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Effects of Five Types of Selenium Supplementation for Treatment of Kashin-Beck disease in children: A Systematic Review and Network Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017883
Article Type:	Research
Date Submitted by the Author:	22-May-2017
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Complementary medicine
Keywords:	Kashin-Beck disease, Selenium supplementation, Network meta-analysis, Randomized controlled trial

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1 **Effects of Five Types of Selenium Supplementation for Treatment**
2 **of Kashin-Beck disease in children: A Systematic Review and**
3 **Network Meta-analysis**

4 **Running title: Selenium Supplementation for Treatment of KBD**

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Abstract

Objective: To compare the effectiveness of five kinds of selenium supplementation for the treatment of patients with Kashin-Beck disease (KBD), and rank these selenium supplementation based on their performance.

Design: Systematic review, conventional meta-analysis, and network meta-analysis. We searched for all publications between January 1, 1966 and October 31, 2016 using seven electronic databases. We used pairwise meta-analyses to estimate direct evidence from intervention-control trials and a network meta-analysis to combine direct and indirect evidence.

Results: A total of 15 randomized controlled trials involving 2931 patients were included. Network meta-analyses showed that: compared with placebo or no treatment groups, sodium selenite (OR 4.68, 95% credible interval (CrI): 2.99 - 7.34), selenium salt (OR 12.37, 95%CrI: 2.81 - 54.41), selenium enriched yeast (OR 5.81, 95% CrI: 1.70 - 19.89), combination of sodium selenite and vitamin E (OR 10.72, 95%CrI: 3.14 - 36.57), and combination of sodium selenite and vitamin C (OR 3.26, 95%CrI: 1.14 - 9.28) had higher metaphysis X-ray improvement. Ranking on efficacy indicated that selenium salt was ranked the most effective, followed by sodium selenite + vitamin E, selenium enriched yeast, sodium selenite and then sodium selenite + vitamin C.

Conclusions: Based on the results of network meta-analysis, all five types of selenium supplements are more effective than placebo or no treatment in promoting the repair of metaphysis impairment. The effect of selenium salt ranked most effective.

Trial registration number: CRD42016051874

Keywords: Kashin-Beck disease; Selenium supplementation; Network meta-analysis; Randomized controlled trial

Strengths of this study:

- The present NMA integrated evidence from direct and indirect comparisons.
- We comprehensively summarized all RCTs of selenium supplements for KBD.

Potential limitations:

- Despite our exhaustive search, only 15 RCTs conducted in China were included in this review. Some trials may have been published in local journals that were missed in our search.
- The age range of participants in our review was 2~16 years old.

78 **Introduction**

79 Kashin-Beck disease (KBD) is a chronic, disabling degenerative disease of the peripheral
80 joints and spine^{1,2}, mainly distributed in southeast Siberia, north Korea, and China³. KBD is
81 prevalent in 377 counties of 14 provinces in China, with 0.64 million cases⁴. In China, pa-
82 tients are mainly concentrated in the remote areas of the north-east (Hei Longjiang provinc-
83 es), north-west (Gan Su, Shan Xi, and Qing Hai provinces), as well as the south-west (Si-
84 chuan and Tibet provinces). KBD occurs in childhood and involves pathologic changes of
85 metaphysis and epiphyseal plate, resulting in multiple symptoms in the growth and the articu-
86 lar cartilages such as bony deformity, joints enlargement, growth retardation, and functional
87 impairment in multiple joints. The resulting disability causes an important human and socio
88 economic burden to both affected children and adults. Moreover, KBD can also cause dis-
89 turbances in the cartilage metabolism, the lipid peroxidation, and sulfur and selenium metab-
90 olism^{5,6}. So far, only palliative measures exist for treatment of KBD because of the incom-
91 plete ability of the cartilage to repair itself. Treatment strategies for symptomatic relief in-
92 clude non-steroidal anti-inflammatory drugs⁷, sodium hyaluronate⁸, physical therapy⁹, and
93 chondroitin sulfate combined with glucosamine¹⁰. Successful surgical treatments to correct
94 joint defects have been reported by orthopaedists^{11,12}.

95 In spite of etiology of KBD is multifactorial, one of the major environmental risk factors is
96 selenium deficiency¹³. Since the 1970s, selenium supplements have been given in some high-
97 ly endemic areas. A meta-analysis including five randomized control trials (RCTs) and 10
98 non-RCTs demonstrated the benefits of selenium supplementation for the primary prevention
99 of KBD in children¹⁴. And another systematic review suggested that sodium selenite (Se) was
100 effective for the treatment of patients that are already affected with KBD¹⁵. Besides Se tablet,
101 there are other selenium supplements used for treating KBD, including selenium salts (Se

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4 102 salt), selenium enriched yeast (Se-enriched yeast), the combination of sodium selenite with
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6 103 vitamin E (Se + VE), and the combination of sodium selenite with vitamin C (Se + VC). At
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8 104 the time of our study, there were few head-to-head comparisons of different types of seleni-
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10 105 um supplement for treatment of KBD. In light of the significance of KBD and the need for
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12 106 government policy makers and clinical care workers to know the effects of a set of alternative
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14 107 options, we conducted a systematic review and network meta-analysis (NMA) to compare the
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16 108 effectiveness of all types of selenium supplementation for the treatment of patients with
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18 109 KBD, and rank these selenium supplementation based on their performance.
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24 111 **Method**

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26 112 A protocol for this systematic review was devised in accordance with the PRISMA guide-
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28 113 lines and registered on PROSPERO, and the trial registration number was CRD42016051874.

30 114 *Search strategy*

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32 115 We searched, without language restrictions, for all publications between January 1, 1966
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34 116 and March 31, 2017 using electronic databases, which included MEDLINE, EMBASE, The
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36 117 Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Re-
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38 118 views, The Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chi-
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40 119 nese Science and Technique Journals Database, and Wan Fang database. The MeSH word and
41
42 120 free word were used as follow: “Kashin-Beck disease”, “Kashin-Bek disease”, “big bone dis-
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44 121 ease”, “endemic osteoarthritis”, “Urov disease” and “selenium”, “Sodium selenite”, and “Se”.
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46 122 The Ovid search strategy was seen in Appendix box 1. Reference lists from published narra-
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48 123 tive review articles and systematic reviews were reviewed to identify additional studies.
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52 124 *Eligibility criteria*

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54 125 We included all randomized, controlled trials (RCTs) that used Se tablet and other types
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4 126 of selenium supplements including Se salt, Se enriched yeast, Se + VE, as well as Se + VC
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6 127 for KBD patients. The control group included placebo or no treatment control, or other active
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8 128 medicines. We excluded the following studies: (1) studies with small sample size (numbers of
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10 129 patients less than 20 in each treatment group); (2) preventive studies; (3) studies without
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12 130 available information of interest. Studies reporting mixed groups of participants (e.g., partici-
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14 131 pants with and without KBD) were included only if the therapeutic effect data could be iden-
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16 132 tified and extracted separately. Outcome of interest to this review was the repair rate of met-
17
18 133 aphyseal lesions on X-ray film. Typically, repair was defined as being cured basically or im-
19
20 134 proved significantly of metaphyseal lesions according to the latest judgment standard of X-
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22 135 ray for treatment effect of KBD¹⁶.

23 24 25 26 136 ***Data extraction and quality evaluation***

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28 137 Two authors (Y. L & D. X) independently screened all citations identified by the searches.
29
30 138 Full-text of potentially study was obtained and assessed according to the aforementioned in-
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32 139 clusion criteria. The data extraction form included publication (first author, year of publica-
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34 140 tion), demographics (sample size and age), interventions (dosage, route of administration, and
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36 141 duration of treatment), the follow-up period, as well as outcomes. We extracted data to the
37
38 142 nearest 12 months to estimate the overall odds ratio (OR) because all the included RCTs re-
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40 143 port this time point. Two reviewers independently evaluated the methodological quality of
41
42 144 individual study according the Cochrane risk-of-bias tool¹⁷. Any disagreements would be re-
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44 145 solved by consulting a third author (J.Y).

45 46 47 146 ***Statistical analysis***

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49 147 As the repair rate of metaphyseal lesions on X-ray film, the outcome of interest in this
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51 148 text, was a discontinuous statistics, we calculated the OR and its 95% confidence intervals
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53 149 (CI) as the effect estimates.

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4 150 Initially, we performed standard pairwise meta-analyses for all available direct compari-
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6 151 sons in STATA. Statistical heterogeneity of treatment effects across studies was assessed by
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8 152 the Cochran Q test, and the extent of between-study heterogeneity was quantified by I^2 , of
9
10 153 which with a value greater than 50% indicates substantial heterogeneity.

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13 154 Then we conducted network meta-analysis in STATA to determine comparative effective-
14
15 155 ness of each therapy by using the network command and self-programmed STATA routines
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17 156 available at <http://www.mtm.uoi.gr>. We present estimates of treatment effects as odds ratios
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19 157 and 95% central credible intervals (CrI). The credible interval shows the degree of uncertain-
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21 158 ty around estimated treatment effects.

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24 159 To evaluate consistency in the entire network, we used the ‘design-by-treatment’ model,
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26 160 which was described by Higgins and colleagues, by using the network meta command in
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28 161 STATA. This method accounts for different source of inconsistency that can occur when stud-
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30 162 ies with different designs (two-arm trials vs. three-arm trials) give different results as well as
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32 163 disagreement between direct and indirect evidence. We inferred about the presence of incon-
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34 164 sistency from any source in the entire network based on a chi-square test, and a P value great-
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36 165 er than 0.05 indicated that the direct and indirect comparisons in the network were consistent.

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39 166 We also estimated the ranking probabilities for all treatments of being at each possible
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41 167 rank. Rankings were obtained by using the surface under the cumulative ranking curve (SU-
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43 168 CRA) values and mean ranks. SUCRA could be expressed as a percentage interpreted as the
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45 169 percentage of effectiveness of a treatment that would be ranked first without uncertainty. To
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47 170 derive these SUCRA values we used the ranking probabilities estimated from the mvmeta
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49 171 command.

50 51 52 172 **Results**

53 54 173 *Systematic review*

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4 174 Initial searches yielded 1686 citations. Of these, 1625 duplicate or irrelevant records were
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6 175 excluded and full-text articles of the remaining 61 studies were retrieved for further assess-
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8 176 ment according to the inclusion criteria. A total of 15 studies¹⁸⁻³² containing 2931 patient
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11 177 were included eventually in our meta-analysis (Fig 1).

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13 178 A total of seven interventions were evaluated: Se, Se salt, Se-enriched yeast, Se + VE, Se
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15 179 + VC, VC, and placebo. Figure 2 shows the network of all treatment comparisons included in
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17 180 this text. The age of participants range from 2 to 16 years old and the duration of follow-up
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19 181 varied from 6 months to 36 months. The main characteristics of the included studies are simi-
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21 182 lar, and the detailed characteristics are presented in the online supplementary Appendix table
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23 183 1. All included trials were reported to be RCTs. The quality of included studies was overall
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25 184 low (Appendix table 2).

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29 30 186 ***Intervention-control pairwise meta-analyses***

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32 187 All RCTs reported repair rate of metaphyseal lesions on X-ray films. Follow-up durations
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34 188 were of included RCTs were varied. We extracted data to the nearest 12 months to estimate
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36 189 the overall OR. The pooled OR (random effects model) of X-ray improvement was in favor
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38 190 of Se (OR 5.0, 95% CI: 3.21 - 7.78, $P < 0.001$), Se salt (OR 7.6, 95% CI: 2.34 - 24.67, $P =$
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40 191 0.001), Se enriched yeast (OR 3.75, 95% CI: 1.76 - 8.20, $P = 0.001$), and Se + VE (OR 11.05,
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42 192 95% CI: 2.61 - 46.80, $P = 0.03$) respectively, which indicated that repairing rate of metaph-
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44 193 yseal lesions on X-ray films was significantly higher in these group than placebo (Fig 3). A
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46 194 few RCTs reported direct comparisons among active interventions. The OR of X-ray im-
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48 195 provement was significantly higher in Se salt group compared with Se + VC (OR 6.00, 95%
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50 196 CI: 1.81 - 19.93, $P=0.003$) and VC alone (OR 4.24, 95% CI: 1.39 - 12.90, $P=0.011$). There
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52 197 were no significant differences were noted in other active interventions comparisons (Fig 3).

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199 ***Results of network meta-analyses and consistency test***

200 The pooled OR and 95% credible interval (CrI) of X-ray improvement for active treatment
201 compared with placebo was 4.68 (2.99 to 7.34) for Se, 12.37 (2.81 to 54.41) for Se salt, 5.81
202 (1.70 to 19.89) for Se enriched yeast, 10.72 (3.14 to 36.57) for Se + VE, and 3.26 (1.14 to
203 9.28) for Se + VC respectively, which indicated a significant difference in efficacy. For the
204 comparison between active treatments, no significant differences were found. More details of
205 direct comparisons were presented in Table 1.

206 There was no inconsistency between direct and indirect evidences according to the design-
207 by-treatment interaction model ($P=0.88$), implying that direct and indirect evidence were
208 mainly consistent (Fig 4). However, the results of the comparison of Se + VC and VC versus
209 placebo showed some degree of inconsistency. Actually, the lower CrI for X-ray improve-
210 ment were nearly equal to 1 (1.13 for Se + VC and 1.27 for VC), showing a trend to be coin-
211 cide with direct results.

212 Table 2 displayed the distribution of probabilities for each treatment being ranked for
213 their efficacy in KBD according the SUCRA values (Fig 5) and mean ranks.

214

215 **Discussion**

216 ***Principal findings***

217 Our network meta-analysis of all 15 available RCTs in 2931 patients with KBD showed that
218 all five kinds of selenium supplementation (including Se, Se salt, Se enriched yeast, Se + VE,
219 Se + VC) were superior to placebo/no treatment in repairing metaphyseal lesions. There was
220 uncertainty around the difference between two active treatments. However, the probabilistic
221 ranking of interventions showed that Se salt was ranked the most effective, followed by Se +

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4 222 VE, Se enriched yeast, Se and then Se + VC.
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8 224 ***Relation to other studies***
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10 225 Studies have proposed that selenium deficiency is the underlying factor that predisposes
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12 226 the target cells (chondrocytes) to oxidative stress from free-radical carriers³³. In most highly
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14 227 endemic area, the level of total soil selenium concentrations is typically low. A meta-analysis
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16 228 of the correlation between selenium and KBD reported that selenium levels in water, soil,
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18 229 cereal, and corn in endemic regions were lower than regions without high rates of KBD³⁵.
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20 230 Furthermore, most of the inhabitants living in areas with KBD have a low selenium nutritive
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22 231 status, which is reflected by low selenium contents in their blood serum, red blood cell, urine,
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24 232 and hair.
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28 233 The effectiveness of various methods of selenium supplementation for children has been
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30 234 demonstrated by many studies including Se salt³⁷, Se enriched yeast²⁴, oral sodium selenite
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32 235 tablet¹⁵, spraying Se on crops³⁸, and Se enriched fertilizer³⁹. Selenium supplementation was
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34 236 associated with a simultaneous decrease in the prevalence of KBD, along with an increased
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36 237 selenium content in the hair of inhabitants living in areas with KBD. It was reported that the
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38 238 incidence of radiographic evidence of metaphysical lesions of the hands was 44.8% in 1990
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40 239 at Cuimu town of the Shaanxi province in children aged 7~12 years. After implementation of
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42 240 comprehensive prevention measures of KBD, especially using Se salt, the incidence these x-
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44 241 ray findings decreased to 0.3% in 2010⁴⁰. The low incidence of KBD also may explain why
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46 242 there has not been any studies about Se treatment for KBD published in recent years.
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49 243 Se salt was produced by adding 0.833 g of sodium selenite powder into every 50 kg of
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51 244 source salt and then expanding it to 1:60,000 Se salt. In our study, the probabilistic ranking of
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53 245 interventions showed that Se salt was ranked the most effective. This result was not surpris-
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4 246 ing because of the high compliance for salt intake. Although administration of Se tablet is
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6 247 effective for preventing and treating KBD in children^{14,15}, it is very difficult for millions of
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8 248 children living in endemic areas to adhere to a long-term medication. However, salt is a nec-
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10 249 essary part of daily life and food intake. The compliance can be more effectively guaranteed.

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13 250 A limitation to the findings about Se salt is that due to the difficulty of carrying out a
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15 251 RCT comparing Se salt with placebo or other active drugs, only one RCT has been done²⁹.
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17 252 However, one meta-analysis involving 11 non-RCTs (2652 participants) also showed that
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19 253 supplement Se salt was effective for preventing and treatment for KBD in Children³⁷. Since
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21 254 Se salt is the most economical way for low-income families, it is anticipated that continuous
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23 255 use of Se salt and other comprehensive prevention measures may help to eliminate the KBD
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25 256 cartilage damages in Children⁴¹.

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28 257 Despite the evidence in our meta-analysis, there remains some controversy around sele-
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30 258 nium supplementation in relationship with iodine deficiency. In a cross sectional study in Ti-
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32 259 bet area, Moreno-Reyes and his colleges found no association between individual selenium
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34 260 status and KBD, whereas iodine deficiency was a risk factor⁴². Similarly, the only RCT³⁰
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36 261 published in English in our NMA showed only 1 case of improvements in X-ray in sodium
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38 262 selenite group. The negative findings of the above studies should, however, be interpreted
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40 263 with caution. These studies were all conducted in Tibet where selenium and iodine are both
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42 264 deficient in the diet. Selenium and iodine deficiency are both risk factors of KBD³³. In animal
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44 265 experiments, growth retardation was observed in rats fed with a low selenium diet⁴³, and im-
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46 266 paired bone development was observed with an iodine deficient diet⁴⁴. We do not exclude the
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48 267 possibility that selenium supplementation may not counterbalance the negative effects of
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50 268 long-term iodine deficiency. So KBD seems unlikely to be due to only one cause. Other ge-
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52 269 netic and environmental factors may confer either a relatively protective effect or accelerate
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4 270 the disease.
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6 271 ***Strengths and weaknesses***
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8 272 The present NMA integrated evidence from direct and indirect comparisons. Conse-
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10 273 quently, estimates in our analysis were more precise than the pairwise meta-analyses. The
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12 274 literature search strategy was extensive, which makes it unlikely that we missed any relevant
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14 275 trial. Trial selection and data extraction including quality assessments were done inde-
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16 276 pendently by two authors to minimize bias and transcription errors. In this NMA, we com-
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18 277 prehensively summarized all RCTs of selenium supplements for treatment of KBD.
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21 278 Potential limitations to this review exist. First, the sample sizes of our included RCTs
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23 279 were all small. Sample size calculations were not mentioned in any of the studies. Second,
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25 280 despite our exhaustive search, only 15 RCTs conducted in China were included in this review.
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27 281 North Korea and Russia also have a high incidence of KBD; some trials may have been pub-
28
29 282 lished in local journals that were missed in our search. Third, the age range of participants in
30
31 283 our review was 2~16 years old. Therefore, the effectiveness of selenium supplementation for
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33 284 adults cannot be estimated. Finally, the heterogeneity in this meta-analysis was somewhat
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35 285 high, which could be explained by a lack of concealment of allocation, failure to perform an
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37 286 ITT analysis, small sample sizes of the studies included and differences between different
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39 287 preparations of selenium. As with heterogeneity between trials, inconsistency between direct
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41 288 and indirect comparisons was also near zero. Although we cannot rule out clinically relevant
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43 289 inconsistency, we have no indication that clinical characteristics of included patients or other
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45 290 trial characteristics confounded the indirect comparisons.
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49 291 **Conclusions**
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52 292 ***Implications for practice***
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54 293 Based on this NMA, it appears that all types of Se supplementation were more effective
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4 294 than placebo or no treatment control groups for the treatment of KBD in children. Ranking on
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6 295 efficacy indicated that Se salt were highest, followed by Se + VE, Se enriched yeast, Se, Se +
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8 296 VC, VC, and placebo/no treatment. Nevertheless, the evidence may be limited by potential
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11 297 biases.

