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Prevention of Keshan Disease by Selenium Supplementation: a Systematic Review and Meta-analysis

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Abstract

Systematic review (SR) of high-quality studies provides superior evidence, but an SR has not been conducted to evaluate the association between Keshan disease (KD) and selenium deficiency because SR was not available when KD was highly prevalent in the 1950s to 1970s. The objective of this study was to update our understanding of the etiology of KD and provide evidence for policies and strategies in KD surveillance, prevention, and control. We identified related studies by searching the CNKI, Wanfang, CQVIP, SinoMed, CMCI, PubMed, Embase, and EBSCO databases from January 1935 to April 2017. Community trials that met the inclusion criteria were included. Risk ratios (RR) with corresponding 95% confidence intervals (CI) were pooled to compare incidences between the two groups. A total of 17 articles (including 41 studies) were included. In total, the studies included 1,983,238 subjects, 683,075 of which were in experimental groups and 1,300,163 of which were in control groups. The protection rates were over 80% in 35 studies, and the overall effect (risk ratio) was 0.14 [95% CI (0.12, 0.16), $P < 0.05$]. Potential publication bias was observed in the funnel plots, but the results of Egger's and Begg's tests showed that there was no evidence of publication bias. Giving selenium supplements to the residents of KD endemic areas significantly reduced the incidence of KD. Selenium deficiency is therefore a cause of KD by the criterion of causation in modern epidemiology. Selenium should be included in the KD surveillance program. The description of "unknown cause" in the definition of KD may be inappropriate.

Keywords Keshan disease · Selenium supplementation · Community trials · Etiology · Systematic review

Context

Keshan disease (KD) is an endemic cardiomyopathy that occurs only in China. Its name was derived from the first reported epidemic of the disease, which occurred in 1935 in Keshan county in the Heilongjiang province [1–3]. KD has been found in a wide belt zone from the northeast to the southwest in 2596 townships in 327 counties in 16 provinces in China. As the prevalence rate of KD has been at a low level for the past 10 years, the goal of KD prevention and control in the National Endemic Disease Prevention and Control Plan (2011–2015) in China was "basically eliminating Keshan disease in 90% or more counties of Keshan disease endemic areas to reach the criteria of Keshan disease elimination" [4]. However, the etiology of KD is not fully known, and the disease still exists to some extent today [5], which suggests that the etiologic factor of KD may still exist and that residents of KD endemic areas may potentially develop KD. Therefore, it is important to update our understanding of the etiology of KD. Among the etiology hypotheses for KD, selenium deficiency is the most recognized and convincing hypothesis based on the quantity and quality of evidence [6]. The findings of the observational epidemiological studies indicated that the soil and grains in endemic areas of KD were generally selenium deficient [7–10]; the levels of selenium in the head-hairs, finger nails, and blood of residents living in endemic areas were low [11, 12], and

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levels of GSH-Px, a seleno-protein, in residents living in endemic areas were low [13, 14]. KD has already been classified as dietary selenium deficiency in International Classification of Disease (ICD) [15]; in other words, the World Health Organization recognizes that selenium deficiency is a cause of KD. The findings of experimental epidemiological studies of selenium supplementation to residents of endemic areas demonstrated a significant reduction in KD incidence [16–18].

Well-conducted systematic reviews (SRs) are regarded as the best-quality evidence [19–21]. SRs have become increasingly popular in medicine since the 1970s [22–25]. In China, therefore, articles of a similar design type were first published in 1990 and have shown a growing trend since 2001 [26]. In modern epidemiology, the cause of a disease is defined as a factor that decreases the incidence of the disease [27]. In China, epidemiology did not develop at the same pace as it did in industrialized countries in the 1950s to1970s, which is the time during which KD was highly prevalent. SR and the concept of causation in modern epidemiology were therefore not widely used in epidemiological studies of KD in this period. On the other hand, this method is suitable for diseases with low incidences, such as KD.

In this paper, we report a SR and meta-analysis of published articles to assess the association between KD and selenium deficiency based on the definition of causation in modern epidemiology in order to update our understanding of the etiology of KD and provide quality evidence for KD surveillance, prevention, and control.

