analysis was relatively small. Second, there exited obvious heterogeneity between studies, although we conducted a sensitivity analysis to evaluate the stability of pooled results. Third, most included studies were case-control designed, and it was more difficult confirm causal relationship between lead exposure and rickets. Forth, the data of vitamin D supplementation in the included studies were unavailable. Fifth, it was unknown whether the association between lead and rickets could be generalizable to populations other than Chinese. In spite of these, we thought our robust subgroup analysis and the further analysis between body lead levels and rickets severity could strongly indicate the relationship between body lead levels and childhood rickets. In the future, it is necessary to conduct a prospective study to warrant the association.

In conclusion, this meta-analysis suggested an association between body lead levels and childhood rickets. Lead exposure might be a risk factor for childhood rickets, and high lead levels should been considered in the diagnosis of childhood rickets. Further study was needed to identify the role of lead-discharging in anti-rickets treatment, especially for the children with high lead levels.

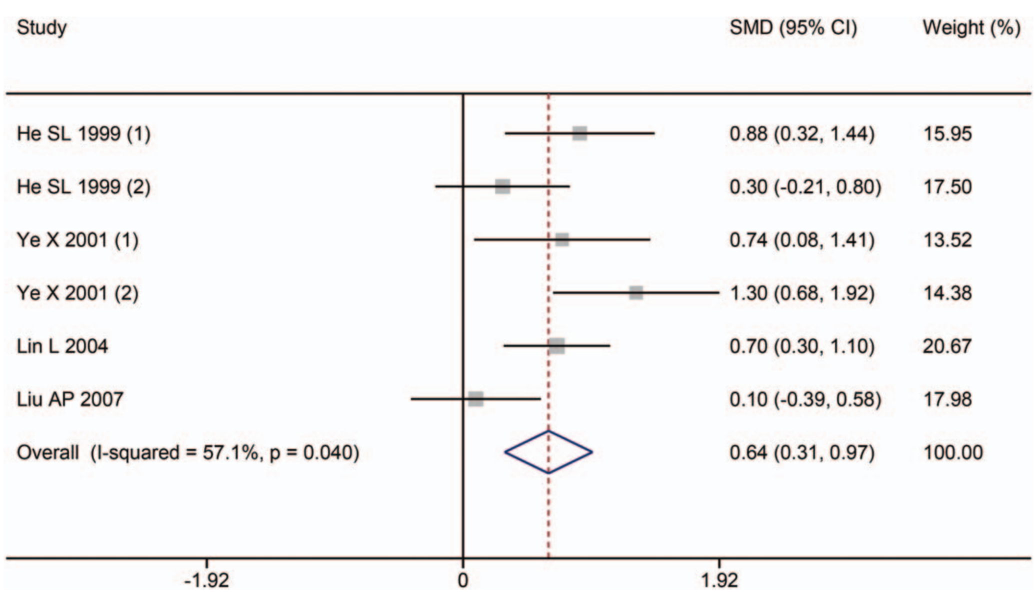

Figure 3. Forest plot of meta-analysis on body lead levels and rickets severity in children.

Author contributions

Conceptualization: Xin-qiao Yu.
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Methodology: Jiang-wei Xu, Xueqin Huang, Xin-qiao Yu.
Software: Yao Yang.
Visualization: Yao Yang.
Writing – original draft: Yong-fang Zhang.
Writing – review & editing: Xin-qiao Yu.

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