12 298 ***Implications for research***

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15 299 Since KBD among children has almost disappeared, we believe it unlikely that future tri-
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17 300 als will involve a RCT to demonstrate the clinically relevant benefit of any selenium supple-
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19 301 mentation for children with KBD. At present, there are no effective clinical measures to re-
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21 302 pair the cartilage damage of KBD in adults. Tissue engineering and gene therapy approaches
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23 303 may become the potential treatment strategy that can applied to the treatment of the KBD car-
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25 304 tilage damages.

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29 306 **Contributors**

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31
32 307 Xie Dongmei and Liao Yulin conceived the review question, reviewed studies for inclusion,
33
34 308 assessed the included studies, extracted data, completed the first draft, and edited the review.
35
36 309 Yue Jirong and Zhang Chao analysed the data, did the literature search, advised and coordi-
37
38 310 nated the review development, performed part of the writing and editing of the review, ap-
39
40 311 proved the final version of the review prior to submission, and is also a guarantor. Yanyan
41
42 312 Wang, Chuanyao Deng and Ling Chen contributed to the development of the review ques-
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44 313 tion, edited and provided intellectual contributions to the review.
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50 315 **Conflict of interest**

51
52 316 We declare that we have no conflicts of interest.

53 54 317 **Role of the funding source**

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4 318 The sponsors of the study had no role in study design, data collection, data analysis, data in-
5
6 319 terpretation, or writing of the report. The corresponding author had full access to all the data
7
8 320 in the study and had final responsibility for the decision to submit for publication.
9

10 321 **Acknowledgments**

11
12 322 This research was funded by China National Science & Technology Pillar Program during the
13
14 323 eleventh 5-year plan period (2007BA125B04).

15
16
17 324 Dr. Joseph H. Flaherty is especially acknowledged for editorial review and language assis-
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19 325 tance.
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Table 1 Results of network meta-analyses of repairing rate of metaphyseal lesions on X-ray films

OR (95%CrI) #	Placebo	Se	Se salt	Se + VC	Se + VE	Selenium yeast
Se	4.68 (2.99 to 7.34)*	-	-	-	-	-
Se salt	12.37 (2.81 to 54.41)*	2.64 (0.59 to 11.84)	-	-	-	-
Se + VC	3.26 (1.14 to 9.28)*	0.70 (0.25 to 1.97)	0.26 (0.06 to 1.20)	-	-	-
Se + VE	10.72 (3.14 to 36.57)*	2.29 (0.62 to 8.43)	0.87 (0.13 to 5.93)	3.29 (0.65 to 16.53)	-	-
Se yeast	5.81 (1.70 to 19.89)*	1.24 (0.36 to 4.25)	0.47 (0.07 to 3.16)	1.78 (0.37 to 8.66)	0.54 (0.10 to 3.08)	-
VC	3.05 (1.29 to 7.20)*	0.65 (0.28 to 1.53)	0.25 (0.06 to 1.06)	0.94 (0.34 to 2.56)	0.28 (0.06 to 1.27)	0.52 (0.12 to 2.27)

the treatment in the column on left compare with the treatment on the first line; * P < 0.05
 CrI = credible interval

Table 2 Probabilistic ranking of effectiveness of different interventions.

Se salt was ranked the most effective followed by Se+VE, Se-yeast, Se and then Se + VC. VC and placebo as a control was ranked the least effective.

Interventions	Probabilistic ranking		
	SCURA (%)	PrBest (%)	MeanRank
Se salt	86	49.1	1.8
Se+VE	82.8	38.5	2
Se yeast	62.5	11.6	3.3
Se	52.5	0.2	3.9
Se+VC	35.7	0.4	4.9
VC	30.1	0.2	5.2
Placebo	0.5	0	7

SUCRA=surface under cumulative ranking

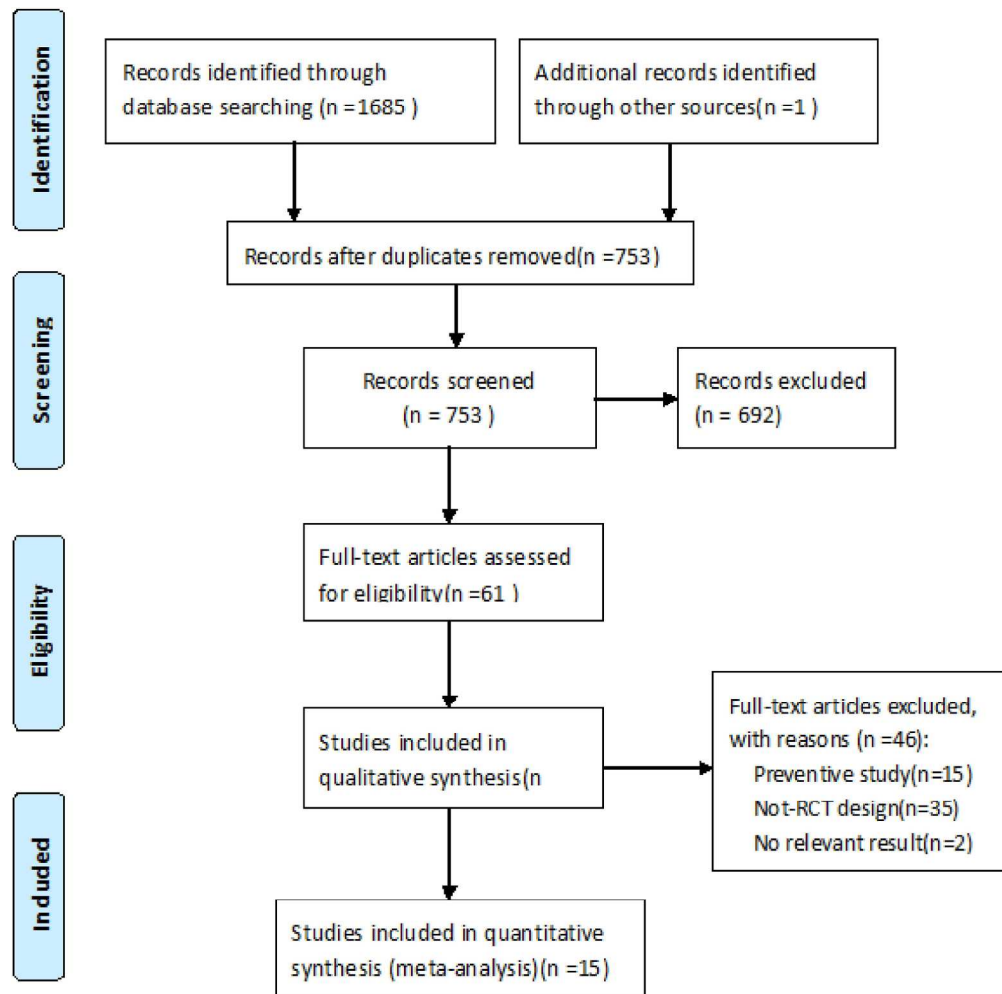


Fig 1 Flow diagram of included study

201x200mm (300 x 300 DPI)

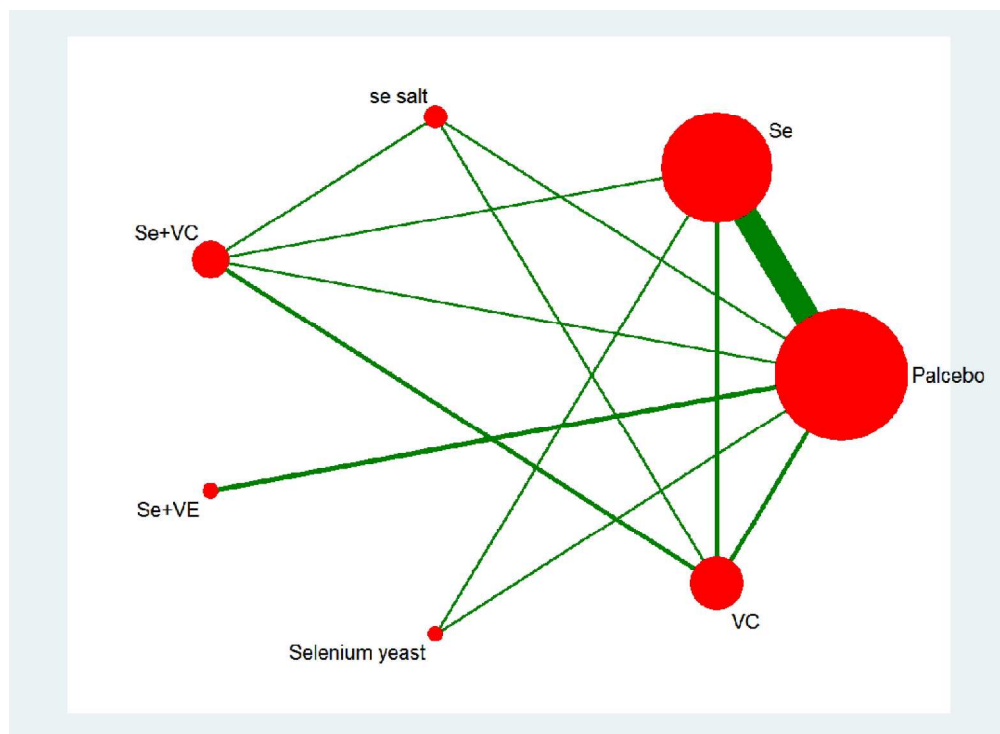


Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD. The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment.

277x201mm (300 x 300 DPI)

view only

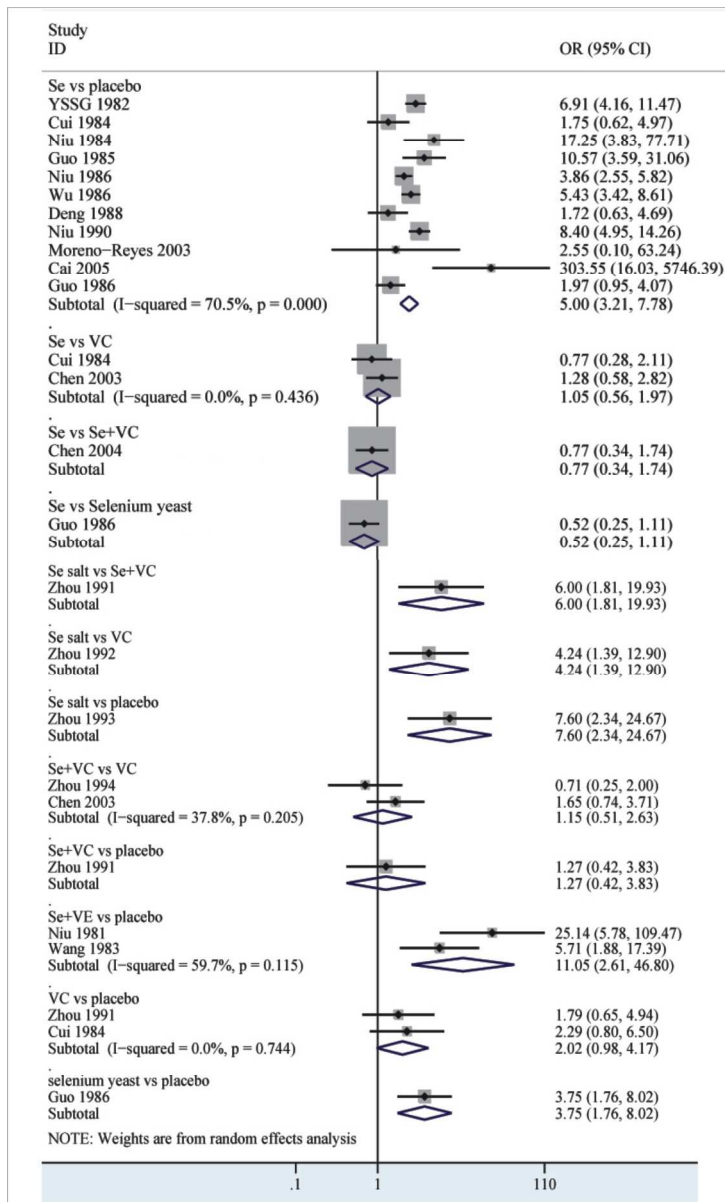


Fig 3 Forest plots of intervention-control pairwise meta-analyses of repairing rate of metaphyseal lesions on X-ray films

258x405mm (300 x 300 DPI)

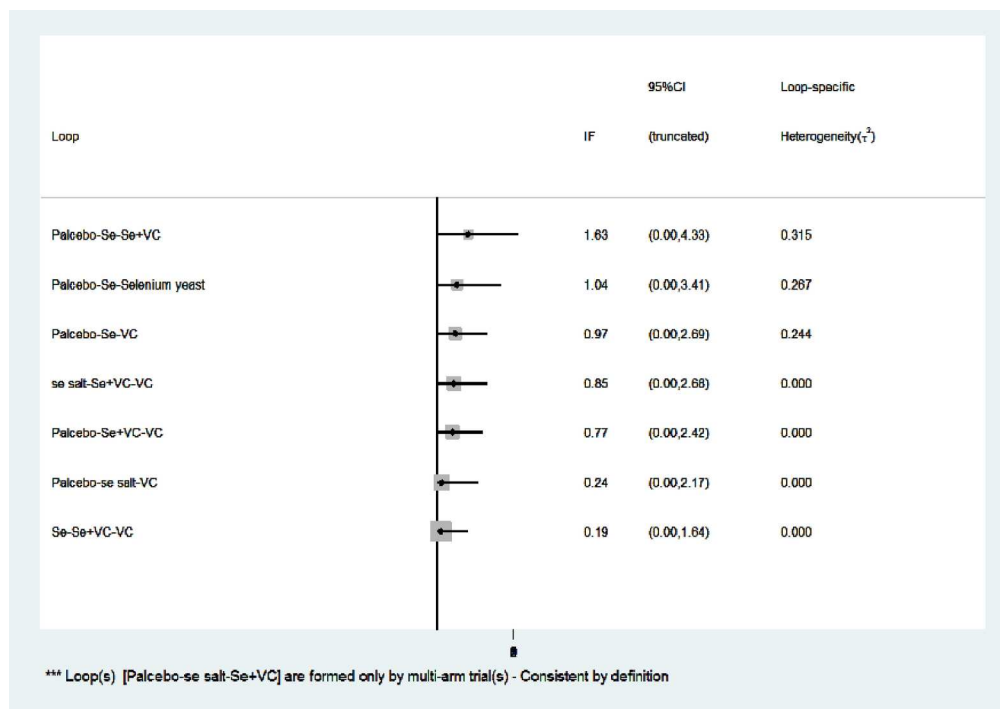


Fig 4 Consistency test in the network Meta-analysis

216x152mm (300 x 300 DPI)

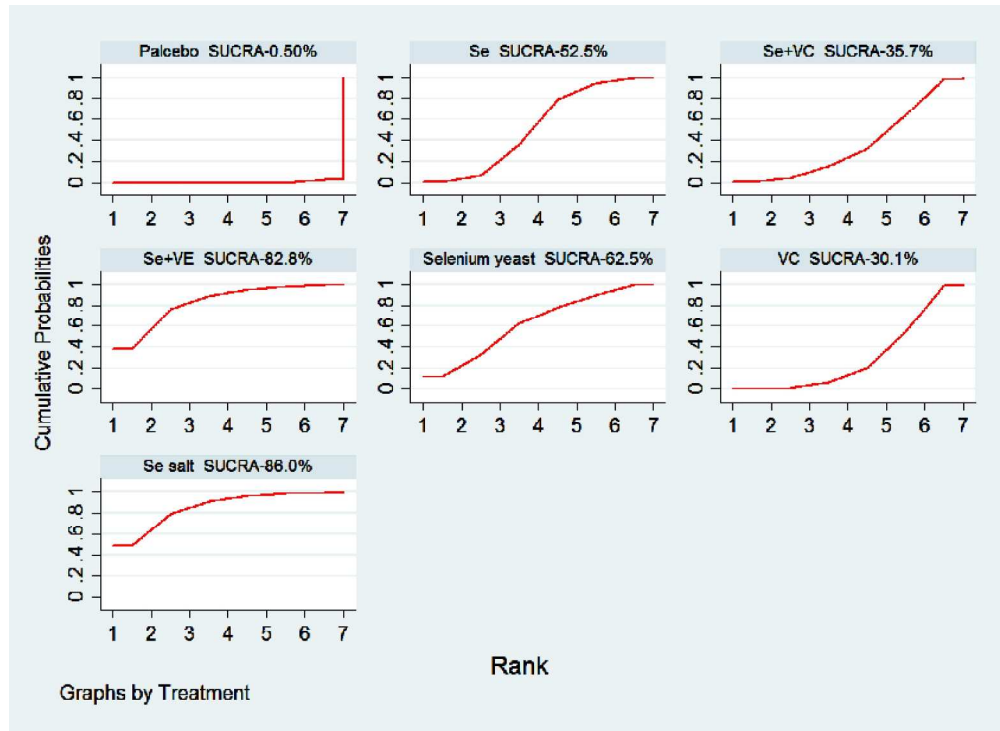


Fig 5 SUCRA for the cumulative probabilities
SUCRA=surface under cumulative ranking

216x157mm (300 x 300 DPI)

Appendix box 1 Ovid search strategy

#1 exp kashin-beck disease/
#2 kashin-beck disease.tw.
#3 kashin-bek disease.tw.
#4 big bone disease.tw.
#5 endemic osteoarthritis.tw.
#6 Urov disease.tw.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 sodium selenite.tw.
#9 selenium .tw.
#10 Se salt.tw.
#11 enriched yeast
#12 8 or 9 or 10 or 11
#13 7 AND 12
#14 randomized controlled trial.pt.
#15 controlled clinical trial.pt.
#16 randmoized.ab.
#17 placebo.ab.
#18 randomly.ab.
#19 trial.ab.
#20 groups.ab.
#21 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 13 and 21
#23 limit #22 to human

Appendix table 1 Characteristics of included trials

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Niu 1981 ¹⁸	27	29	6~13	6~13	Se + VE: Se tablet 2mg/week +VE 15mg/day	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
YSSG 1982 ¹⁹	166	159	3~13	3~13	Se tablet, 1 mg/week (3-10 yrs), 2 mg/week (11-13 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
Wang 1983 ²⁰	47	42	5~15	5~15	Se + VC: Se tablet 2mg/week +VE 15mg/day	No treatment	11	Improvement of metaphyseal lesions on X-ray
Cui 1984 ²¹	30	30/30	7~19	7~19	Se tablet, 1 mg/week (7-10 yrs), 2 mg/week (11-19 yrs)	①VC 200 mg 3 times/day; ②Placebo/week	6~12	Improvement of metaphyseal lesions on X-ray
Niu 1984 ²²	56	59	6~13	6~13	Se tablet first week: 1.0 mg/day (< 10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/week (< 10 yrs), 2.0 mg/week (> 11 yrs)	Placebo/week	24	X-ray improvement
Guo 1985 ²³	50	50	5~15	5~15	Se tablet, 1 mg/week (<5 yrs), 2 mg/week (>5 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Guo 1986 ²⁴	60/60	60	5~14	5~14	①Se tablet, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs); ②Se enriched yeast, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs);	Placebo/week	13	Improvement of metaphyseal lesions on X-ray
Niu 1986 ²⁵	285	277	6~13	6~13	Se tablet, 1 mg/week (<10 yrs), 2 mg/week (>10 yrs)	Placebo/week	12~24	X-ray improvement
Wu 1986 ²⁶	171	177	5~16	5~16	Se tablet, 1 mg/week (< 10 yrs), 2 mg/week (> 10 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
Deng 1988 ²⁷	43	46	2~13	2~13	Se tablet, no details	No treatment	36	X-ray improvement
Niu 1990 ²⁸	210	228	6~13	6~13	Se tablet, first week: 0.5 mg/day (< 5 yrs), 1.0 mg/day (6-10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/month (< 5 yrs), 2.0 mg/month (6-10 yrs), 4.0 mg/month (> 11 yrs)	Placebo/month	12	Improvement of metaphyseal lesions on X-ray

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Zhou 1991 ²⁹	25/30	35/29	4~12	4~12	①Se + VC: Se tablet 1mg/10day+ VC 100mg/day; ②Se salt (sodium selenite: salt = 1:60,000) /10day	③VC, 300mg/ day; ④No treatment	12	Improvement of metaphyseal lesions on X-ray
Chen 2003 ³¹	50/50	50	6~11	6~11	①Se tablet 1mg/week; ② Se + VC: Se tablet 1mg/week+ VC 300 mg 2 times/day	VC 300mg bid	12	Improvement of metaphyseal lesions on X-ray
Moreno-Reyes 2003 ³⁰	113	95	10±0.28	10±0.3	Se tablet, 1 mg/week	Placebo/week	12	X-ray improvement
Cai 2005 ³²	31	31	7~13	7~13	Se tablet, 2mg/10 days (7-10 yrs), 3 mg/10 days (11-13 yrs)	No treatment	18	X-ray improvement

I= intervention, C = control, YSSG = Yongshou scientific survey group of Kashin-Beck Disease, yrs = years, Se = Sodium selenite, Se salt = selenium salt,
 Se + VC = the combination of selenium selenite with vitamin C ; Se + VE = the combination of selenium selenite with vitamin E

Appendix table 2 Risk of Bias of Included Studies

Study	Balanced allocation	Allocation concealment	Blinding	Completeness of outcome	Selective reporting	outcome	Other Bias
Niu 1981 ¹⁸	Unclear	Unclear	Double-blind	Low	Low		Low
YSSG 1982 ¹⁹	Unclear	Unclear	Double-blind	Low, No dropout	Low		Low
Wang 1983 ²⁰	unclear	unclear	Double-blind	High, dropouts >20%	Low		High, no ITT analysis
Cui 1984 ²¹	unclear	unclear	Double-blind	High, dropouts >20%	Low		High, no ITT analysis
Niu 1984 ²²	Unclear	Unclear	Double-blind	Low, No dropout	Low		High, no ITT analysis
Guo 1985 ²³	Unclear	Unclear	Not Used	High, dropouts >20%	Low		High, no ITT analysis
Guo 1986 ²⁴	Unclear	Unclear	Unclear	High, dropouts >20%	Low		High, no ITT analysis
Niu 1986 ²⁵	Unclear	Unclear	Double-blind	Low, No dropout	Low		Low

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Wu 1986 ²⁶	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High, no ITT analysis
Deng 1988 ²⁷	Unclear	Unclear	Unclear	Low, drop out < 10%	Low	High, no ITT analysis
Niu 1990 ²⁸	Unclear	Unclear	Single-blind	Low, No dropout	Low	Low
Zhou 1991 ²⁹	Unclear	Unclear	Unclear	Low, No dropout	Low	Low
Chen 2003 ³¹	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis
Moreno-Reyes 2003 ³⁰	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High, no ITT analysis
Cai 2005 ³²	Unclear	Unclear	Not Used	Low, No dropout	Low	Low

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PROSPERO International prospective register of systematic reviews

Review title and timescale

- 1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Effects of five types of selenium supplementation for treatment of Kashin-Beck disease in children: a systematic review and network meta-analysis
- 2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.
- 3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
07/03/2016
- 4 Anticipated completion date
Give the date by which the review is expected to be completed.
31/12/2016
- 5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started **x**

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No

Provide any other relevant information about the stage of the review here.