Evidence Acquisition

Data Sources

SR and meta-analysis were conducted according to the Preferred Reporting Items for SR and Meta-Analysis (PRIAMA) guidelines [28–30]. We searched for potentially relevant studies that were published from January 1935 to April 2017. The following search terms were used without restrictions: “selenium or Se” and “Keshan disease or KD” in the databases of CNKI (China National Knowledge Infrastructure), Wanfang (Wanfang Data Knowledge Service Platform), CQVIP (Chinese Science and Technique Journals Database), SinoMed (Service System for Chinese Biomedical Literature), CMCI (Chinese Medical Citation Index), PubMed (Public Medline), Embase (Excerpta Medical Database), and EBSCO (Elton B. Stephens Company). In addition, we complemented the search using the method of citation pearl growing.

Study Selection

Studies meeting the following criteria were included in the SR: human study articles; community trials; an experimental group and control group in each individual study; selenium supplementation as the intervention; and reported number of participants and morbidity number.

The exclusion criteria were as follows: repeated published studies in which data were included in this analysis and incomplete data.

Data Extraction and Quality Assessment

We extracted the following information from each retrieved article: article title, name of the first author, journal and publication year, sample sizes of the experimental and control groups, and case numbers, and a chi-square test was used to compare the incidence between the two groups. In addition, the protection rate (PR) was not calculated in the original studies because of the lagging development of epidemiology in this country, so we calculated this metric with the extracted data according to the following formula:

$$\mathrm{PR} = (p1 - p2)/p1 \times 100$$

where $p1$ and $p2$ are the incidence of the control group and experimental group, respectively. The methodological quality of the studies was evaluated using the following criteria: defining the source of information (the risk of bias is low if the reference type was a survey, whereas the risk of bias is high if the reference type was a review); rationality of the research design and choice of control group; description of confounding assessments and/or controls; and completeness of data collection. The level of bias assessment was divided into three categories: high risk of bias, low risk of bias, and unclear risk of bias. Both reviewers independently evaluated the articles, and any disagreement was resolved by consensus.

Statistical Analysis

All analyses were performed using Review Manager Software (version 5.3) and STATA Software (version 12.2). Standard statistical tables and graphs were used to describe the characteristics of the surveyed subjects.

To visually assess the risk ratio (RR) and corresponding 95% confidence intervals (CI) across studies, we generated forest plots sorted by publication year. We assessed the heterogeneity of the risk ratio across studies using forest plots and the inconsistency index (I^2). When heterogeneity was not obvious ($I^2 \leq 50\%$), we chose fixed effects models to obtain pooled effect estimates across studies. In the presence of heterogeneity ($I^2 > 50\%$), random effects models were used (rather than fixed effects models) to obtain pooled effect estimates across studies. In addition, sensitivity analysis was performed to assess the stability of this meta-analysis. Finally, we used qualitative visual inspections of funnel plots and quantitative

Egger's or Begg's tests to assess publication bias. All reported P values were two-sided, and $P < 0.05$was considered significant.

Evidence Synthesis

Literature Search

The literature search strategy identified 2230 unique citations, 164 of which were selected manually (Fig. 1). After an initial screen of titles and abstracts, we identified 250 distinct studies as potentially relevant studies for further investigation. Of these articles, 202 did not have a community trial study design, 27 studies had incomplete data, two studies did not have control groups, and two studies were duplicate publications. Thus, 17 articles (including 41 studies) ultimately met the inclusion criteria and were included in this SR and meta-analysis [16–18, 31–44].

Study Characteristics

The details of the included studies are shown in Table 1. Of the 17 articles, 12 (70.6%) articles (including 32 studies) were reported in the 1970s, and the studies were conducted during the peak period in which KD was highly prevalent, so the data from the studies were representative. The protection rates were between 80 and 100% in the 35 studies, and the details are shown in Table 1.

The quality of studies included in the meta-analysis was assessed by applying the above criteria. The assessments of the authors on the risk of bias of the included studies are displayed in the left panel of Fig. 2. The percentages of assessments of the authors on the risk of bias of the included studies are shown in the right panel. The data were mostly derived from retrospective studies and did not describe how confounding was assessed and/or controlled.