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- 10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

None.

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11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

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12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

None

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
-------	------------	-----------	----------------------

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

Comparing the effectiveness of five kinds of selenium supplementation for the treatment of patients with Kashin-Beck disease (KBD), and ranking these selenium supplementation based on their performance.

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We will search, without language restrictions, for all publications between January 1966 and 31 Oct 2016 using electronic databases, which included MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews, The Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technique Journals Database, and Wan Fang database.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Kashin-Beck disease.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Children.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Selenium tablet and other types of selenium supplements including Selenium salt, selenium enriched yeast, Selenium+ VE, or Selenium + VC .

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Placebo or no treatment or other other types of selenium supplements.

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Randomized, controlled trials (RCTs).

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)

Give the most important outcomes.

The repairing rate of metaphyseal lesions on X-ray film.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

None.

Give information on timing and effect measures, as appropriate.

26 Data extraction (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two reviewers will independently evaluate the methodological quality of individual study according the Cochrane risk-of-bias tool. Any disagreements will be resolved by consulting a third author.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where

appropriate a brief outline of analytic approach should be given.

Initially, we will perform standard pairwise meta-analyses for all available direct comparisons in STATA. Statistical heterogeneity of treatment effects across studies will be assessed by the Cochrane Q test, and the extent of between-study heterogeneity will be quantified by I-squared. Then we will conduct network meta-analysis in STATA to determine comparative effectiveness of each therapy. We will present estimates of treatment effects as odds ratios and 95% central credible intervals (CrI).

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

'None planned.'

Review general information

30 Type and method of review

Select the type of review and the review method from the drop down list.

Systematic review

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

China

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available

Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36 Keywords

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

37 Details of any existing review of the same topic by the same authors

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status

Review status should be updated when the review is completed and when it is published.

Ongoing

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5 39 Any additional information
6 Provide any further information the review team consider relevant to the registration of the review.
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8 40 Details of final report/publication(s)
9 This field should be left empty until details of the completed review are available.
10 Give the full citation for the final report or publication of the systematic review.
11 Give the URL where available.
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For peer review only

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review
Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Page 4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Page 5 Registration number: CRD42016051874
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	Page 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5-6
12				
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14	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Page 6-7 & Fig 2
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
22				
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Page 6-7
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	Page 6-7
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 7
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 6
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	Page 7
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RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7 & Fig 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Page 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8 & Appendix table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 8 & Appendix table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Page 8-9 & Fig 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Page 8-9 & Table 1
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Page 9 & Fig 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 9 & Fig 4
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Page 9 Table 2 Fig 5

DISCUSSION

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2	Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).
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6	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>
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13	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
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18	FUNDING		
19	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.
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PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

BMJ Open

Effects of Five Types of Selenium Supplementation for Treatment of Kashin-Beck disease in children: A Systematic Review and Network Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017883.R1
Article Type:	Research
Date Submitted by the Author:	13-Oct-2017
Complete List of Authors:	Xie, Dongmei; West China Hospital, Sichuan University, Department of Geriatrics Liao, Yulin; West China Hospital, Sichuan University, Department of Geriatrics Yue, Jirong; West China Hospital, Sichuan University, Department of Geriatrics Zhang, Chao; Taihe Hospital, Hubei University of Medicine, Center for Evidence-based Medicine and Clinical Research Wang, Yanyan; West China Hospital, Sichuan University, Department of Geriatrics Deng, Chuanyao; West China Hospital, Sichuan University, Department of Geriatrics Chen, Ling; West China Hospital, Sichuan University, Department of Geriatrics
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Complementary medicine, Evidence based practice, Medical management, Nutrition and metabolism
Keywords:	Kashin-Beck disease, Selenium supplementation, Network meta-analysis, Randomized controlled trial

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Manuscripts

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4 **Effects of Five Types of Selenium Supplementation for Treatment**
5 **of Kashin-Beck disease in children: A Systematic Review and**
6 **Network Meta-analysis**
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10 **Running title: Selenium Supplementation for Treatment of KBD**

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Abstract

Objective: To compare the effectiveness of five kinds of selenium supplementation for the treatment of patients with Kashin-Beck disease (KBD), and rank these selenium supplementation based on their performance.

Design: We searched for all publications between January 1, 1966 and March 31, 2017 using seven electronic databases. GRADE system to NMAs was applied to rate the quality of the evidence. We conducted a random effects model network meta-analysis in STATA to determine comparative effectiveness of each intervention. Rankings were obtained by using the surface under the cumulative ranking curve (SUCRA) values and mean ranks.

Results: A total of 15 randomized controlled trials involving 2931 patients were included. After assessment of the overall quality of the evidence, we downgraded our primary outcomes from high to low or very low quality. Network meta-analyses showed that all five kinds of selenium supplementation had higher metaphysis X-ray improvement which were superior to placebo. Ranking on efficacy indicated that selenium salt was ranked the most effective, followed by sodium selenite + vitamin E, selenium enriched yeast, sodium selenite and then sodium selenite + vitamin C.

Conclusions: Based on the results of network meta-analysis, all five types of selenium supplements are more effective than placebo in promoting the repair of metaphysis impairment. The effect of selenium salt ranked most effective. Since the overall quality of the evidence was low or very low, the SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison. Se salt can be an economical and convenient strategy for controlling KBD in endemic areas. However, suitable dosages should be strictly controlled and the content of selenium should be closely monitored.

Trial registration number: CRD42016051874

Keywords: Kashin-Beck disease; Selenium supplementation; Network meta-analysis; Randomized controlled trial

Strengths of this study:

- The present NMA integrated evidence from direct and indirect comparisons.
- We comprehensively summarized all RCTs of selenium supplements for KBD.
- We applied GRADE system to NMAs based GRADE working group to rate the quality of the evidence.

Potential limitations:

- Despite our exhaustive search, only 15 RCTs conducted in China were included in this review. Some trials may have been published in local journals that were missed in our search.
- The overall quality of the evidence was low or very low.
- The SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison.

Introduction

Kashin-Beck disease (KBD) is a chronic, disabling degenerative disease of the peripheral joints and spine^{1,2}. It is present primarily among people in southeast Siberia, north Korea, and China³. KBD is prevalent in 377 counties of 14 provinces in China, with 0.64 million cases⁴. KBD occurs in childhood and involves pathologic changes of metaphysis and epiphyseal plate, resulting in multiple symptoms in the growth and the articular cartilages such as bony deformity, joints enlargement, growth retardation and functional impairment in multiple joints. The resulting disability causes an important human and social economic burden to both affected children and adults. Moreover, KBD can also cause disturbances in the cartilage metabolism, the lipid peroxidation, and sulfur and selenium metabolism^{5,6}. So far, some measures exist for treatment of KBD because of the incomplete ability of the cartilage to repair itself. Treatment strategies for symptomatic relief include non-steroidal anti-inflammatory drugs⁷, sodium hyaluronate⁸, physical therapy⁹ and chondroitin sulfate combined with glucosamine¹⁰. Successful surgical treatments to correct joint defects have been reported by orthopaedists^{11,12}.

Although the etiology of KBD is multifactorial, one of the major environmental risk factors is selenium deficiency¹³. Since the 1970s, selenium supplements have been given in some highly endemic areas. A meta-analysis including five randomized control trials (RCTs) and 10 non-RCTs demonstrated the benefits of selenium supplementation for the primary prevention of KBD in children¹⁴. Another systematic review suggested that sodium selenite (Se) was effective for the treatment of patients already affected with KBD¹⁵. Besides Se tablet, there are other selenium supplements used for treating KBD, including selenium salts (Se salt), selenium enriched yeast (Se yeast), the combination of sodium selenite with vitamin E (Se + VE), and the combination of sodium selenite with vitamin C (Se + VC). At the time of

our review, there were few head-to-head comparisons of different types of selenium supplementation for treatment of KBD. In light of the need for government policy makers and clinical care workers to know the effects of a set of alternative options, we conducted a systematic review and network meta-analysis (NMA). The aim of this systematic review and NMA was to compare the effectiveness of all types of selenium supplementation for the treatment of patients with KBD, and rank these selenium supplementation based on their performance.

Method

A protocol for this systematic review was devised in accordance with the PRISMA guidelines and registered on PROSPERO, and the trial registration number was CRD42016051874.

Search strategy

We searched, without language restrictions, for all publications between January 1, 1966 and March 31, 2017 using electronic databases, which included MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Reviews, The Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technique Journals Database, and Wan Fang database. The following MeSH words and free words were used: “Kashin-Beck disease,” “Kashin-Beck disease,” “big bone disease,” “endemic osteoarthritis,” “Urov disease” and “selenium,” “Sodium selenite,” and “Se”. The Ovid search strategy is available in Appendix box 1. Reference lists from published narrative review articles and systematic reviews were reviewed to identify additional studies.

Eligibility criteria

We included all randomized, controlled trials (RCTs) that used Se tablet and other types of selenium supplements including Se salt, Se yeast, Se + VE, as well as Se + VC for KBD

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4 patients. The control groups included placebo or no treatment controls, or other active medi-
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6 cines. The diagnostic criteria used for KBD was based on the Diagnosis Criteria for Kashin-
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8 Beck Disease (GB16003-1995), which was developed by National Health and Family Plan-
9
10 ning Commission of the People's Republic of China¹⁶. We excluded the following studies: (1)
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12 studies with small sample sizes (numbers of patients less than 20 in each treatment group);
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14 (2) preventive studies; (3) studies without available information of interest. Studies reporting
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16 mixed groups of participants (e.g., participants with and without KBD) were included only if
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18 the therapeutic effect data could be identified and extracted separately. Outcome of interest to
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20 this review was the repair rate of metaphyseal lesions on X-ray film. Typically, repair was
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22 defined as being cured basically or improved significantly of metaphyseal lesions according
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24 to the latest judgment standard of X-ray for treatment effect of KBD¹⁷.

25 26 27 28 ***Data extraction and quality evaluation***

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30 Two authors (Y. L & D. X) independently screened all citations identified by the searches.
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32 Full-text articles of potential studies were obtained and assessed according to the aforemen-
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34 tioned inclusion criteria. The data extraction form included publication (first author, year of
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36 publication), demographics (sample size and age), interventions (dosage, route of administra-
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38 tion, and duration of treatment), the follow-up period, as well as outcomes. We extracted data
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40 to the nearest 12 months to estimate the overall odds ratio (OR) because all the included
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42 RCTs report this time point. Two reviewers independently evaluated the methodological qual-
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44 ity of individual study according the Cochrane risk-of-bias tool¹⁸. In our review, we applied
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46 the GRADE system to our NMA based on the GRADE working group¹⁹. The methods of rat-
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48 ing the quality of direct comparison are the same for GRADE in traditional meta-analysis.
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50 We downgraded the evidence from “high quality” by one level for serious (or by two for very
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52 serious) study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision
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4 of effect estimates or potential publication bias. The rating of the quality of the indirect esti-
5 mates is based on the ratings of the two pair-wise estimates that contributes to the indirect
6 estimate of the comparison of interest. The lower confidence rating of the two direct compar-
7 isons constitutes the confidence rating of the indirect comparison. When both direct and indi-
8 rect evidence are available, we used the higher of the two quality ratings as the quality rating
9 for the NMA estimate. In addition, we needed to consider the intransitivity among different
10 groups and the inconsistency between direct comparison and indirect comparison. Further-
11 more, we used the GRADE profiler to help us create "Summary of findings" tables
12 (GRADEpro 2008), and reported outcomes in this tables. Any disagreements would be re-
13 solved by consulting a third author (J.Y).

24 *Statistical analysis*

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28 As the repair rate of metaphyseal lesions on X-ray film, the outcome of interest in this
29 text, was a discontinuous statistics, we calculated the OR and its 95% confidence intervals
30 (CI) as the effect estimates. Initially, we performed standard pair-wise meta-analyses for all
31 available direct comparisons using a random effects model in STATA. Statistical heterogenei-
32 ty of treatment effects across studies was assessed by the Cochrane Q test, and the extent of
33 between-study heterogeneity was quantified by I^2 , of which with a value greater than 50%
34 indicates substantial heterogeneity. Then we conducted a random effects model network me-
35 ta-analysis in STATA to determine comparative effectiveness of each intervention by using
36 the network command and self-programmed STATA routines available at
37 <http://www.mtm.uoi.gr>. We present the mean effect sizes for the network estimates (OR)
38 along with their 95% confidence intervals (CI) and predictive intervals (PrI). The PrI shows
39 the degree of uncertainty around estimated treatment effects.

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43 To evaluate consistency in the entire network, we used the 'design-by-treatment' model,
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4 which was described by Higgins and colleagues, by using the network meta command in
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6 STATA. This method accounts for different source of inconsistency that can occur when stud-
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8 ies with different designs (two-arm trials vs. three-arm trials) give different results as well as
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10 disagreement between direct and indirect evidence. We inferred about the presence of incon-
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12 sistency from any source in the entire network based on a chi-square test, and a P value great-
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14 er than 0.05 indicated that the direct and indirect comparisons in the network were consistent.
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16 We also estimated the ranking probabilities for all treatments of being at each possible rank.
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18 Rankings were obtained by using the surface under the cumulative ranking curve (SUCRA)
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20 values and mean ranks. SUCRA could be expressed as a percentage interpreted as the per-
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22 centage of effectiveness of a treatment that would be ranked first without uncertainty. To de-
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24 rive these SUCRA values we used the ranking probabilities estimated from the mvmeta
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26 command.
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30 **Results**

31 *Study inclusion and characteristics*

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34 Initial searches yielded 1686 citations. Of these, 1645 duplicate or irrelevant records were
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36 excluded and full-text articles of the remaining 41 studies were retrieved for further assess-
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38 ment according to the inclusion criteria. A total of 15 studies²⁰⁻³⁴ containing 2931 patient were
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40 included eventually in our meta-analysis (Fig 1). We excluded 26 trials for the reasons docu-
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42 mented in the Characteristics of excluded studies table (Appendix table 1).
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46 A total of seven interventions were evaluated: Se, Se salt, Se yeast, Se + VE, Se + VC, VC,
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48 and placebo. Figure 2 shows the network of all treatment comparisons included in this re-
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50 view. The age of participants range from 2 to 16 years old and the duration of follow-up var-
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52 ied from 6 months to 36 months. The main characteristics of the included studies were simi-
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54 lar, and the characteristics (e.g. interventions dosage, route of administration, duration of
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treatment, the follow-up period, and outcomes) are presented in the online supplementary Appendix table 2.

Overall assessment for evidence quality

All included trials were reported to be RCTs. The quality of included studies was overall low. Study quality for each study can be seen in Appendix table 3. We downgraded this outcome from high to low or very low quality for possible bias, inconsistency, or imprecision. Overall assessment for evidence quality was seen in table 1.

Table 1 Quality ratings for comparison of different interventions

Comparison	Quality of direct evidence	Quality of Indirect evidence	Quality of network meta-analysis evidence
Se vs. placebo	Low*,†	Low*,#	Low*,†
Se salt vs. placebo	Low*,†	Low*,#,	Low*,†
Se+VC vs. placebo	Moderate*	Low*,#	Moderate*
Se+VE vs. placebo	Very low*,†,‡	Low*,#	Low*,#
Se yeast vs. placebo	Moderate*	Low*,#	Moderate*
VC vs. placebo	Moderate*	Low*,#	Moderate*
Se salt vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se+VC vs. Se	Moderate*	Low*,‡	Moderate*
Se+VE vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se	Moderate*	Very low*,‡,¶	Moderate*
VC vs. Se	Moderate*	Low*,¶	Moderate*
Se+VC vs. Se salt	Low*,‡	Low*,¶	Low*,¶
Se+VE vs. Se salt	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se salt	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se salt	Low*,‡	Very low*,‡,¶	Low*,¶
Se+VE vs. Se+VC	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se+VC	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se+VC	Moderate*	Very low*,‡,¶	Moderate*
Se yeast vs. Se+VE	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se+VE	—	Very low*,‡,¶	Very low*,‡,¶

VC vs. Se yeast	—	Very low ^{*,‡,¶,¶¶}	Very low ^{*,‡,¶,¶¶}
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*Limitations (risk of bias). †Inconsistency. ‡Imprecision. #Inconsistency: predictive intervals for treatment effect include effects that would have different interpretations. ¶Indirectness: no convincing evidence for the plausibility of the transitivity assumption.

Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Intervention-control pair-wise meta-analyses

All RCTs reported repair rate of metaphyseal lesions on X-ray films. Follow-up duration of included RCTs were varied. We extracted data to the nearest 12 months to estimate the overall OR. When compared to placebo, the pooled OR (random effects model) of X-ray improvement was in favor of Se (OR 5.0, 95% CI: 3.21 - 7.78, $P < 0.001$), Se salt (OR 7.6, 95% CI: 2.34 - 24.67, $P = 0.001$), Se enriched yeast (OR 3.75, 95% CI: 1.76 - 8.02, $P = 0.001$), and Se + VE (OR 11.05, 95% CI: 2.61 - 46.80, $P = 0.03$) respectively, which indicated that repairing rate of metaphyseal lesions on X-ray films was significantly higher for these drugs than placebo. Summary of findings for each selenium supplements compare to placebo was seen in table 2. A few RCTs reported direct comparisons among active interventions. There were two RCTs compared Se with VC, and the result of traditional meta-analysis showed that no significant difference was found between Se and VC^{23,31}. For Se+ VC compared to VC, the pooled OR of two RCTs also showed no significant difference existed (OR 1.15, 95% CI: 0.51 - 2.63, $P=0.93$)^{31,33}. There was only one RCT for Se vs. Se + VC³¹, Se vs. Se yeast²⁶, Se salt vs. Se + VC³¹, Se salt vs. VC³¹, respectively. OR of X-ray improvement was significantly higher in Se salt group compared with Se + VC (OR 6.00, 95% CI: 1.81 - 19.93, $P=0.003$) and VC alone (OR 4.24, 95% CI: 1.39 - 12.90, $P=0.011$). There were no significant differences noted in other active interventions comparisons (See table 3).