Meta-analysis and Sensitivity Analysis

Figure 3 is the forest plot, and it presents little statistical evidence of heterogeneity ($P < 0.05$, $I^2 = 41.8\%$); thus, we choose fixed effects models to obtain pooled effect estimates across studies. In total, the 41 studies included 1,983,238 subjects, 683,075 of which were in experimental groups and 1,300,163 of which were in control groups. Of the 41 studies, 16 studies (39%) had 95% confidence intervals of the risk ratio that crossed the invalid line, but their overall point estimates were < 1.0. The overall effect was 0.14 (95% CI 0.12 to 0.16). In addition, we performed sensitivity analysis by excluding individual studies sequentially. Almost all of the results were similar to the overall effect of the meta-analysis, suggesting that this meta-analysis was stable (Fig. 4).

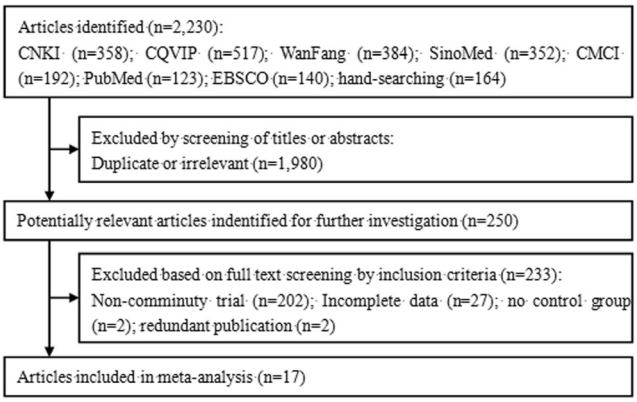

Fig. 1 Flow diagram of study selection for review

Publication Bias

The funnel plot showed an asymmetrical distribution of the outcomes of the included studies, indicating that there was likely significant publication bias (Fig. 5). However, we used quantitative Egger's and Begg's tests to assess publication bias, and the result confirmed that there was no evidence of publication bias (P for Egger's test: 0.285; P for Begg's test: 0.379).

Discussion

KD is an endemic cardiomyopathy occurring only in China. KD has been found in a wide belt zone from the northeast to the southwest in 2596 townships in 327 counties in 16 provinces in China. Now, the prevalence rate of KD is at a low level, so the goal of KD prevention and control is "basically eliminating Keshan disease in 90% or more counties of Keshan disease endemic areas to reach the criteria of Keshan disease elimination." Elimination was defined as "zero disease in a defined geographic area as a result of deliberate efforts" [45]. People have been concentrating on eliminating many diseases with a known etiology, including polio, measles, and malaria. Not only were these diseases eliminated but also their causes [46–48]. However, the etiology of KD is not fully known, but the major hypothesis of its etiology was selenium deficiency. It is necessary to clarify whether selenium deficiency is a cause of KD. Therefore, we conducted this SR and meta-analysis because this method has not been applied to the association between selenium deficiency and KD.

In this study, the protection rates presented in Table 1 quantitatively demonstrate that supplementation of selenium effectively prevented the occurrence of KD. In addition, the details of the forest plot indicate that the risk of occurrence of KD in the control group was eight times of the risk in the experimental group. This quantitative result revealed that reduction of the incidence of KD was causally associated with selenium supplementation. Although the funnel plot, which presented asymmetry, suggested that publication bias might exist, the

Table 1 Characteristics and quality of the included studies

First author	Year	Experimental group			Control Group			*P* value	PR (%)
		Total no.	Cases no.	Incidence (%)	Total no.	Cases no.	Incidence (%)		
KDRG of CAMS[16]	1972	198	0	0.00	727	8	1.10	> 0.05	100
KDRG of CAMS[17]	1972	164	7	4.27	168	8	4.76	> 0.05	10
AES of Jilin[18]	1973	49	0	0.00	23	0	0.00	–	–
RLKD in XMU[31]	1973	50	1	2.00	50	5	10.00	> 0.05	80
		798	1	0.13	451	5	1.11	< 0.05	89
CGPKDSS[32]	1975	182	0	0.00	583	6	1.03	> 0.05	100
		566	0	0.00	569	4	0.70	> 0.05	100
		4202	0	0.00	5116	5	0.10	> 0.05	100
		1687	0	0.00	2377	5	0.21	> 0.05	100
		10,456	0	0.00	7140	3	0.04	> 0.05	100
		6946	0	0.00	5831	9	0.15	< 0.05	100
		4510	10	0.22	3985	52	1.30	< 0.05	83
CGPKDSS[33]	1976	1734	0	0.00	1870	3	0.16	> 0.05	100
		3038	1	0.03	2900	2	0.07	> 0.05	52
		4432	0	0.00	4221	0	0.00	–	–
		1231	0	0.00	1036	1	0.10	> 0.05	100
		594	0	0.00	548	1	0.18	> 0.05	100
		704	0	0.00	673	1	0.15	> 0.05	100
CGPKDSS[34]	1976	6767	3	0.04	5445	55	1.01	< 0.05	96
AES of Jilin[35]	1977	52,971	0	0.00	12,463	9	0.07	< 0.05	100
RLKD in XMU[36]	1978	537	4	0.74	540	31	5.74	< 0.05	87
		67	0	0.00	59	5	8.47	< 0.05	100
		978	3	0.31	849	26	3.06	< 0.05	90
		1686	1	0.06	183	3	1.64	< 0.05	96
		978	3	0.31	1276	20	1.57	< 0.05	80
		1686	1	0.06	1026	11	1.07	< 0.05	94
AES of Jilin[37]	1979	62,481	0	0.00	36,012	1	0.00	> 0.05	100
		64,480	0	0.00	9634	0	0.00	–	–
NCGERKD: TFS[38]	1979	36,603	21	0.06	9642	107	1.11	< 0.05	95
		7752	7	0.09	7423	55	0.74	< 0.05	88
		19,552	5	0.03	12,549	86	0.69	< 0.05	96
RLKD in XMU[39]	1979	7215	3	0.04	6883	24	0.35	< 0.05	88
Cao[40]	1982	26,240	0	0.00	24,198	11	0.05	< 0.05	100
Yu[41]	1983	14,140	9	0.06	13,099	24	0.18	=0.05	65
Liu[42]	1988	6534	1	0.02	6730	9	0.13	< 0.05	89
Li[43]	1992	4248	9	0.22	4248	57	1.35	< 0.05	84
		323,872	88	0.03	1,107,568	1713	0.16	< 0.05	83
Song[44]	1992	96	0	0.00	92	5	5.43	> 0.05	100
		811	1	0.12	450	5	1.11	< 0.05	89
		716	4	0.56	720	31	4.31	< 0.05	87
		1124	1	0.09	806	14	1.74	< 0.05	95

KDRG of CAMS The Keshan Disease Research Group of the Chinese Academy of Medical Sciences, *RLKD in XMU* Research Laboratory of Keshan Disease in Xi'an Medical University, *AES of Jilin* Anti-epidemic Station of Jilin city, *CGPKDSS* The Collaborator Group of Preventing Keshan Disease by Sodium Selenite, *NCGERKD: TFS* The National Collaboration Group of Etiological Research for Keshan Disease: Task Force on Selenium

results of Egger's and Begg's tests indicate that there is no publication bias in this study. As demonstrated above, selenium deficiency is a cause of KD. It should be noted that the cause of a non-communicated disease is normally not the