Table 2 Summary of findings**Patient or population:** Treatment of Kashin-Beck disease in children**Outcomes:** Improvement of metaphyseal lesions on X-ray

Intervention: See list Comparison: placebo

Intervention/Comparison:	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	● Risk with placebo	● Risk with Se			
Se compared to placebo	422 per 1,000	785 per 1,000 (701 to 850)	OR 5.00 (3.21 to 7.78)	2427 (11 RCTs)	⊕⊕○○ LOW ^{a,b}
Se salt compared to placebo	345 per 1,000	800 per 1,000 (552 to 928)	OR 7.60 (2.34 to 24.67)	59 (1 RCT)	⊕⊕○○ LOW ^{a,c}
Se+VC compared to placebo	345 per 1,000	401 per 1,000 (181 to 668)	OR 1.27 (0.42 to 3.83)	54 (1 RCT)	⊕⊕⊕○ MODERATE ^a
Se+VE compared to placebo	451 per 1,000	901 per 1,000 (682 to 975)	OR 11.05 (2.61 to 46.80)	145 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}
Se yeast compared to placebo	383 per 1,000	700 per 1,000 (522 to 833)	OR 3.75 (1.76 to 8.02)	120 (1 RCT)	⊕⊕⊕○ MODERATE ^a
VC compared to placebo	339 per 1,000	509 per 1,000 (334 to 681)	OR 2.02 (0.98 to 4.17)	124 (2 RCTs)	⊕⊕⊕○ MODERATE ^a

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Limitations (risk of bias): no studies described adequate methods regarding the sequence of randomization and reported allocation concealment. Some studies did not use of a blinding method and ITT analysis.

b. Inconsistency: small sample size or have a higher I², or both.

c. Imprecision: the effects are large but the overall sample size are low.

Table 3 Results of pair-wise and network meta-analyses of repairing rate of metaphyseal lesions on X-ray films

OR (95% CI) #	Placebo	Se	Se salt	Se + VC	Se + VE	Se yeast
Se	4.68 (2.99 to 7.34)* 5.00 (3.21 to 7.78)	-	-	-	-	-
Se salt	12.37 (2.81 to 54.41)* 7.60 (2.34 to 24.67)	2.64 (0.59 to 11.84) -	-	-	-	-
Se + VC	3.26 (1.14 to 9.28)* 1.27 (0.42 to 3.83)	0.70 (0.25 to 1.97) 1.30 (0.57 to 2.94)	0.26 (0.06 to 1.20) 0.17 (0.05 to 0.55)	-	-	-
Se + VE	10.72 (3.14 to 36.57)* 11.05 (2.61 to 46.80)	2.29 (0.62 to 8.43) -	0.87 (0.13 to 5.93) -	3.29 (0.65 to 16.53) -	-	-
Se yeast	5.81 (1.70 to 19.89)* 3.75 (1.76 to 8.02)	1.24 (0.36 to 4.25) 1.92 (0.90 to 4.00)	0.47 (0.07 to 3.16) -	1.78 (0.37 to 8.66) -	0.54 (0.10 to 3.08) -	-
VC	3.05 (1.29 to 7.20)* 2.02 (0.98 to 4.17)	0.65 (0.28 to 1.53) 0.95 (0.51 to 1.79)	0.25 (0.06 to 1.06) 0.24 (0.08 to 0.72)	0.94 (0.34 to 2.56) 0.87 (0.38 to 1.96)	0.28 (0.06 to 1.27) -	0.52(0.12 to 2.27) -

ORs represent odds of repair in row-treatment versus column-treatment. ORs larger than 1 denote higher repair rate in row-treatment than column-treatment. In each cell, the first line represents the result of network meta-analyses, and the second row represents the result of pair-wise meta-analyses. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Results of network meta-analyses and consistency test

The pooled OR and 95% CI of X-ray improvement for active treatment compared with placebo was 4.68 (2.99 to 7.34) for Se, 12.37 (2.81 to 54.41) for Se salt, 5.81 (1.70 to 19.89) for Se enriched yeast, 10.72 (3.14 to 36.57) for Se + VE, and 3.26 (1.14 to 9.28) for Se + VC respectively, which indicated a significant difference in efficacy. For the comparison between active treatments, no significant differences were found. More details were presented in Table 3. In Figure 3, we presented the OR for the network estimates along with 95% CI and PrI.

There was no inconsistency between direct and indirect evidences according to the design-by-treatment interaction model ($P=0.88$), implying that direct and indirect evidence were mainly consistent (Fig 4). However, the results of the comparison of Se + VC and VC versus placebo showed some degree of inconsistency. Actually, the lower CI for X-ray improvement were nearly equal to 1 (1.13 for Se + VC and 1.27 for VC), showing a trend to coincide with direct results.

Table 4 displayed the distribution of probabilities for each treatment being ranked for their efficacy in KBD according the SUCRA values (Fig 5) and mean ranks.

Table 4 Probabilistic ranking of effectiveness of different interventions

Interventions	Probabilistic ranking		
	SUCRA (%)	Pr Best (%)	Mean Rank
Se salt	86	49.1	1.8
Se+VE	82.8	38.5	2
Se yeast	62.5	11.6	3.3
Se	52.5	0.2	3.9
Se+VC	35.7	0.4	4.9
VC	30.1	0.2	5.2

Placebo	0.5	0	7
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SUCRA=surface under cumulative ranking, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Se salt was ranked the most effective followed by Se+VE, Se-yeast, Se and then Se + VC. VC and placebo as a control was ranked the least effective.

Discussion

Principal findings

Our network meta-analysis of all 15 available RCTs in 2931 patients with KBD showed that all five kinds of selenium supplementation (including Se, Se salt, Se enriched yeast, Se + VE, Se + VC) were superior to placebo/no treatment in repairing metaphyseal lesions. There was uncertainty around the difference between two active treatments. However, the probabilistic ranking of interventions showed that Se salt was ranked the most effective, followed by Se + VE, Se enriched yeast, Se and then Se + VC.

Relation to other studies

Studies have proposed that selenium deficiency is the underlying factor that predisposes the target cells (chondrocytes) to oxidative stress from free-radical carriers³⁵. In most highly endemic area, the level of total soil selenium concentrations is typically low. A meta-analysis of the correlation between selenium and KBD reported that selenium levels in water, soil, cereal, and corn in endemic regions were lower than regions without high rates of KBD³⁶. Furthermore, most of the inhabitants living in areas with KBD have a low selenium nutritive status, which is reflected by low selenium contents in their blood serum, red blood cell, urine, and hair.

The effectiveness of various methods of selenium supplementation for children has been

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4 demonstrated by many studies including Se salt³⁷, Se enriched yeast²⁶, oral sodium selenite
5 tablet¹⁵, spraying Se on crops³⁸, and Se enriched fertilizer³⁹. Selenium supplementation was
6 associated with a simultaneous decrease in the prevalence of KBD, along with an increased
7 selenium content in the hair of inhabitants living in areas with KBD. It was reported that the
8 incidence of radiographic evidence of metaphysical lesions of the hands was 44.8% in 1990
9 at Cuimu town of the Shaanxi province in children aged 7~12 years. After implementation of
10 comprehensive prevention measures of KBD, especially using Se salt, the incidence these x-
11 ray findings decreased to 0.3% in 2010⁴⁰. The low incidence of KBD also may explain why
12 there has not been any studies about Se treatment for KBD published in recent years.
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24 Se salt was produced by adding 0.833 g of sodium selenite powder into every 50 kg of
25 source salt and then expanding it to 1:60,000 Se salt. In our study, the probabilistic ranking of
26 interventions showed that Se salt was ranked the most effective. This result was not surpris-
27 ing because of the high compliance for salt intake. Although administration of Se tablet is
28 effective for preventing and treating KBD in children^{14,15}, it is very difficult for millions of
29 children living in endemic areas to adhere to a long-term medication. However, salt is a nec-
30 essary part of daily life and food intake. The compliance can be more effectively guaranteed.
31 A limitation to the findings about Se salt is that due to the difficulty of carrying out a RCT
32 comparing Se salt with placebo or other active drugs, only one RCT has been done³¹. Howev-
33 er, one meta-analysis involving 11 non-RCTs (2652 participants) also showed that supple-
34 ment Se salt was effective for preventing and treatment for KBD in Children³⁷. Since Se salt
35 is the most economical way for low-income families, it is anticipated that continuous use of
36 Se salt and other comprehensive prevention measures may help to eliminate the KBD carti-
37 lage damages in Children⁴¹.
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54 Despite the evidence in our meta-analysis, there remains some controversy around sele-
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4 nium supplementation in relationship with iodine deficiency. In a cross sectional study in Ti-
5 bet area, Moreno-Reyes and his colleges found no association between individual selenium
6 status and KBD, whereas iodine deficiency was a risk factor⁴². Similarly, the only RCT³²
7 published in English in our review showed only 1 case of improvements in X-ray in sodium
8 selenite group. The negative findings of the above studies should, however, be interpreted
9 with caution. These studies were all conducted in Tibet where selenium and iodine are both
10 deficient in the diet. Selenium and iodine deficiency are both risk factors of KBD³⁵. In animal
11 experiments, growth retardation was observed in rats fed with a low selenium diet⁴³, and im-
12 paired bone development was observed with an iodine deficient diet⁴⁴. We do not exclude the
13 possibility that selenium supplementation may not counterbalance the negative effects of
14 long-term iodine deficiency. So KBD seems unlikely to be due to only one cause. Other ge-
15 netic and environmental factors may confer either a relatively protective effect or accelerate
16 the disease.

31 32 ***Limitations of the trials included in this review***

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34 Overall, the methodological quality of the included trails was low. The method of ran-
35 domization and allocation concealment were not described in all the included trials. Double-
36 blinding was reported in 8 trials and details of the blinding methods were reported in 3 trials.
37 Withdrawal rates of participants were less than 20% in 8 trails. Only Six trials performed
38 intention to treat analysis.

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40 After assessment of the overall quality of the evidence, we downgraded our primary
41 outcomes from high to low or very low quality, because of the high risk of bias due to unclear
42 sequence generation and allocation concealment. In addition, we also found in some trials
43 that there were very small sample sizes and higher levels of statistical heterogeneity, which
44 caused serious inconsistency between the included trials.

Strengths and weaknesses

The present NMA integrated evidence from direct and indirect comparisons. Consequently, estimates in our analysis were more precise than the pair-wise meta-analyses. The literature search strategy was extensive, which makes it unlikely that we missed any relevant trial. Trial selection and data extraction including quality assessments were done independently by two authors to minimize bias and transcription errors. In this NMA, we applied the GRADE system to NMAs based on the GRADE working group to rate the quality of the evidence.

Potential limitations to this review exist. Firstly, the sample sizes of our included RCTs were all small. Sample size calculations were not mentioned in any of the studies. Secondly, despite our exhaustive search, only 15 RCTs conducted in China were included in this review. North Korea and Russia also have a high incidence of KBD; some trials may have been published in local journals that were missed in our search. Finally, the heterogeneity in this meta-analysis was somewhat high, which could be explained by a lack of concealment of allocation, failure to perform an ITT analysis, small sample sizes of the studies included and differences between different preparations of selenium. As with heterogeneity between trials, inconsistency between direct and indirect comparisons was also near zero. Although we cannot rule out clinically relevant inconsistency, we have no indication that clinical characteristics of included patients or other trial characteristics confounded the indirect comparisons.

Conclusions

Implications for clinical practice

Based on this NMA, it appears that all types of Se supplementation were more effective than placebo for the treatment of KBD in children. Ranking on efficacy indicated that Se salt were highest, followed by Se + VE, Se enriched yeast, Se, Se + VC, VC, and placebo/no

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4 treatment. Se salt was ranked the most effective. It can be an economical and convenient
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6 strategy for controlling KBD in endemic areas. However, selenium over-dose is toxic. There-
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8 fore, suitable dosages should be strictly controlled and content of selenium should be closely
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10 monitored in order to avoid harmful effects on health. Since the overall quality of the evi-
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12 dence was low or very low, the SUCRA values may be misleading and should be considered
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14 jointly with the GRADE confidence in the estimates for each comparison.
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17 18 19 ***Implications for research***

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21 Since KBD among children has almost disappeared, we believe it unlikely that future tri-
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23 als will involve a RCT to demonstrate the clinically relevant benefit of any selenium supple-
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25 mentation for children with KBD. At present, there are no effective clinical measures to re-
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27 pair the cartilage damage of KBD in adults. Tissue engineering and gene therapy approaches
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29 may become the potential treatment strategy that can applied to the treatment of the KBD car-
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31 tilage damages.
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36 37 **Contributors**

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39 Dongmei Xie and Yulin Liao conceived the review question, reviewed studies for inclusion,
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41 assessed the included studies, extracted data, completed the first draft, and edited the review.
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43 Jirong Yue and Chao Zhang analyzed the data, did the literature search, advised and coordi-
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45 nated the review development, performed part of the writing and editing of the review, ap-
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47 proved the final version of the review prior to submission, and is also a guarantor. Yanyan
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49 Wang, Chuanyao Deng and Ling Chen contributed to the development of the review ques-
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51 tion, edited and provided intellectual contributions to the review.
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Funding Statement: This research was funded by China National Science & Technology Pillar Program (2007BA125B04).

Conflict of interest: We declare that we have no conflicts of interest.

Role of the funding source: The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments: Dr. Joseph H. Flaherty is especially acknowledged for editorial review and language assistance.

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Figure Legends

Fig 1 Flow diagram of included study

Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD.

The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment.

OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% predictive intervals (red extensions).

OR = Odds ratio, CI = Confidence intervals, PrI = predictive intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 4 Consistency test in the network Meta-analysis

IF= inconsistency factor, OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

The x-axis is Log OR, and the vertical line is 0. IF is the absolute inconsistency factor, meaning the logarithm of the rate ratio for OR (RoR) of direct and indirect evidence for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at zero indicate no significant difference of inconsistency.

Fig 5 SUCRA for the cumulative probabilities

SUCRA=surface under cumulative ranking

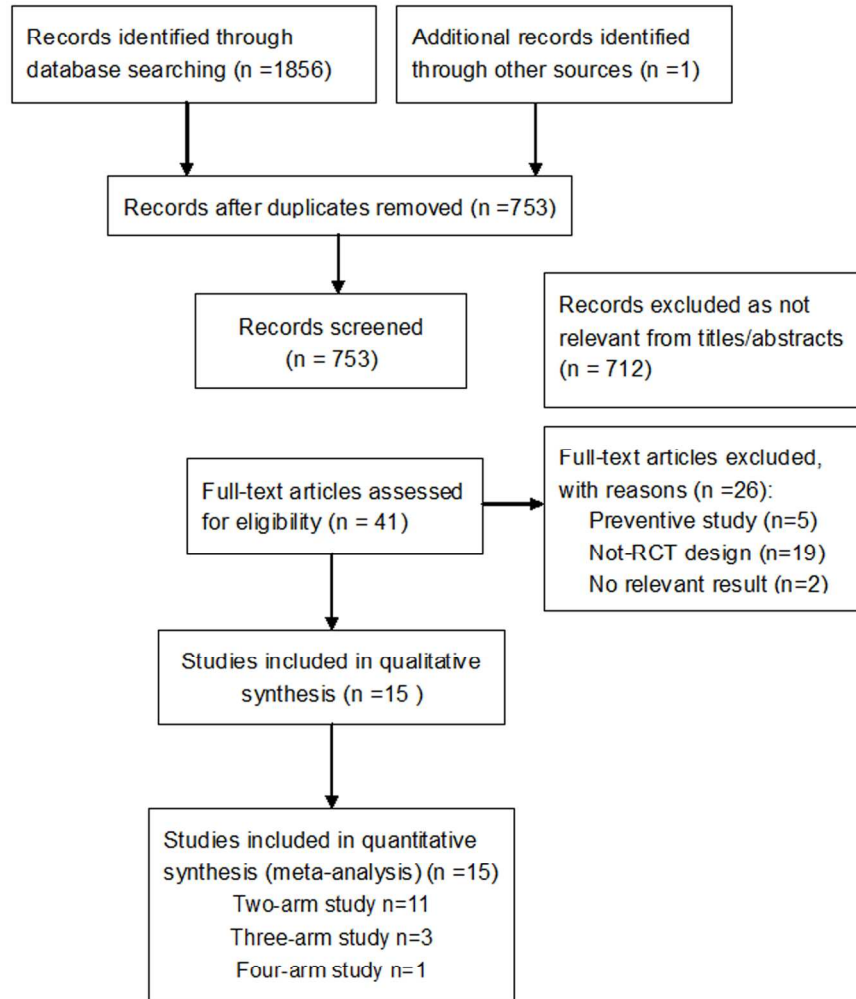


Fig 1 Flow diagram of included study

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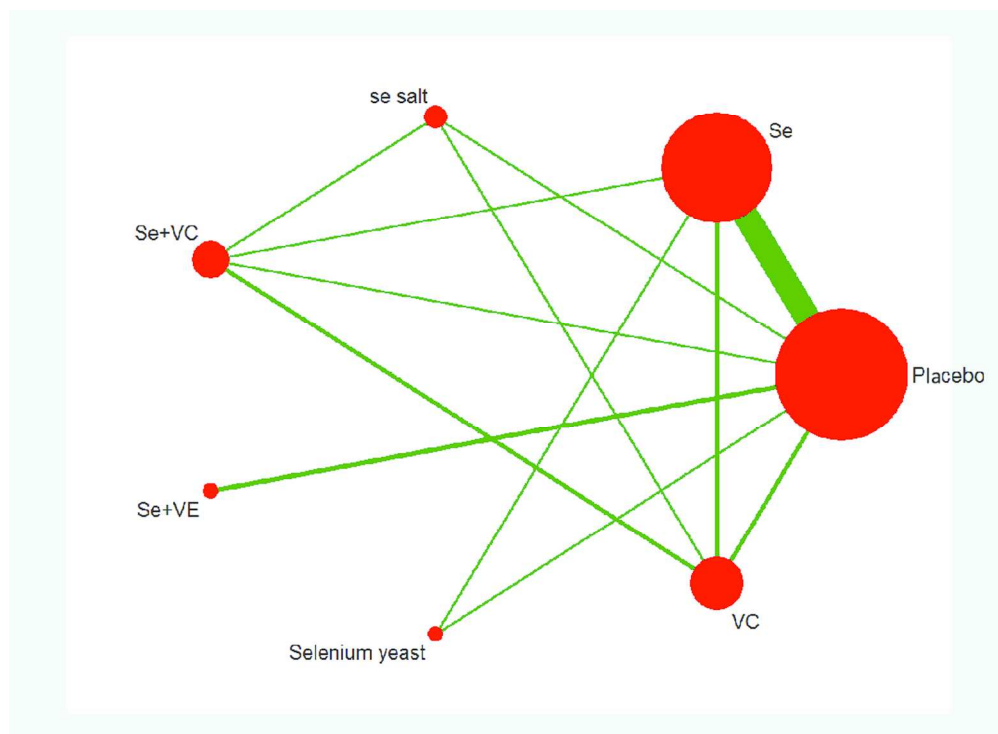


Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD. The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

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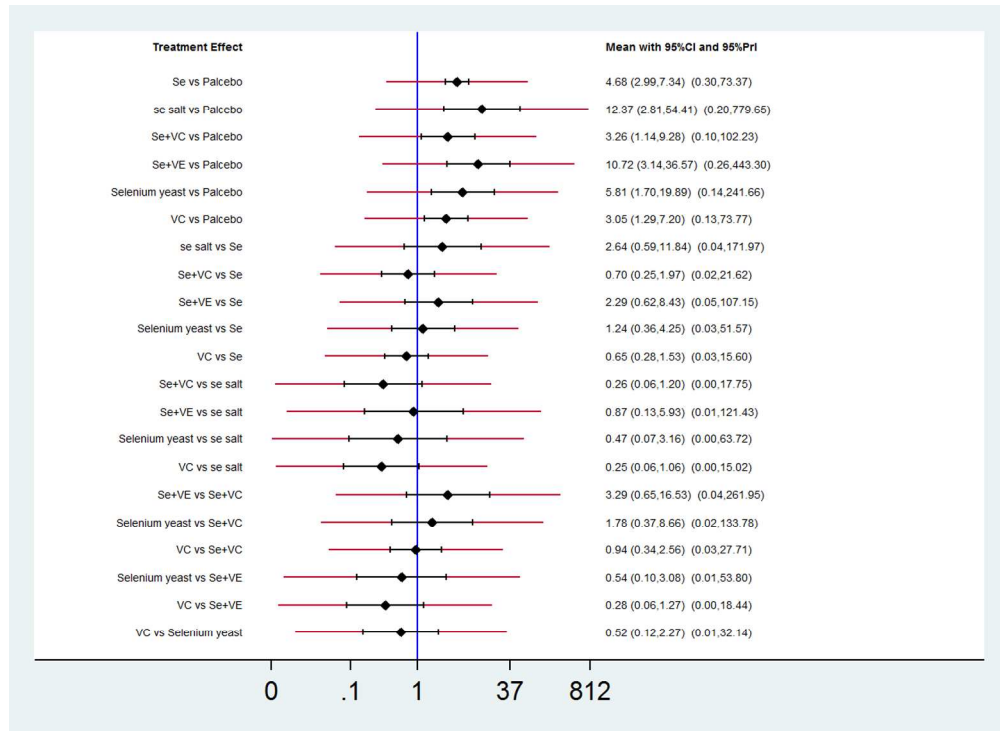


Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% predictive intervals (red extensions).