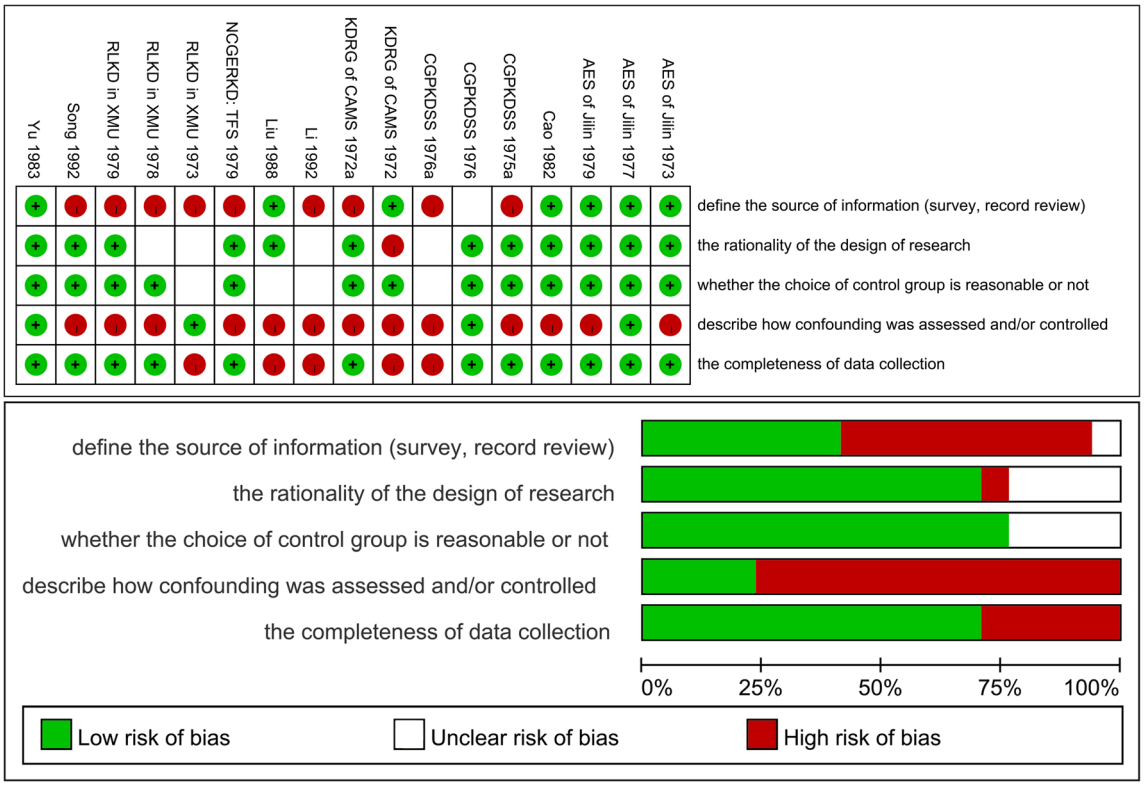

Fig. 2 Summary of each quality item for each included study and graph of each quality item presented as percentages across all included studies. A, source of information; B, rationality of the research design; C, rationality for choosing a control group; D, description of confounding assessments and/or controls; E, completeness of data collection. Risk of bias summary for each included study and risk of bias graph

only or full cause of the disease. Therefore, we state that selenium deficiency is a cause of KD, which does not mean that selenium deficiency is the only and full cause of KD.

Importance of the Study

The importance of an etiological study is to provide quality evidence for the prevention and control of disease, or in other words, to translate the findings of an etiological study into the practice of prevention and control. In this case, the findings of this study have two aspects of importance: one is that the description of "unknown cause" in the definition of KD does not make sense, and the other is that selenium should be included in national KD surveillance. There are several issues with the current definition of KD. First, "unknown cause" in the definition of any disease does not make sense for the purpose of prevention and control. Second, selenium deficiency has been obviously demonstrated as a cause of KD. Third, the definition is conflicting and confusing. It is conflicting because it neglects the fact that selenium supplementation has effectively reduced the incidence of KD. It is confusing because selenium supplementation has been the primary recommended preventative intervention since the 1970s. Regarding the inclusion of selenium in the national KD surveillance, disease surveillance should normally cover four aspects. The first aspect is incidence or prevalence of the disease. The second aspect is etiology or risks of the disease. The third aspect is implemented interventions for the prevention and control of the disease. The fourth aspect is assessment of the effectiveness of the interventions taken [49]. Regardless of whether selenium deficiency is a cause of KD or not, it is at least a risk factor of KD, so it should be indicated in the etiology or risk of KD and the effectiveness of KD prevention in order to provide evidence for KD elimination and assessment.