OR = Odds ratio, CI = Confidence intervals, PrI = predictive intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

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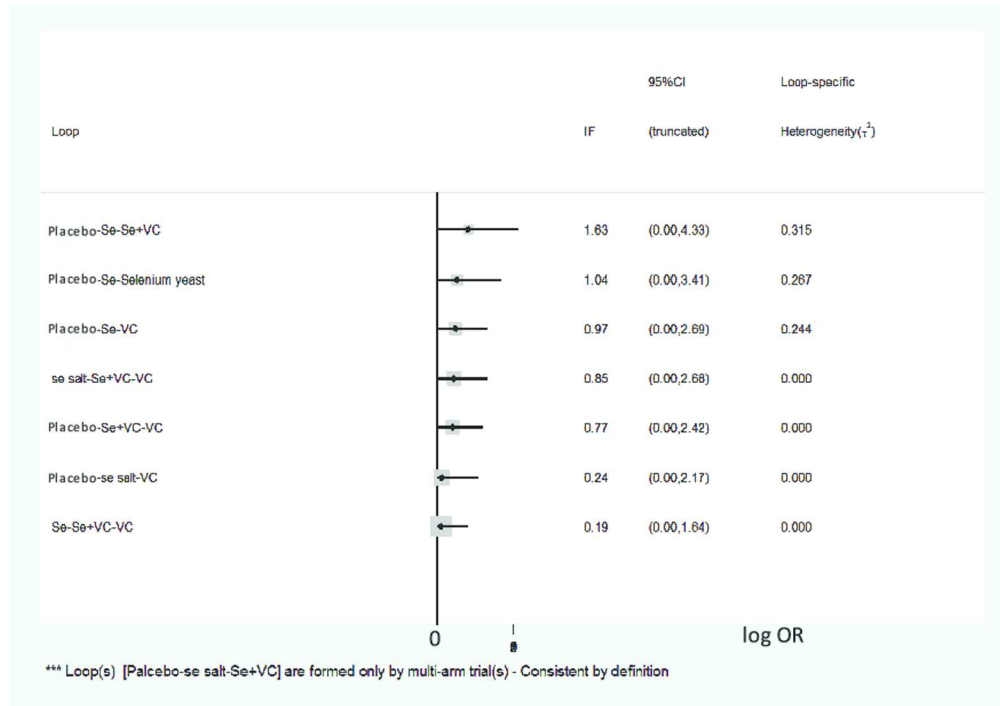


Fig 4 Consistency test in the network Meta-analysis

IF= inconsistency factor, OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

The x-axis is Log OR, and the vertical line is 0. IF is the absolute inconsistency factor, meaning the logarithm of the rate ratio for OR (RoR) of direct and indirect evidence for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at zero indicate no significant difference of inconsistency.

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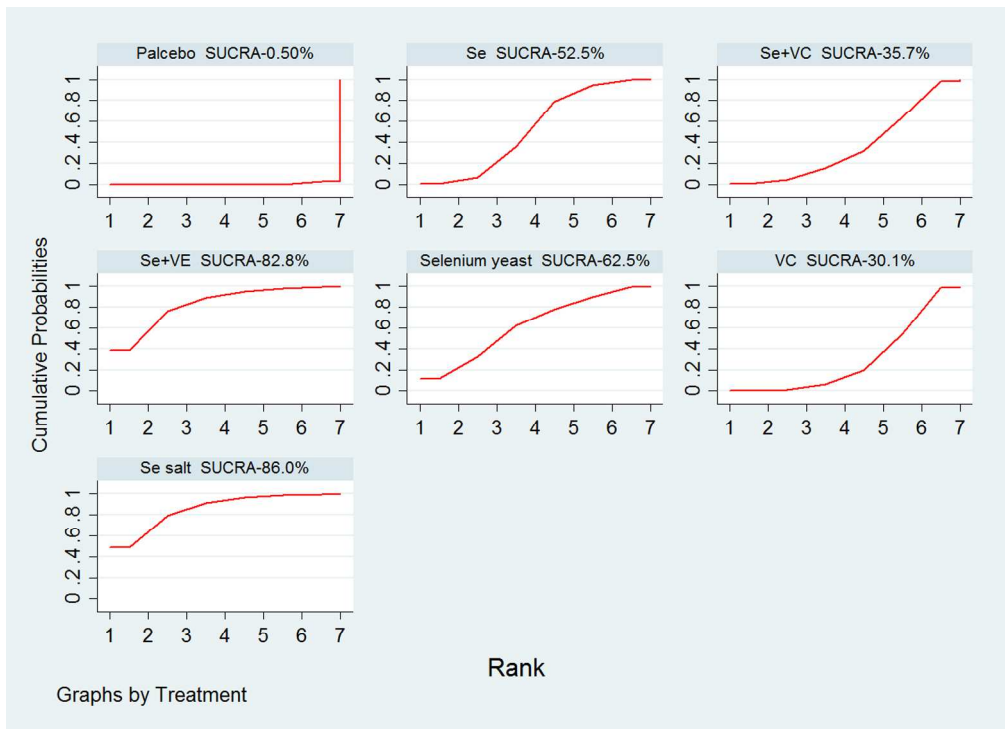


Fig 5 SUCRA for the cumulative probabilities
SUCRA=surface under cumulative ranking

450x328mm (300 x 300 DPI)

For peer review only

Appendix box 1 Ovid search strategy

#1 exp kashin-beck disease/
#2 kashin-beck disease.tw.
#3 kashin-bek disease.tw.
#4 big bone disease.tw.
#5 endemic osteoarthritis.tw.
#6 Urov disease.tw.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 sodium selenite.tw.
#9 selenium .tw.
#10 Se salt.tw.
#11 enriched yeast
#12 8 or 9 or 10 or 11
#13 7 AND 12
#14 randomized controlled trial.pt.
#15 controlled clinical trial.pt.
#16 randmoized.ab.
#17 placebo.ab.
#18 randomly.ab.
#19 trial.ab.
#20 groups.ab.
#21 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 13 and 21
#23 limit #22 to human

Appendix table 1 Characteristics of excluded studies(ordered by study ID)

Study	Reason for exclusion
Ding 1985	No relevant result
Fan 1986	Not a RCT
Guo 1990	Not a RCT
Han 2013	Not a RCT
He 1988	Not a RCT
Huang 1959	Not a RCT
Li 1986	Not a RCT
Li 2004	Preventive study
Liang 1986	Preventive study
Ma 1996	Not a RCT
Sun 2008	Not a RCT
Suolang 2008	Not a RCT
Wang 1983	Preventive study
Wang 1988	Not a RCT
Wang 1989	Preventive study
Wu 1991	Preventive study
Yang 2009	Not a RCT
Yang 2010	Not a RCT
Yi 2006	Not a RCT
Yu 2016	Not a RCT
Zhang 1989	Not a RCT
Zhang 1996	No relevant result
Zhang 2006	Not a RCT
Zhang 2009	Not a RCT
Zhong 1986	Not a RCT
Zhou 1998	Not a RCT

Appendix table 2 Characteristics of included trials

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Niu 1981 ²⁰	27	29	6~13	6~13	Se + VE: Se tablet 2mg/week +VE 15mg/day	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
YSSG 1982 ²¹	166	159	3~13	3~13	Se tablet, 1 mg/week (3-10 yrs), 2 mg/week (11-13 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
Wang 1983 ²²	47	42	5~15	5~15	Se + VC: Se tablet 2mg/week +VE 15mg/day	No treatment	11	Improvement of metaphyseal lesions on X-ray
Cui 1984 ^{23*}	30	30/30	7~19	7~19	Se tablet, 1 mg/week (7-10 yrs), 2 mg/week (11-19 yrs)	①VC 200 mg 3 times/day; ②Placebo/week	6~12	Improvement of metaphyseal lesions on X-ray
Niu 1984 ²⁴	56	59	6~13	6~13	Se tablet first week: 1.0 mg/day (< 10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/week (< 10 yrs), 2.0 mg/week (> 11 yrs)	Placebo/week	24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films
Guo 1985 ²⁵	50	50	5~15	5~15	Se tablet, 1 mg/week (<5 yrs), 2 mg/week (>5 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome	
	I	C	I	C					
Guo 1986 ^{26*}	60/60	60	5~14	5~14	①Se tablet, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs); ②Se yeast, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs);	Placebo/week	13	Improvement of metaphyseal lesions on X-ray	
Niu 1986 ²⁷	285	277	6~13	6~13	Se tablet, 1 mg/week (<10 yrs), 2 mg/week (>10 yrs)	Placebo/week	12~24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	
Wu 1986 ²⁸	171	177	5~16	5~16	Se tablet, 1 mg/week (< 10 yrs), 2 mg/week (> 10 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray	
Deng 1988 ²⁹	43	46	2~13	2~13	Se tablet, no details	No treatment	36	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome	
	I	C	I	C					
Niu 1990 ³⁰	210	228	6~13	6~13	Se tablet, first week: 0.5 mg/day (< 5 yrs), 1.0 mg/day (6-10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/month (< 5 yrs), 2.0 mg/month (6-10 yrs), 4.0 mg/month (> 11 yrs)	Placebo/month	12	Improvement of lesions on X-ray	metaphyseal
Zhou 1991 ^{31#}	25/30	35/29	4~12	4~12	①Se + VC: Se tablet 1mg/10day+ VC 100mg/day; ②Se salt (sodium selenite: salt = 1:60,000) /10day	③VC, 300mg/day; ④No treatment	12	Improvement of lesions on X-ray	metaphyseal
Moreno-Reyes 2003 ³²	113	95	10±0.28	10±0.3	Se tablet, 1 mg/week	Placebo/week	12	Improvement of lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	metaphyseal
Chen 2003 ^{33*}	50/50	50	6~11	6~11	①Se tablet 1mg/week; ② Se + VC: Se tablet 1mg/week+ VC 300 mg 2 times/day	VC 300mg bid	12	Improvement of lesions on X-ray	metaphyseal

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Cai 2005 ³⁴	31	31	7~13	7~13	Se tablet, 2mg/10 days (7-10 yrs), 3 mg/10 days (11-13 yrs)	No treatment	18	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films

I= intervention, C = control, YSSG = Yongshou scientific survey group of Kashin-Beck Disease, yrs = years, Se = Sodium selenite, Se salt =selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast. * Three arms study, # Four arms study

Appendix table 3 Risk of Bias of Included Studies

Study	Balanced allocation	Allocation concealment	Blinding	Completeness of outcome	Selective outcome reporting	Other Bias	overall assessment*
Niu 1981 ²⁰	Unclear	Unclear	Double-blind	Low	Low	Low	Unclear
YSSG 1982 ²¹	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear
Wang 1983 ²²	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Cui 1984 ²³	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1984 ²⁴	Unclear	Unclear	Double-blind	Low, No dropout	Low	High, no ITT analysis	High
Guo 1985 ²⁵	Unclear	Unclear	Not Used	High, dropouts >20%	Low	High, no ITT analysis	High
Guo 1986 ²⁶	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1986 ²⁷	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear

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3	Wu 1986 ²⁸	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High, no ITT analysis	High
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8	Deng 1988 ²⁹	Unclear	Unclear	Unclear	Low, drop out <10%	Low	High, no ITT analysis	High
9								
10								
11								
12	Niu 1990 ³⁰	Unclear	Unclear	Single-blind	Low, No dropout	Low	Low	Unclear
13								
14								
15	Zhou 1991 ³¹	Unclear	Unclear	Unclear	Low, No dropout	Low	Low	Unclear
16								
17								
18	Moreno-Reyes 2003 ³²	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High no ITT analysis	High
19								
20	Chen 2003 ³³	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
21								
22								
23								
24								
25								
26	Cai 2005 ³⁴	Unclear	Unclear	Not Used	Low, No dropout	Low	Low	Unclear
27								
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29 *: Overall Score: Low risk of bias = no bias detected in any domain; Unclear risk of bias = one category or more is potentially at risk of bias; High risk of bias = one
 30 category or more is at high risk of bias.

31 ITT = intention to treat
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Appendix table 4 Repair rate of metaphyseal lesions of different comparisons in included studies

comparison	No. of study	No. of patients	Repair rate	
			Treatment 1 (n1/N1)	Treatment 2 (n2/N2)
Se vs. placebo	11	2427	887/1215	511/1212
Se vs. Se+VC	1	100	30/50	33/50
Se vs. Se yeast	1	120	33/60	42/60
Se vs. VC	2	160	44/80	41/80
Se salt vs. placebo	1	59	24/30	10/29
Se salt vs. Se+VC	1	55	24/30	10/25
Se salt vs. VC	1	65	24/30	17/35
Se+VC vs. placebo	2	154	43/75	32/79
Se+VC vs. VC	2	160	43/75	44/85
Se+VE vs. placebo	2	145	68/74	32/71
Se yeast vs. placebo	1	120	42/60	23/60
VC vs. placebo	2	124	33/65	20/59

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Effects of five types of selenium supplementation for treatment of Kashin-Beck disease in children: a systematic review and network meta-analysis

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date

Give the date when the systematic review commenced, or is expected to commence.

07/03/2016

4 Anticipated completion date

Give the date by which the review is expected to be completed.

31/12/2016

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Yulin Liao

7 Named contact email

Enter the electronic mail address of the named contact.

yulinliao_2015@163.com

8 Named contact address

Enter the full postal address for the named contact.

West China Hospital, Sichuan University, Chengdu , China

9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.

15198147968

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

None.

Website address:

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Miss	Yulin	Liao	West China Hospital, Sichuan University, Chengdu , China
Mrs	Dongmei	Xie	West China Hospital, Sichuan University, Chengdu , China
Professor	Jirong	Yue	West China Hospital, Sichuan University, Chengdu , China
Professor	Chao	Zhang	Center for Evidence-Based Medicine and Clinical Research, Taihe Hospital Hubei University of Medicine
Mrs	Yanyan	Wang	West China Hospital, Sichuan University, Chengdu , China
Miss	Chuanyao	Deng	West China Hospital, Sichuan University, Chengdu , China
Miss	Ling	Chen	West China Hospital, Sichuan University, Chengdu , China

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

None

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
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Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

Comparing the effectiveness of five kinds of selenium supplementation for the treatment of patients with Kashin-Beck disease (KBD), and ranking these selenium supplementation based on their performance.

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We will search, without language restrictions, for all publications between January 1966 and 31 Oct 2016 using electronic databases, which included MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews, The Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technique Journals Database, and Wan Fang database.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Kashin-Beck disease.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Children.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Selenium tablet and other types of selenium supplements including Selenium salt, selenium enriched yeast, Selenium+ VE, or Selenium + VC .

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Placebo or no treatment or other other types of selenium supplements.

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Randomized, controlled trials (RCTs).

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)

Give the most important outcomes.

The repairing rate of metaphyseal lesions on X-ray film.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

None.

Give information on timing and effect measures, as appropriate.

26 Data extraction (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two reviewers will independently evaluate the methodological quality of individual study according the Cochrane risk-of-bias tool. Any disagreements will be resolved by consulting a third author.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where

appropriate a brief outline of analytic approach should be given.

Initially, we will perform standard pairwise meta-analyses for all available direct comparisons in STATA. Statistical heterogeneity of treatment effects across studies will be assessed by the Cochrane Q test, and the extent of between-study heterogeneity will be quantified by I-squared. Then we will conduct network meta-analysis in STATA to determine comparative effectiveness of each therapy. We will present estimates of treatment effects as odds ratios and 95% central credible intervals (CrI).

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

'None planned.'

Review general information

30 Type and method of review

Select the type of review and the review method from the drop down list.

Systematic review

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

China

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available

Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36 Keywords

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

37 Details of any existing review of the same topic by the same authors

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status

Review status should be updated when the review is completed and when it is published.

Ongoing

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- 39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

- 40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

For peer review only

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Page 5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Page 6 Registration number: CRD42016051874
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	Page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7
5				
6				
7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
8				
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6-8
12				
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14	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Page 9 & Fig 2
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Page 8-9
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	Page 8-9
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 8-9
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 10
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	Page 7-9
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RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9 & Fig 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Page 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 10 & Appendix table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 10 & Appendix table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Page 10-11 & Appendix table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Page 10-11 & Table 2
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Page 11 & Fig 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 11 & Fig 4
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Page 11 Table 4 Fig 4 Fig 5

1	DISCUSSION			
2	Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Page 11-12
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6	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	Page 14
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14	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15-16
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18	FUNDING			
19	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Page 16
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PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

BMJ Open

Effects of Five Types of Selenium Supplementation for Treatment of Kashin-Beck disease in children: A Systematic Review and Network Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017883.R2
Article Type:	Research
Date Submitted by the Author:	23-Nov-2017
Complete List of Authors:	Xie, Dongmei; West China Hospital, Sichuan University, Department of Geriatrics Liao, Yulin; West China Hospital, Sichuan University, Department of Geriatrics Yue, Jirong; West China Hospital, Sichuan University, Department of Geriatrics Zhang, Chao; Taihe Hospital, Hubei University of Medicine, Center for Evidence-based Medicine and Clinical Research Wang, Yanyan; West China Hospital, Sichuan University, Department of Geriatrics Deng, Chuanyao; West China Hospital, Sichuan University, Department of Geriatrics Chen, Ling; West China Hospital, Sichuan University, Department of Geriatrics
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Complementary medicine, Evidence based practice, Medical management, Nutrition and metabolism
Keywords:	Kashin-Beck disease, Selenium supplementation, Network meta-analysis, Randomized controlled trial

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6 **Network Meta-analysis**
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10 **Running title: Selenium Supplementation for Treatment of KBD**

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Abstract

Objective: To compare the effectiveness of five kinds of selenium supplementation for the treatment of patients with Kashin-Beck disease (KBD), and rank these selenium supplementation based on their performance.

Design: We searched for all publications between January 1, 1966 and March 31, 2017 using seven electronic databases. GRADE system to NMAs was applied to rate the quality of the evidence. We conducted a random effects model network meta-analysis in STATA to determine comparative effectiveness of each intervention. Rankings were obtained by using the surface under the cumulative ranking curve (SUCRA) values and mean ranks.