Strengths and Limitations

This study has several strengths. First, this work is the first large-scale SR and meta-analysis of community trials for the prevention of KD in which selenium was supplement to residents of endemic areas of KD; it included a literature search of publications from the past 50 years and included 1,983,238 individuals with 683,075 subjects in experimental groups. Second, we updated our understanding of selenium deficiency as a cause of KD by using the criterion of causation in modern epidemiology and provided the most comprehensive synthesis of evidence on this issue so far. Third, we suggested that the findings of this study should be translated into practice for KD prevention and control by including measurements of selenium

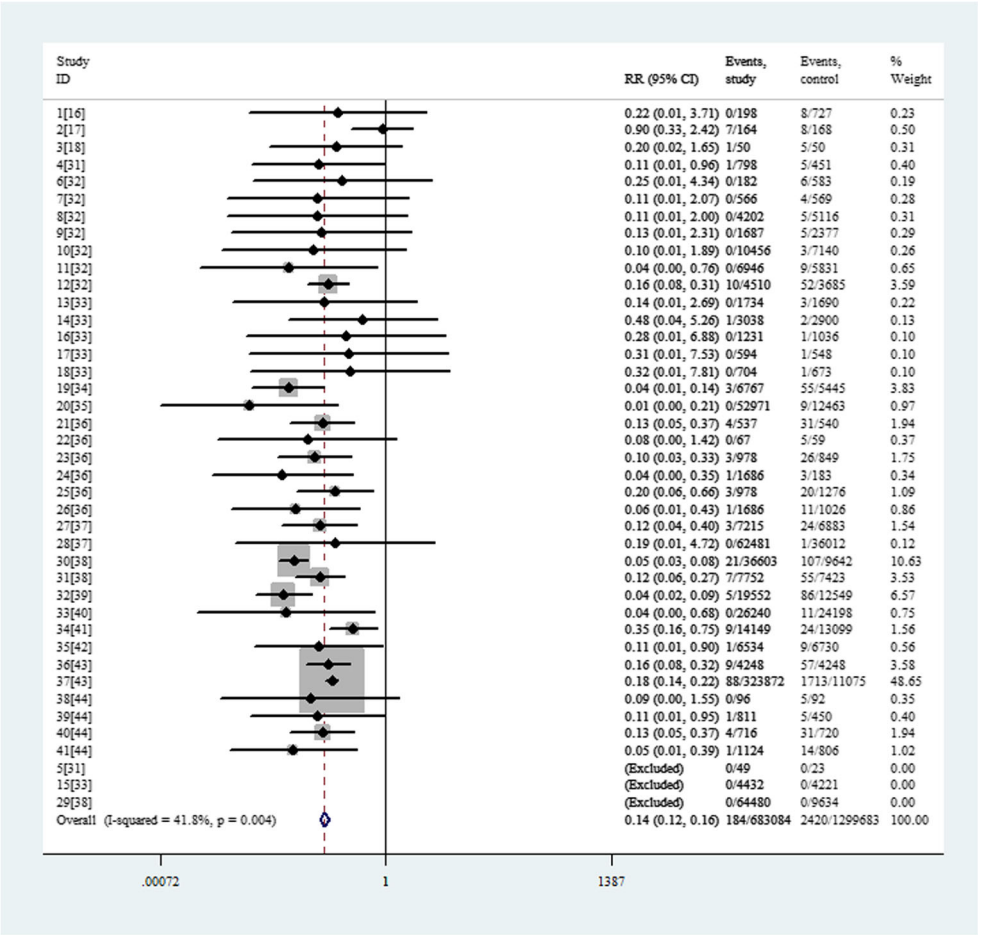

Fig. 3 Forest plot for prevention of Keshan disease by selenium supplementation. *M-H* Mantel-Haenszel, *CI* confidence interval

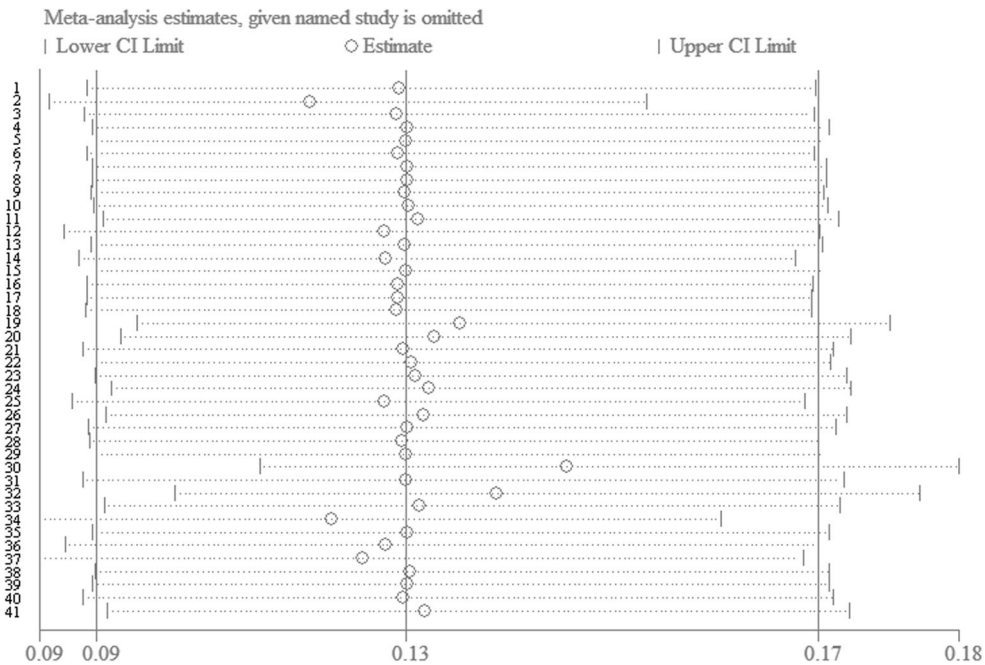

Fig. 4 Sensitivity analysis for prevention of Keshan disease by selenium supplementation

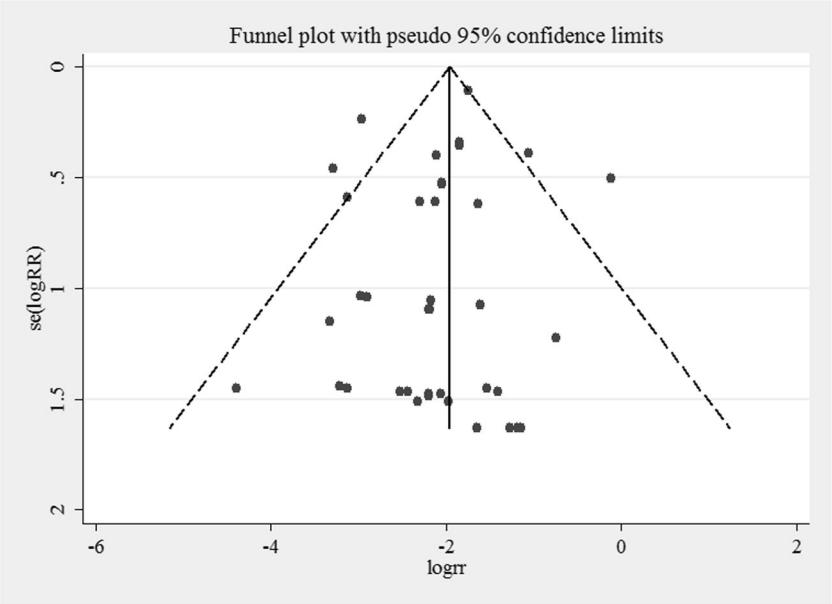

Fig. 5 Funnel plot for prevention of Keshan disease by selenium supplementation

levels in residents of KD endemic areas in the KD surveillance program and revising the definition of KD.

However, the limitation of this study is that most of the data were derived from studies conducted as early as the 1970s to 1990s.

Conclusion

In summary, supplementation of selenium effectively prevented people from getting KD, and selenium deficiency is a cause of KD. The measurement of selenium levels in residents of KD endemic areas should be included in the KD surveillance program. Defining KD as endemic cardiomyopathy is inappropriate. The description of "unknown cause" should not be included in its definition. KD should be listed in the contemporary definitions and classifications of cardiomyopathies.

Author Contributions Huihui Zhou was the principal investigator of this paper. Huihui Zhou and Tong Wang developed the hypothesis and study design and supervised this study. All authors contributed to the study concept and design, analysis, and interpretation of data and drafted or critically revised the manuscript for important intellectual content and/or data acquisition.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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