Results: A total of 15 randomized controlled trials involving 2931 patients were included. After assessment of the overall quality of the evidence, we downgraded our primary outcomes from high to low or very low quality. Network meta-analyses showed that all five kinds of selenium supplementation had higher metaphysis X-ray improvement which were superior to placebo. Ranking on efficacy indicated that selenium salt was ranked the highest, followed by sodium selenite + vitamin E, selenium enriched yeast, sodium selenite and then sodium selenite + vitamin C.

Conclusions: Based on the results of network meta-analysis, all five types of selenium supplements are more effective than placebo and so that selenium supplementation is of help in repairing metaphyseal lesions. Since the overall quality of the evidence was low or very low, the SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison. The quality of the evidence is insufficient to draw a conclusion about what method of selenium supplementation is most effective.

Trial registration number: CRD42016051874

Keywords: Kashin-Beck disease; Selenium supplementation; Network meta-analysis; Randomized controlled trial

Strengths of this study:

- The present NMA integrated evidence from direct and indirect comparisons.
- We comprehensively summarized all RCTs of selenium supplements for KBD.
- We applied GRADE system to NMAs based GRADE working group to rate the quality of the evidence.

Potential limitations:

- Despite our exhaustive search, only 15 RCTs conducted in China were included in this review. Some trials may have been published in local journals that were missed in our search.
- The overall quality of the evidence was low or very low.
- The SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison.

Introduction

Kashin-Beck disease (KBD) is a chronic, disabling degenerative disease of the peripheral joints and spine^{1,2}. It is present primarily among people in southeast Siberia, north Korea, and China³. KBD is prevalent in 377 counties of 14 provinces in China, with 0.64 million cases⁴. KBD occurs in childhood and involves pathologic changes of metaphysis and epiphyseal plate, resulting in multiple symptoms in the growth and the articular cartilages such as bony deformity, joints enlargement, growth retardation and functional impairment in multiple joints. The resulting disability causes an important human and social economic burden to both affected children and adults. Moreover, KBD can also cause disturbances in the cartilage metabolism, the lipid peroxidation, and sulfur and selenium metabolism^{5,6}. So far, some measures exist for treatment of KBD because of the incomplete ability of the cartilage to repair itself. Treatment strategies for symptomatic relief include non-steroidal anti-inflammatory drugs⁷, sodium hyaluronate⁸, physical therapy⁹ and chondroitin sulfate combined with glucosamine¹⁰. Successful surgical treatments to correct joint defects have been reported by orthopaedists^{11,12}.

Although the etiology of KBD is multifactorial, one of the major environmental risk factors is selenium deficiency¹³. Since the 1970s, selenium supplements have been given in some highly endemic areas. A meta-analysis including five randomized control trials (RCTs) and 10 non-RCTs demonstrated the benefits of selenium supplementation for the primary prevention of KBD in children¹⁴. Another systematic review suggested that sodium selenite (Se) was effective for the treatment of patients already affected with KBD¹⁵. Besides Se tablet, there are other selenium supplements used for treating KBD, including selenium salts (Se salt), selenium enriched yeast (Se yeast), the combination of sodium selenite with vitamin E (Se + VE), and the combination of sodium selenite with vitamin C (Se + VC). At the time of

our review, there were few head-to-head comparisons of different types of selenium supplementation for treatment of KBD. In light of the need for government policy makers and clinical care workers to know the effects of a set of alternative options, we conducted a systematic review and network meta-analysis (NMA). The aim of this systematic review and NMA was to compare the effectiveness of all types of selenium supplementation for the treatment of patients with KBD, and rank these selenium supplementation based on their performance.

Method

A protocol for this systematic review was devised in accordance with the PRISMA guidelines and registered on PROSPERO, and the trial registration number was CRD42016051874.

Search strategy

We searched, without language restrictions, for all publications between January 1, 1966 and March 31, 2017 using electronic databases, which included MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Reviews, The Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technique Journals Database, and Wan Fang database. The following MeSH words and free words were used: “Kashin-Beck disease,” “Kashin-Beck disease,” “big bone disease,” “endemic osteoarthritis,” “Urov disease” and “selenium,” “Sodium selenite,” and “Se”. The Ovid search strategy is available in Appendix box 1. Reference lists from published narrative review articles and systematic reviews were reviewed to identify additional studies.

Eligibility criteria

We included all randomized, controlled trials (RCTs) that used Se tablet and other types of selenium supplements including Se salt, Se yeast, Se + VE, as well as Se + VC for KBD

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4 patients. The control groups included placebo or no treatment controls, or other active medi-
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6 cines. The diagnostic criteria used for KBD was based on the Diagnosis Criteria for Kashin-
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8 Beck Disease (GB16003-1995), which was developed by National Health and Family Plan-
9
10 ning Commission of the People's Republic of China¹⁶. We excluded the following studies: (1)
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12 studies with small sample sizes (numbers of patients less than 20 in each treatment group);
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14 (2) preventive studies; (3) studies without available information of interest. Studies reporting
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16 mixed groups of participants (e.g., participants with and without KBD) were included only if
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18 the therapeutic effect data could be identified and extracted separately. Outcome of interest to
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20 this review was the repair rate of metaphyseal lesions on X-ray film. Typically, repair was
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22 defined as being cured basically or improved significantly of metaphyseal lesions according
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24 to the latest judgment standard of X-ray for treatment effect of KBD¹⁷.

25 26 27 28 ***Data extraction and quality evaluation***

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30 Two authors (Y. L & D. X) independently screened all citations identified by the searches.
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32 Full-text articles of potential studies were obtained and assessed according to the aforemen-
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34 tioned inclusion criteria. The data extraction form included publication (first author, year of
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36 publication), demographics (sample size and age), interventions (dosage, route of administra-
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38 tion, and duration of treatment), the follow-up period, as well as outcomes. We extracted data
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40 to the nearest 12 months to estimate the overall odds ratio (OR) because all the included
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42 RCTs report this time point. Two reviewers independently evaluated the methodological qual-
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44 ity of individual study according the Cochrane risk-of-bias tool¹⁸. In our review, we applied
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46 the GRADE system to our NMA based on the GRADE working group¹⁹. The methods of rat-
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48 ing the quality of direct comparison are the same for GRADE in traditional meta-analysis.
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50 We downgraded the evidence from “high quality” by one level for serious (or by two for very
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52 serious) study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision
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4 of effect estimates or potential publication bias. The rating of the quality of the indirect esti-
5 mates is based on the ratings of the two pair-wise estimates that contributes to the indirect
6 estimate of the comparison of interest. The lower confidence rating of the two direct compar-
7 isons constitutes the confidence rating of the indirect comparison. When both direct and indi-
8 rect evidence are available, we used the higher of the two quality ratings as the quality rating
9 for the NMA estimate. In addition, we needed to consider the intransitivity among different
10 groups and the inconsistency between direct comparison and indirect comparison. Further-
11 more, we used the GRADE profiler to help us create "Summary of findings" tables, and re-
12 ported outcomes in this tables. Any disagreements would be resolved by consulting a third
13 author (J.Y).

24 ***Statistical analysis***

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28 As the repair rate of metaphyseal lesions on X-ray film, the outcome of interest in this
29 text, was a discontinuous statistics, we calculated the OR and its 95% confidence intervals
30 (CI) as the effect estimates. Initially, we performed standard pair-wise meta-analyses for all
31 available direct comparisons using a random effects model in STATA. Statistical heterogenei-
32 ty of treatment effects across studies was assessed by the Cochrane Q test, and the extent of
33 between-study heterogeneity was quantified by I^2 , of which with a value greater than 50%
34 indicates substantial heterogeneity. Then we conducted a random effects model network me-
35 ta-analysis in STATA to determine comparative effectiveness of each intervention by using
36 the network command and self-programmed STATA routines available at
37 <http://www.mtm.uoi.gr>. We present the mean effect sizes for the network estimates (OR)
38 along with their 95% confidence intervals (CI) and prediction intervals (PrI). The PrI shows
39 the predicted parameter around estimated treatment effects in the future study.

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43 To evaluate consistency in the entire network, we used the 'design-by-treatment' model,
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4 which was described by Higgins and colleagues, by using the network meta command in
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6 STATA. This method accounts for different source of inconsistency that can occur when stud-
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8 ies with different designs (two-arm trials vs. three-arm trials) give different results as well as
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10 disagreement between direct and indirect evidence. We inferred about the presence of incon-
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12 sistency from any source in the entire network based on a chi-squared test, and a P value
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14 greater than 0.05 indicated that the direct and indirect comparisons in the network were con-
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16 sistent.
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19 We also estimated the ranking probabilities for all treatments of being at each possible
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21 rank. Rankings were obtained by using the surface under the cumulative ranking curve (SU-
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23 CRA) values and mean ranks. SUCRA could be expressed as a percentage interpreted as the
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25 percentage of effectiveness of a treatment that would be ranked first without uncertainty. To
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27 derive these SUCRA values we used the ranking probabilities estimated from the mvmeta
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29 command.
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31 32 **Results**

33 34 *Study inclusion and characteristics*

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36 Initial searches yielded 1686 citations. Of these, 1645 duplicate or irrelevant records were
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38 excluded and full-text articles of the remaining 41 studies were retrieved for further assess-
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40 ment according to the inclusion criteria. A total of 15 studies²⁰⁻³⁴ containing 2931 patient were
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42 included eventually in our meta-analysis (Fig 1). We excluded 26 trials for the reasons docu-
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44 mented in the Characteristics of excluded studies table (Appendix Table 1).
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48 A total of seven interventions were evaluated: Se, Se salt, Se yeast, Se + VE, Se + VC, VC,
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50 and placebo. Figure 2 shows the network of all treatment comparisons included in this re-
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52 view. The age of participants range from 2 to 16 years old and the duration of follow-up var-
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54 ied from 6 months to 36 months. The main characteristics of the included studies were simi-
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lar, and the characteristics (e.g. interventions dosage, route of administration, duration of treatment, the follow-up period, and outcomes) are presented in the online supplementary Appendix Table 2.

Overall assessment for evidence quality

All included trials were reported to be RCTs. The quality of included studies was overall low. Study quality for each study can be seen in Appendix Table 3. We downgraded this outcome from high to low or very low quality for possible bias, inconsistency, or imprecision. Overall assessment for evidence quality was seen in Table 1.

Table 1 Quality ratings for comparison of different interventions

Comparison	Quality of direct evidence	Quality of indirect evidence	Quality of network meta-analysis evidence
Se vs. placebo	Low*,†	Low*,#	Low*,†
Se salt vs. placebo	Low*,†	Low*,#,	Low*,†
Se+VC vs. placebo	Moderate*	Low*,#	Moderate*
Se+VE vs. placebo	Very low*,†,‡	Low*,#	Low*,#
Se yeast vs. placebo	Moderate*	Low*,#	Moderate*
VC vs. placebo	Moderate*	Low*,#	Moderate*
Se salt vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se+VC vs. Se	Moderate*	Low*,‡	Moderate*
Se+VE vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se	Moderate*	Very low*,‡,¶	Moderate*
VC vs. Se	Moderate*	Low*,¶	Moderate*
Se+VC vs. Se salt	Low*,‡	Low*,¶	Low*,¶
Se+VE vs. Se salt	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se salt	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se salt	Low*,‡	Very low*,‡,¶	Low*,¶
Se+VE vs. Se+VC	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se+VC	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se+VC	Moderate*	Very low*,‡,¶	Moderate*
Se yeast vs. Se+VE	—	Very low*,‡,¶	Very low*,‡,¶

VC vs. Se+VE	—	Very low*,‡,¶,¶	Very low*,‡,¶,¶
VC vs. Se yeast	—	Very low*,‡,¶,¶	Very low*,‡,¶,¶

*Limitations (risk of bias). †Inconsistency. ‡Imprecision. #Inconsistency for indirect evidence: prediction intervals for treatment effect include effects that would have different interpretations. ¶Indirectness: no convincing evidence for the plausibility of the transitivity assumption. Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Intervention-control pair-wise meta-analyses

All RCTs reported repair rate of metaphyseal lesions on X-ray films. Follow-up duration of included RCTs were varied. We extracted data to the nearest 12 months to estimate the overall OR. When compared to placebo, the pooled OR (random effects model) of X-ray improvement was in favor of Se (OR 5.0, 95% CI: 3.21 - 7.78, $P < 0.001$, $I^2 = 70\%$), Se salt (OR 7.6, 95% CI: 2.34 - 24.67, $P = 0.001$), Se enriched yeast (OR 3.75, 95% CI: 1.76 - 8.02, $P = 0.001$), and Se + VE (OR 11.05, 95% CI: 2.61 - 46.80, $P = 0.03$, $I^2 = 60\%$) respectively, which indicated that repairing rate of metaphyseal lesions on X-ray films was significantly higher for these drugs than placebo. Summary of findings for each selenium supplements compare to placebo was seen in Table 2. A few RCTs reported direct comparisons among active interventions. There were two RCTs compared Se with VC, the pooled OR of two RCTs also showed no significant difference existed (OR 1.15, 95% CI: 0.51 - 2.63, $P=0.93$, $I^2 = 0\%$)^{23, 33}. There was only one RCT for Se vs. Se yeast²⁶, Se vs. Se +VC³¹, Se salt vs. Se + VC³¹, Se salt vs. VC³¹, respectively. OR of X-ray improvement was significantly higher in Se salt group compared with Se + VC (OR 6.00, 95% CI: 1.81 - 19.93, $P=0.003$) and VC alone (OR 4.24, 95% CI: 1.39 - 12.90, $P=0.011$). There were no significant differences noted in other active interventions comparisons (See Table 3). The data of repair rate for metaphyseal lesions were listed in appendix Table 4.

Table 2 Summary of findings

Patient or population: Treatment of Kashin-Beck disease in children					
Outcomes: Improvement of metaphyseal lesions on X-ray					
Intervention: See list Comparison: placebo					
Intervention/Comparison:	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Repair rate with placebo	Repair rate with Se			
	42 per 100	79 per 100 (701 to 850)	OR 5.00 (3.21 to 7.78)	2427 (11 RCTs)	⊕⊕○○ LOW ^{a,b}
Se salt compared to placebo	35 per 1,00	80 per 100 (552 to 928)	OR 7.60 (2.34 to 24.67)	59 (1 RCT)	⊕⊕○○ LOW ^{a,c}
Se+VC compared to placebo	35 per 100	40 per 100 (181 to 668)	OR 1.27 (0.42 to 3.83)	54 (1 RCT)	⊕⊕⊕○ MODERATE ^a
Se+VE compared to placebo	45 per 100	90 per 100 (682 to 975)	OR 11.05 (2.61 to 46.80)	145 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}
Se yeast compared to placebo	38 per 100	70 per 100 (522 to 833)	OR 3.75 (1.76 to 8.02)	120 (1 RCT)	⊕⊕⊕○ MODERATE ^a
VC compared to placebo	34 per 100	51 per 100 (334 to 681)	OR 2.02 (0.98 to 4.17)	124 (2 RCTs)	⊕⊕⊕○ MODERATE ^a

***The repair rate in the intervention group** (and its 95% confidence interval) is based on the assumed rate in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Limitations (risk of bias): no studies described adequate methods regarding the sequence of randomization and reported allocation concealment. Some studies did not use of a blinding method and ITT analysis.

b. Inconsistency: small sample size or have a higher I², or both.

c. Imprecision: the effects are large but the overall sample size are low.

Table 3 Results of pair-wise and network meta-analyses of repairing rate of metaphyseal lesions on X-ray films

OR (95%CI) #	Placebo	Se	Se salt	Se + VC	Se + VE	Se yeast
Se	4.68 (2.99 to 7.34)* 5.00 (3.21 to 7.78)	-	-	-	-	-
Se salt	12.37 (2.81 to 54.41)* 7.60 (2.34 to 24.67)	2.64 (0.59 to 11.84)	-	-	-	-
Se + VC	3.26 (1.14 to 9.28)* 1.27 (0.42 to 3.83)	0.70 (0.25 to 1.97) 1.30 (0.57 to 2.94)	0.26 (0.06 to 1.20) 0.17 (0.05 to 0.55)	-	-	-
Se + VE	10.72 (3.14 to 36.57)* 11.05 (2.61 to 46.80)	2.29 (0.62 to 8.43)	0.87 (0.13 to 5.93)	3.29 (0.65 to 16.53)	-	-
Se yeast	5.81 (1.70 to 19.89)* 3.75 (1.76 to 8.02)	1.24 (0.36 to 4.25) 1.92 (0.90 to 4.00)	0.47 (0.07 to 3.16)	1.78 (0.37 to 8.66)	0.54 (0.10 to 3.08)	-
VC	3.05 (1.29 to 7.20)* 2.02 (0.98 to 4.17)	0.65 (0.28 to 1.53) 0.95 (0.51 to 1.79)	0.25 (0.06 to 1.06) 0.24 (0.08 to 0.72)	0.94 (0.34 to 2.56) 0.87 (0.38 to 1.96)	0.28 (0.06 to 1.27)	0.52(0.12 to 2.27)

ORs represent odds of repair in row-treatment versus column-treatment. ORs larger than 1 denote higher repair rate in row-treatment than column-treatment. In each cell, the first line represents the result of network meta-analyses, and the second row represents the result of pair-wise meta-analyses. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Results of network meta-analyses and consistency test

The pooled OR and 95% CI of X-ray improvement for active treatment compared with placebo was 4.68 (2.99 to 7.34) for Se, 12.37 (2.81 to 54.41) for Se salt, 5.81 (1.70 to 19.89) for Se enriched yeast, 10.72 (3.14 to 36.57) for Se + VE, and 3.26 (1.14 to 9.28) for Se + VC respectively, which indicated a significant difference in efficacy. For the comparison between active treatments, no significant differences were found. More details were presented in Table 3. In Figure 3, we presented the OR for the network estimates along with 95% CI and PrI.

There was no inconsistency between direct and indirect evidences according to the design-by-treatment interaction model ($P=0.88$), implying that direct and indirect evidence were mainly consistent (Fig 4). However, the results of the comparison of Se + VC and VC versus placebo showed some degree of inconsistency. Actually, the lower CI for X-ray improvement were nearly equal to 1 (1.13 for Se + VC and 1.27 for VC), showing a trend to coincide with direct results.

Table 4 displayed the distribution of probabilities for each treatment being ranked for their efficacy in KBD according the SUCRA values (Fig 5) and mean ranks.

Table 4 Probabilistic ranking of effectiveness of different interventions

Interventions	Probabilistic ranking		
	SUCRA (%)	Pr Best (%)	Mean Rank
Se salt	86	49.1	1.8
Se+VE	82.8	38.5	2
Se yeast	62.5	11.6	3.3
Se	52.5	0.2	3.9
Se+VC	35.7	0.4	4.9
VC	30.1	0.2	5.2
Placebo	0.5	0	7

SUCRA=surface under cumulative ranking, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Se salt was ranked the most effective followed by Se+VE, Se-yeast, Se and then Se + VC. VC and placebo as a control was ranked the least effective.

Discussion

Principal findings

Our network meta-analysis of all 15 available RCTs in 2931 patients with KBD showed that all five kinds of selenium supplementation (including Se, Se salt, Se enriched yeast, Se + VE, Se + VC) were superior to placebo/no treatment in repairing metaphyseal lesions. There was uncertainty around the difference between two active treatments. However, the probabilistic ranking of interventions showed that Se salt was ranked the most effective, followed by Se + VE, Se enriched yeast, Se and then Se + VC.

Relation to other studies

Studies have proposed that selenium deficiency is the underlying factor that predisposes the target cells (chondrocytes) to oxidative stress from free-radical carriers³⁵. In most highly endemic area, the level of total soil selenium concentrations is typically low. A meta-analysis of the correlation between selenium and KBD reported that selenium levels in water, soil, cereal, and corn in endemic regions were lower than regions without high rates of KBD³⁶. Furthermore, most of the inhabitants living in areas with KBD have a low selenium nutritive status, which is reflected by low selenium contents in their blood serum, red blood cell, urine, and hair.

The effectiveness of various methods of selenium supplementation for children has been demonstrated by many studies including Se salt³⁷, Se enriched yeast²⁶, oral sodium selenite tablet¹⁵, spraying Se on crops³⁸, and Se enriched fertilizer³⁹. Selenium supplementation was associated with a simultaneous decrease in the prevalence of KBD, along with an increased selenium content in the hair of inhabitants living in areas with KBD. It was reported that the

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4 incidence of radiographic evidence of metaphysical lesions of the hands was 44.8% in 1990
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6 at Cuimu town of the Shaanxi province in children aged 7~12 years. After implementation of
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8 comprehensive prevention measures of KBD, especially using Se salt, the incidence these x-
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10 ray findings decreased to 0.3% in 2010⁴⁰. The low incidence of KBD also may explain why
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12 there has not been any studies about Se treatment for KBD published in recent years.
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15 Se salt was produced by adding 0.833 g of sodium selenite powder into every 50 kg of
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17 source salt and then expanding it to 1:60,000 Se salt. Although administration of Se tablet is
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19 effective for preventing and treating KBD in children^{14,15}, it is very difficult for millions of
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21 children living in endemic areas to adhere to a long-term medication. However, salt is a nec-
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23 essary part of daily life and food intake. The compliance can be more effectively guaranteed.
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25 A limitation to the findings about Se salt is that due to the difficulty of carrying out a RCT
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27 comparing Se salt with placebo or other active drugs, only one RCT has been done³¹. Howev-
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29 er, one meta-analysis involving 11 non-RCTs (2652 participants) also showed that supple-
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31 ment Se salt was effective for preventing and treatment for KBD in Children³⁷. Since Se salt
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33 is the most economical way for low-income families, it is anticipated that continuous use of
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35 Se salt and other comprehensive prevention measures may help to eliminate the KBD carti-
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37 lage damages in Children⁴¹.
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41 Despite the evidence in our meta-analysis, there remains some controversy around sele-
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43 nium supplementation in relationship with iodine deficiency. In a cross sectional study in Ti-
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45 bet area, Moreno-Reyes and his colleges found no association between individual selenium
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47 status and KBD, whereas iodine deficiency was a risk factor⁴². Similarly, the only RCT³²
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49 published in English in our review showed only 1 case of improvements in X-ray in sodium
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51 selenite group. The negative findings of the above studies should, however, be interpreted
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53 with caution. These studies were all conducted in Tibet where selenium and iodine are both
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4 deficient in the diet. Selenium and iodine deficiency are both risk factors of KBD³⁵. In animal
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6 experiments, growth retardation was observed in rats fed with a low selenium diet⁴³, and im-
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8 paired bone development was observed with an iodine deficient diet⁴⁴. We do not exclude the
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10 possibility that selenium supplementation may not counterbalance the negative effects of
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12 long-term iodine deficiency. So KBD seems unlikely to be due to only one cause. Other ge-
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14 netic and environmental factors may confer either a relatively protective effect or accelerate
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16 the disease.
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18 19 ***Limitations of the trials included in this review*** 20

21 Overall, the methodological quality of the included trails was low. The method of ran-
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23 domization and allocation concealment were not described in all the included trials. Double-
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25 blinding was reported in 8 trials and details of the blinding methods were reported in 3 trials.
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27 Withdrawal rates of participants were less than 20% in 8 trails. Only Six trials performed in-
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29 tention to treat analysis.
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32 After assessment of the overall quality of the evidence, we downgraded our primary
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34 outcomes from high to low or very low quality, because of the high risk of bias due to unclear
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36 sequence generation and allocation concealment. In addition, we also found in some trials
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38 that there were very small sample sizes and higher levels of statistical heterogeneity, which
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40 caused serious inconsistency between the included trials.
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43 ***Strengths and weaknesses*** 44

45 The present NMA integrated evidence from direct and indirect comparisons. The litera-
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47 ture search strategy was extensive, which makes it unlikely that we missed any relevant trial.
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49 Trial selection and data extraction including quality assessments were done independently by
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51 two authors to minimize bias and transcription errors. In this NMA, we applied the GRADE
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53 system to NMAs based on the GRADE working group to rate the quality of the evidence.
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Potential limitations to this review exist. Firstly, the sample sizes of our included RCTs were all small. Sample size calculations were not mentioned in any of the studies. Secondly, despite our exhaustive search, only 15 RCTs conducted in China were included in this review. North Korea and Russia also have a high incidence of KBD; some trials may have been published in local journals that were missed in our search. Finally, the heterogeneity in this meta-analysis was somewhat high, which could be explained by a lack of concealment of allocation, failure to perform an ITT analysis, small sample sizes of the studies included and differences between different preparations of selenium. As with heterogeneity between trials, inconsistency between direct and indirect comparisons was also near zero. Although we cannot rule out clinically relevant inconsistency, we have no indication that clinical characteristics of included patients or other trial characteristics confounded the indirect comparisons.

Conclusions

Implications for clinical practice

Based on this NMA, it appears that all types of Se supplementation were more effective than placebo for the treatment of KBD in children. Ranking on efficacy indicated that Se salt were highest, followed by Se + VE, Se enriched yeast, Se, Se + VC, VC, and placebo/no treatment. Since the overall quality of the evidence was low or very low, the SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison. The quality of the evidence is insufficient to draw a conclusion about what method of selenium supplementation is most effective. Se salt can be an economical and convenient strategy for controlling KBD in endemic areas. However, selenium overdose is toxic. Therefore, suitable dosages should be strictly controlled and content of selenium should be closely monitored in order to avoid harmful effects on health.

Implications for research

Since KBD among children has almost disappeared, we believe it unlikely that future trials will involve a RCT to demonstrate the clinically relevant benefit of any selenium supplementation for children with KBD. At present, there are no effective clinical measures to repair the cartilage damage of KBD in adults. Tissue engineering and gene therapy approaches may become the potential treatment strategy that can applied to the treatment of the KBD cartilage damages.

Contributors

Dongmei Xie and Yulin Liao conceived the review question, reviewed studies for inclusion, assessed the included studies, extracted data, completed the first draft, and edited the review. Jirong Yue and Chao Zhang analyzed the data, did the literature search, advised and coordinated the review development, performed part of the writing and editing of the review, approved the final version of the review prior to submission, and is also a guarantor. Yanyan Wang, Chuanyao Deng and Ling Chen contributed to the development of the review question, edited and provided intellectual contributions to the review.

Funding Statement: This research was funded by China National Science & Technology Pillar Program (2007BA125B04).

Conflict of interest: We declare that we have no conflicts of interest.

Role of the funding source: The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments: Dr. Joseph H. Flaherty is especially acknowledged for editorial review and language assistance.

Data sharing statement: No additional data are available.

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For peer review only

Figure Legends

Fig 1 Flow diagram of included study

Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD

The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment. Two-arm study n=11; Three-arm study n=3 (Cui 1984²³, Guo 1986²⁶, Chen 2003³³); Four-arm study n=1 (Zhou 1991³¹)
OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% prediction intervals (red extensions)

OR = Odds ratio, CI = Confidence intervals, PrI = prediction intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 4 Consistency test in the network Meta-analysis

IF= inconsistency factor, OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

The x-axis is Log OR, and the vertical line is 0. IF is the absolute inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at zero indicate no significant difference of inconsistency.

Fig 5 SUCRA for the cumulative probabilities

SUCRA=surface under cumulative ranking

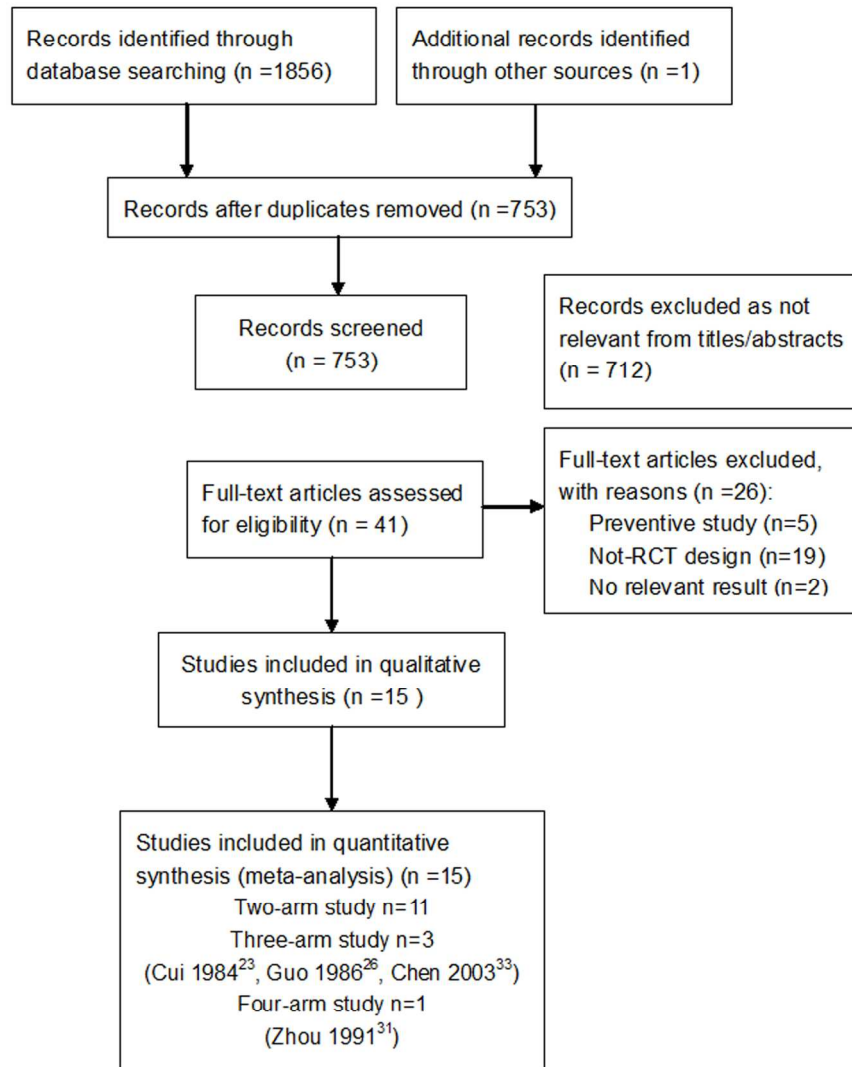


Fig 1 Flow diagram of included study

154x182mm (300 x 300 DPI)

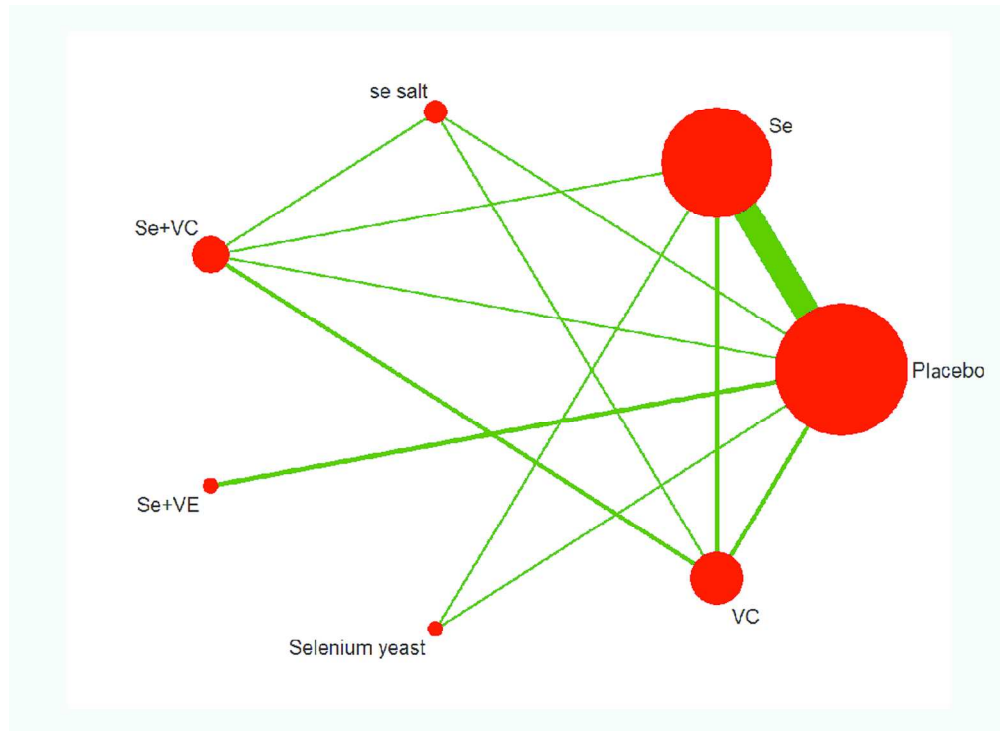


Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD. The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment. Two-arm study $n=11$; Three-arm study $n=3$ (Cui 1984, Guo 1986, Chen 2003); Four-arm study $n=1$ (Zhou 1991)_T. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

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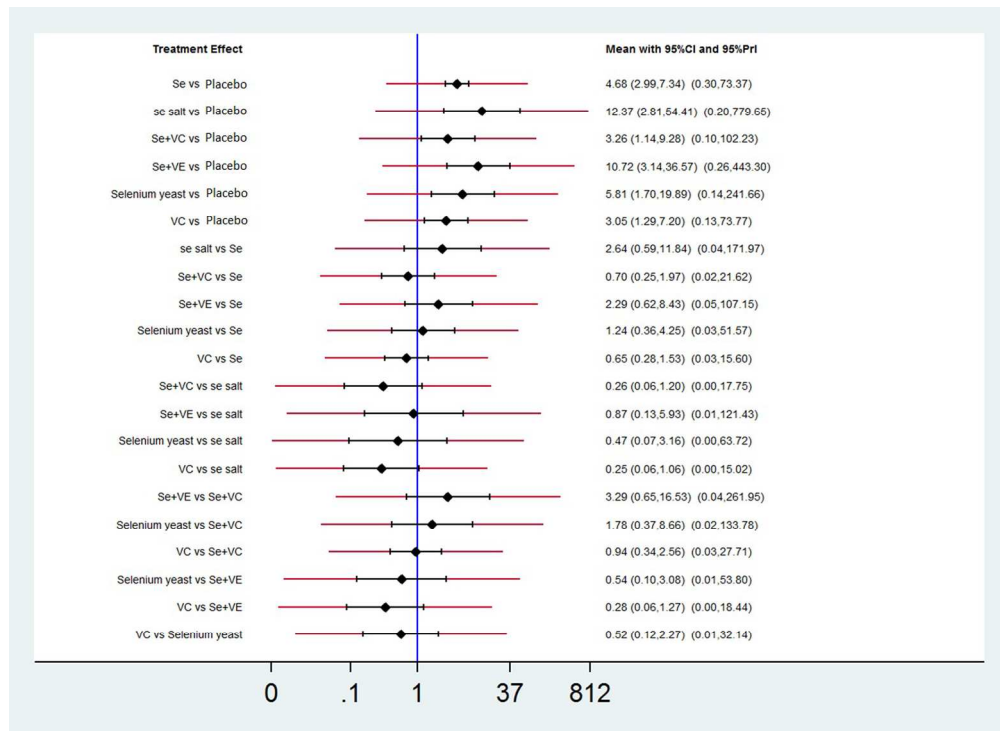


Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% prediction in-tervals (red extensions)[†]. OR = Odds ratio, CI = Confidence intervals, PrI = prediction intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.[†]

454x330mm (300 x 300 DPI)

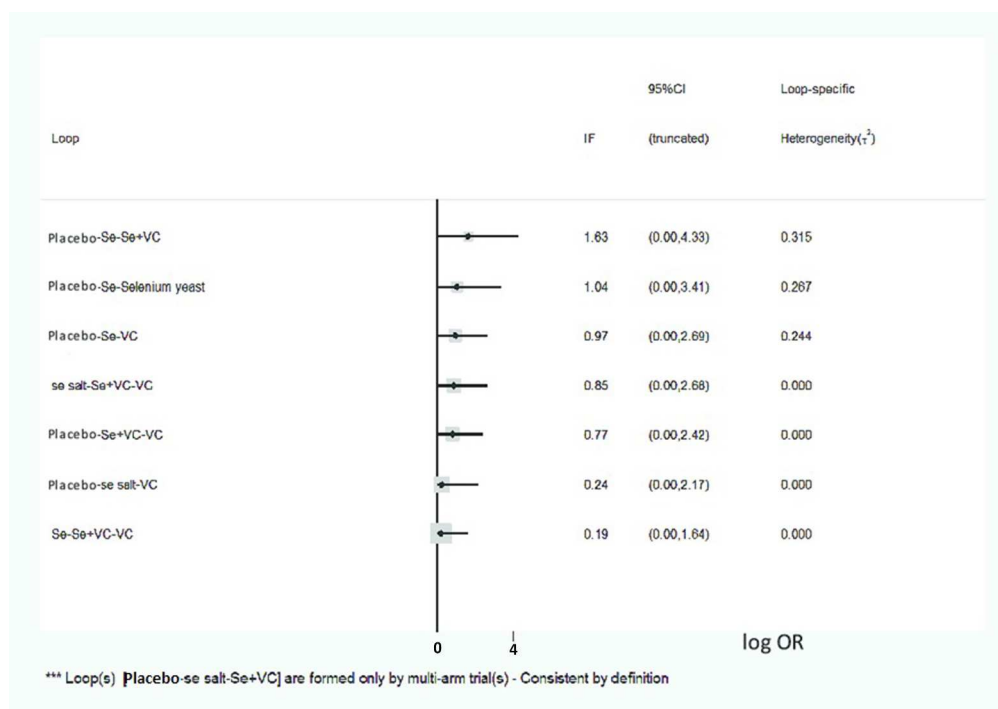


Fig 4 Consistency test in the network Meta-analysis. † IF= inconsistency factor, OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.† The x-axis is Log OR, and the vertical line is 0. IF is the absolute inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at zero indicate no significant difference of inconsistency.†

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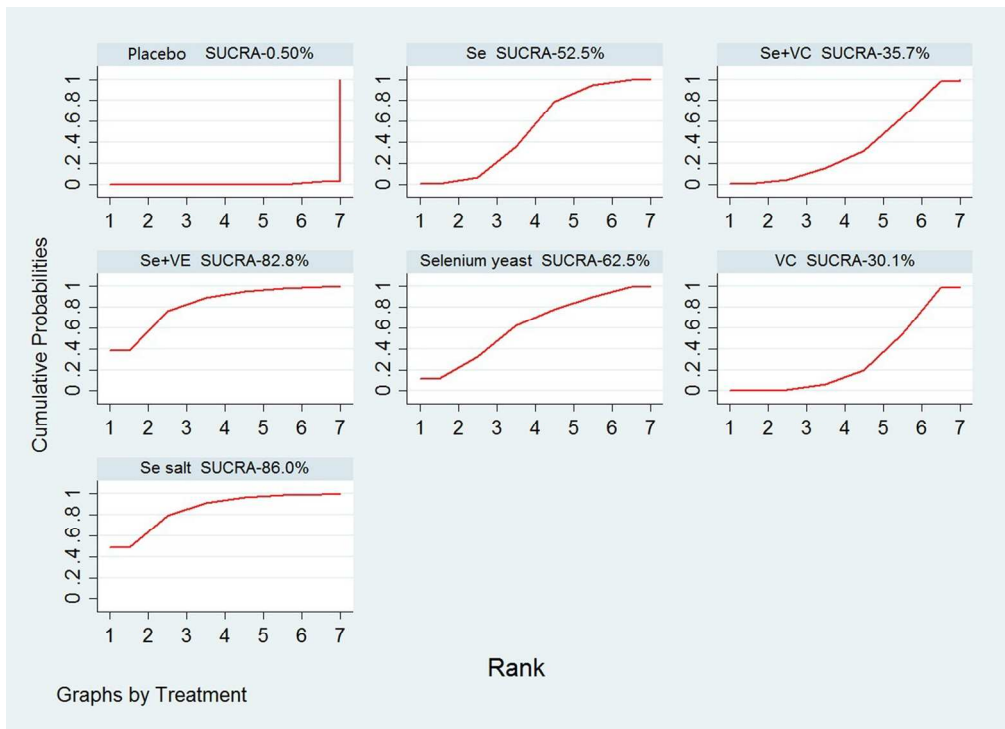


Fig 5 SUCRA for the cumulative probabilities† . SUCRA=surface under cumulative ranking†

450x328mm (300 x 300 DPI)

Pre-view only

Appendix box 1 Ovid search strategy

#1 exp kashin-beck disease/
#2 kashin-beck disease.tw.
#3 kashin-bek disease.tw.
#4 big bone disease.tw.
#5 endemic osteoarthritis.tw.
#6 Urov disease.tw.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 sodium selenite.tw.
#9 selenium .tw.
#10 Se salt.tw.
#11 enriched yeast
#12 8 or 9 or 10 or 11
#13 7 AND 12
#14 randomized controlled trial.pt.
#15 controlled clinical trial.pt.
#16 randmoized.ab.
#17 placebo.ab.
#18 randomly.ab.
#19 trial.ab.
#20 groups.ab.
#21 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 13 and 21
#23 limit #22 to human

Appendix Table 1 Characteristics of excluded studies (ordered by study ID)

Study	Reason for exclusion
Ding 1985	No relevant result
Fan 1986	Not a RCT
Guo 1990	Not a RCT
Han 2013	Not a RCT
He 1988	Not a RCT
Huang 1959	Not a RCT
Li 1986	Not a RCT
Li 2004	Preventive study
Liang 1986	Preventive study
Ma 1996	Not a RCT
Sun 2008	Not a RCT
Suolang 2008	Not a RCT
Wang 1983	Preventive study
Wang 1988	Not a RCT
Wang 1989	Preventive study
Wu 1991	Preventive study
Yang 2009	Not a RCT
Yang 2010	Not a RCT
Yi 2006	Not a RCT
Yu 2016	Not a RCT
Zhang 1989	Not a RCT
Zhang 1996	No relevant result
Zhang 2006	Not a RCT
Zhang 2009	Not a RCT
Zhong 1986	Not a RCT
Zhou 1998	Not a RCT

Appendix Table 2 Characteristics of included trials

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Niu 1981 ²⁰	27	29	6~13	6~13	Se + VE: Se tablet 2mg/week +VE 15mg/day	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
YSSG 1982 ²¹	166	159	3~13	3~13	Se tablet, 1 mg/week (3-10 yrs), 2 mg/week (11-13 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
Wang 1983 ²²	47	42	5~15	5~15	Se + VC: Se tablet 2mg/week +VE 15mg/day	No treatment	11	Improvement of metaphyseal lesions on X-ray
Cui 1984 ^{23*}	30	30/30	7~19	7~19	Se tablet, 1 mg/week (7-10 yrs), 2 mg/week (11-19 yrs)	①VC 200 mg 3 times/day; ②Placebo/week	6~12	Improvement of metaphyseal lesions on X-ray
Niu 1984 ²⁴	56	59	6~13	6~13	Se tablet first week: 1.0 mg/day (< 10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/week (< 10 yrs), 2.0 mg/week (> 11 yrs)	Placebo/week	24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films
Guo 1985 ²⁵	50	50	5~15	5~15	Se tablet, 1 mg/week (<5 yrs), 2 mg/week (>5 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Guo 1986 ^{26*}	60/60	60	5~14	5~14	①Se tablet, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs); ②Se yeast, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs);	Placebo/week	13	Improvement of metaphyseal lesions on X-ray
Niu 1986 ²⁷	285	277	6~13	6~13	Se tablet, 1 mg/week (<10 yrs), 2 mg/week (>10 yrs)	Placebo/week	12~24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films
Wu 1986 ²⁸	171	177	5~16	5~16	Se tablet, 1 mg/week (< 10 yrs), 2 mg/week (> 10 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
Deng 1988 ²⁹	43	46	2~13	2~13	Se tablet, no details	No treatment	36	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Niu 1990 ³⁰	210	228	6~13	6~13	Se tablet, first week: 0.5 mg/day (< 5 yrs), 1.0 mg/day (6-10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/month (< 5 yrs), 2.0 mg/month (6-10 yrs), 4.0 mg/month (> 11 yrs)	Placebo/month	12	Improvement of metaphyseal lesions on X-ray
Zhou 1991 ^{31#}	25/30	35/29	4~12	4~12	①Se + VC: Se tablet 1mg/10day+ VC 100mg/day; ②Se salt (sodium selenite: salt = 1:60,000) /10day	③VC, 300mg/day; ④No treatment	12	Improvement of metaphyseal lesions on X-ray
Moreno-Reyes 2003 ³²	113	95	10±0.28	10±0.3	Se tablet, 1 mg/week	Placebo/week	12	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films
Chen 2003 ^{33*}	50/50	50	6~11	6~11	①Se tablet 1mg/week; ② Se + VC: Se tablet 1mg/week+ VC 300 mg 2 times/day	VC 300mg bid	12	Improvement of metaphyseal lesions on X-ray

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Cai 2005 ³⁴	31	31	7~13	7~13	Se tablet, 2mg/10 days (7-10 yrs), 3 mg/10 days (11-13 yrs)	No treatment	18	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films

I= intervention, C = control, YSSG = Yongshou scientific survey group of Kashin-Beck Disease, yrs = years, Se = Sodium selenite, Se salt =selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast. * Three arms study, # Four arms study

Appendix Table 3 Risk of Bias of Included Studies

Study	Balanced allocation	Allocation concealment	Blinding	Completeness of outcome	Selective outcome reporting	Other Bias	overall assessment*
Niu 1981 ²⁰	Unclear	Unclear	Double-blind	Low	Low	Low	Unclear
YSSG 1982 ²¹	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear
Wang 1983 ²²	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Cui 1984 ²³	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1984 ²⁴	Unclear	Unclear	Double-blind	Low, No dropout	Low	High, no ITT analysis	High
Guo 1985 ²⁵	Unclear	Unclear	Not Used	High, dropouts >20%	Low	High, no ITT analysis	High
Guo 1986 ²⁶	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1986 ²⁷	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear

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2								
3	Wu 1986 ²⁸	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High, no ITT analysis	High
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7								
8	Deng 1988 ²⁹	Unclear	Unclear	Unclear	Low, drop out <10%	Low	High, no ITT analysis	High
9								
10								
11								
12	Niu 1990 ³⁰	Unclear	Unclear	Single-blind	Low, No dropout	Low	Low	Unclear
13								
14								
15	Zhou 1991 ³¹	Unclear	Unclear	Unclear	Low, No dropout	Low	Low	Unclear
16								
17								
18	Moreno-Reyes 2003 ³²	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High no ITT analysis	High
19								
20	Chen 2003 ³³	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
21								
22								
23								
24								
25								
26	Cai 2005 ³⁴	Unclear	Unclear	Not Used	Low, No dropout	Low	Low	Unclear
27								
28								

29 *: Overall Score: Low risk of bias = no bias detected in any domain; Unclear risk of bias = one category or more is potentially at risk of bias; High risk of bias = one
30 category or more is at high risk of bias.

31 ITT = intention to treat

Appendix Table 4 Repair rate of metaphyseal lesions of different comparisons in included studies

comparison	No. of study	No. of patients	Repair rate	
			Treatment 1 (n1/N1)	Treatment 2 (n2/N2)
Se vs. placebo	11	2427	887/1215	511/1212
Se vs. Se+VC	1	100	30/50	33/50
Se vs. Se yeast	1	120	33/60	42/60
Se vs. VC	2	160	44/80	41/80
Se salt vs. placebo	1	59	24/30	10/29
Se salt vs. Se+VC	1	55	24/30	10/25
Se salt vs. VC	1	65	24/30	17/35
Se+VC vs. placebo	2	154	43/75	32/79
Se+VC vs. VC	2	160	43/75	44/85
Se+VE vs. placebo	2	145	68/74	32/71
Se yeast vs. placebo	1	120	42/60	23/60
VC vs. placebo	2	124	33/65	20/59

1 **PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review**
 2 **Involving a Network Meta-analysis**

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Page 5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Page 6 Registration number: CRD42016051874
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	Page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6-8
12				
13				
14	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Page 9 & Fig 2
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Page 8-9
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	Page 8-9
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 8-9
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 10
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	Page 7-9
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RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9 & Fig 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Page 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 10 & Appendix table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 10 & Appendix table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Page 10-11 & Appendix table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Page 10-11 & Table 2
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Page 11 & Fig 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 11 & Fig 4
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Page 11 Table 4 Fig 4 Fig 5

DISCUSSION

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2	Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).
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6	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>
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13	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
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18	FUNDING		
19	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.
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PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

BMJ Open

Effects of Five Types of Selenium Supplementation for Treatment of Kashin-Beck disease in children: A Systematic Review and Network Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017883.R3
Article Type:	Research
Date Submitted by the Author:	19-Dec-2017
Complete List of Authors:	Xie, Dongmei; West China Hospital, Sichuan University, Department of Geriatrics Liao, Yulin; West China Hospital, Sichuan University, Department of Geriatrics Yue, Jirong; West China Hospital, Sichuan University, Department of Geriatrics Zhang, Chao; Taihe Hospital, Hubei University of Medicine, Center for Evidence-based Medicine and Clinical Research Wang, Yanyan; West China Hospital, Sichuan University, Department of Geriatrics Deng, Chuanyao; West China Hospital, Sichuan University, Department of Geriatrics Chen, Ling; West China Hospital, Sichuan University, Department of Geriatrics
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Complementary medicine, Evidence based practice, Medical management, Nutrition and metabolism
Keywords:	Kashin-Beck disease, Selenium supplementation, Network meta-analysis, Randomized controlled trial

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Manuscripts

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4 **Effects of Five Types of Selenium Supplementation for Treatment**
5 **of Kashin-Beck disease in children: A Systematic Review and**
6 **Network Meta-analysis**
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10 **Running title: Selenium Supplementation for Treatment of KBD**

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Abstract

Objective: To compare the effectiveness of five kinds of selenium supplementation for the treatment of patients with Kashin-Beck disease (KBD), and rank these selenium supplementation based on their performance.

Design: We searched for all publications between January 1, 1966 and March 31, 2017 using seven electronic databases. GRADE system to NMAs was applied to rate the quality of the evidence. We conducted a random effects model network meta-analysis in STATA to determine comparative effectiveness of each intervention. Rankings were obtained by using the surface under the cumulative ranking curve (SUCRA) values and mean ranks.

Results: A total of 15 randomized controlled trials involving 2931 patients were included. After assessment of the overall quality of the evidence, we downgraded our primary outcomes from high to low or very low quality. Network meta-analyses showed that all five kinds of selenium supplementation had higher metaphysis X-ray improvement which were superior to placebo. Ranking on efficacy indicated that selenium salt was ranked the highest, followed by sodium selenite + vitamin E, selenium enriched yeast, sodium selenite and then sodium selenite + vitamin C.

Conclusions: Based on the results of network meta-analysis, all five types of selenium supplements are more effective than placebo and so that selenium supplementation is of help in repairing metaphyseal lesions. Since the overall quality of the evidence was low or very low, the SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison. The quality of the evidence is insufficient to draw a conclusion about what method of selenium supplementation is most effective.

Trial registration number: CRD42016051874

Keywords: Kashin-Beck disease; Selenium supplementation; Network meta-analysis; Randomized controlled trial

Strengths of this study:

- The present NMA integrated evidence from direct and indirect comparisons. We applied GRADE system to NMAs based GRADE working group to rate the quality of the evidence.
- We comprehensively summarized all RCTs of selenium supplements for KBD.

Potential limitations:

- Despite our exhaustive search, only 15 RCTs conducted in China were included in this review. Some trials may have been published in local journals that were missed in our search.
- The overall quality of the evidence was low or very low. The SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison.

Introduction

Kashin-Beck disease (KBD) is a chronic, disabling degenerative disease of the peripheral joints and spine^{1,2}. It is present primarily among people in southeast Siberia, north Korea, and China³. KBD is prevalent in 377 counties of 14 provinces in China, with 0.64 million cases⁴. KBD occurs in childhood and involves pathologic changes of metaphysis and epiphyseal plate, resulting in multiple symptoms in the growth and the articular cartilages such as bony deformity, joints enlargement, growth retardation and functional impairment in multiple joints. The resulting disability causes an important human and social economic burden to both affected children and adults. Moreover, KBD can also cause disturbances in the cartilage metabolism, the lipid peroxidation, and sulfur and selenium metabolism^{5,6}. So far, some measures exist for treatment of KBD because of the incomplete ability of the cartilage to repair itself. Treatment strategies for symptomatic relief include non-steroidal anti-inflammatory drugs⁷, sodium hyaluronate⁸, physical therapy⁹ and chondroitin sulfate combined with glucosamine¹⁰. Successful surgical treatments to correct joint defects have been reported by orthopaedists^{11,12}.

Although the etiology of KBD is multifactorial, one of the major environmental risk factors is selenium deficiency¹³. Since the 1970s, selenium supplements have been given in some highly endemic areas. A meta-analysis including five randomized control trials (RCTs) and 10 non-RCTs demonstrated the benefits of selenium supplementation for the primary prevention of KBD in children¹⁴. Another systematic review suggested that sodium selenite (Se) was effective for the treatment of patients already affected with KBD¹⁵. Besides Se tablet, there are other selenium supplements used for treating KBD, including selenium salts (Se salt), selenium enriched yeast (Se yeast), the combination of sodium selenite with vitamin E (Se + VE), and the combination of sodium selenite with vitamin C (Se + VC). At the time of

our review, there were few head-to-head comparisons of different types of selenium supplementation for treatment of KBD. In light of the need for government policy makers and clinical care workers to know the effects of a set of alternative options, we conducted a systematic review and network meta-analysis (NMA). The aim of this systematic review and NMA was to compare the effectiveness of all types of selenium supplementation for the treatment of patients with KBD, and rank these selenium supplementation based on their performance.

Method

A protocol for this systematic review was devised in accordance with the PRISMA guidelines and registered on PROSPERO, and the trial registration number was CRD42016051874.

Search strategy

We searched, without language restrictions, for all publications between January 1, 1966 and March 31, 2017 using electronic databases, which included MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Reviews, The Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technique Journals Database, and Wan Fang database. The following MeSH words and free words were used: “Kashin-Beck disease,” “Kashin-Beck disease,” “big bone disease,” “endemic osteoarthritis,” “Urov disease” and “selenium,” “Sodium selenite,” and “Se”. The Ovid search strategy is available in Appendix box 1. Reference lists from published narrative review articles and systematic reviews were reviewed to identify additional studies.

Eligibility criteria

We included all randomized, controlled trials (RCTs) that used Se tablet and other types of selenium supplements including Se salt, Se yeast, Se + VE, as well as Se + VC for KBD

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4 patients. The control groups included placebo or no treatment controls, or other active medi-
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6 cines. The diagnostic criteria used for KBD was based on the Diagnosis Criteria for Kashin-
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8 Beck Disease (GB16003-1995), which was developed by National Health and Family Plan-
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10 ning Commission of the People's Republic of China¹⁶. We excluded the following studies: (1)
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12 studies with small sample sizes (numbers of patients less than 20 in each treatment group);
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14 (2) preventive studies; (3) studies without available information of interest. Studies reporting
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16 mixed groups of participants (e.g., participants with and without KBD) were included only if
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18 the therapeutic effect data could be identified and extracted separately. Outcome of interest to
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20 this review was the repair rate of metaphyseal lesions on X-ray film. Typically, repair was
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22 defined as being cured basically or improved significantly of metaphyseal lesions according
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24 to the latest judgment standard of X-ray for treatment effect of KBD¹⁷.

25 26 27 28 ***Data extraction and quality evaluation***

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30 Two authors (Y. L & D. X) independently screened all citations identified by the searches.
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32 Full-text articles of potential studies were obtained and assessed according to the aforemen-
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34 tioned inclusion criteria. The data extraction form included publication (first author, year of
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36 publication), demographics (sample size and age), interventions (dosage, route of administra-
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38 tion, and duration of treatment), the follow-up period, as well as outcomes. We extracted data
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40 to the nearest 12 months to estimate the overall odds ratio (OR) because all the included
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42 RCTs report this time point. Two reviewers independently evaluated the methodological qual-
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44 ity of individual study according the Cochrane risk-of-bias tool¹⁸. In our review, we applied
45
46 the GRADE system to our NMA based on the GRADE working group¹⁹. The methods of rat-
47
48 ing the quality of direct comparison are the same for GRADE in traditional meta-analysis.
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50 We downgraded the evidence from “high quality” by one level for serious (or by two for very
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52 serious) study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision
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4 of effect estimates or potential publication bias. The rating of the quality of the indirect esti-
5 mates is based on the ratings of the two pair-wise estimates that contributes to the indirect
6 estimate of the comparison of interest. The lower confidence rating of the two direct compar-
7 isons constitutes the confidence rating of the indirect comparison. When both direct and indi-
8 rect evidence are available, we used the higher of the two quality ratings as the quality rating
9 for the NMA estimate. In addition, we needed to consider the intransitivity among different
10 groups and the inconsistency between direct comparison and indirect comparison. Further-
11 more, we used the GRADE profiler to help us create "Summary of findings" tables, and re-
12 ported outcomes in this tables. Any disagreements would be resolved by consulting a third
13 author (J.Y).

24 ***Statistical analysis***

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26
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28 As the repair rate of metaphyseal lesions on X-ray film, the outcome of interest in this
29 text, was a discontinuous statistics, we calculated the OR and its 95% confidence intervals
30 (CI) as the effect estimates. The reason why OR were used instead of Risk Ratios (RR) was
31 following: the inferential fallacies with use of RR in indirect comparison provide scope for
32 abuse with respect to choice in framing of outcomes, and confound decision making where
33 both results are presented. The use of ORs overcomes this inferential fallacy, consistently in-
34 forming inference with respect to direction of treatment effect in indirect comparisons. Ini-
35 tially, we performed standard pair-wise meta-analyses for all available direct comparisons
36 using a random effects model in Revman 5.3. Statistical heterogeneity of treatment effects
37 across studies was assessed by the Cochrane Q test, and the extent of between-study hetero-
38 geneity was quantified by I^2 , of which with a value greater than 50% indicates substantial
39 heterogeneity. Then we conducted a random effects model network meta-analysis in STATA
40 to determine comparative effectiveness of each intervention by using the network command
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4 and self-programmed STATA routines available at <http://www.mtm.uoi.gr>. We present the
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6 mean effect sizes for the network estimates (OR) along with their 95% confidence intervals
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8 (CI) and prediction intervals (PrI). The PrI shows the predicted parameter around estimated
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10 treatment effects in the future study.

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13 To evaluate consistency in the entire network, we used the ‘design-by-treatment’ model,
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15 which was described by Higgins and colleagues, by using the network meta command in
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17 STATA. This method accounts for different source of inconsistency that can occur when stud-
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19 ies with different designs (two-arm trials vs. three-arm trials) give different results as well as
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21 disagreement between direct and indirect evidence. We inferred about the presence of incon-
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23 sistency from any source in the entire network based on a chi-squared test, and a P value
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25 greater than 0.05 indicated that the direct and indirect comparisons in the network were con-
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27 sistent.
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30 We also estimated the ranking probabilities for all treatments of being at each possible
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32 rank. Rankings were obtained by using the surface under the cumulative ranking curve (SU-
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34 CRA) values and mean ranks. SUCRA could be expressed as a percentage interpreted as the
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36 percentage of effectiveness of a treatment that would be ranked first without uncertainty. To
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38 derive these SUCRA values we used the ranking probabilities estimated from the mvmeta
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40 command.
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43 **Results**

44 ***Study inclusion and characteristics***

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47 Initial searches yielded 1686 citations. Of these, 1645 duplicate or irrelevant records were
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49 excluded and full-text articles of the remaining 41 studies were retrieved for further assess-
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51 ment according to the inclusion criteria. A total of 15 studies²⁰⁻³⁴ containing 2931 patient were
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53 included eventually in our meta-analysis (Fig 1). We excluded 26 trials for the reasons docu-
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mented in the Characteristics of excluded studies table (Appendix Table 1).

A total of seven interventions were evaluated: Se, Se salt, Se yeast, Se + VE, Se + VC, VC, and placebo. Figure 2 shows the network of all treatment comparisons included in this review. The age of participants range from 2 to 16 years old and the duration of follow-up varied from 6 months to 36 months. The main characteristics of the included studies were similar, and the characteristics (e.g. interventions dosage, route of administration, duration of treatment, the follow-up period, and outcomes) are presented in the online supplementary Appendix Table 2.

Overall assessment for evidence quality

All included trials were reported to be RCTs. The quality of included studies was overall low. Study quality for each study can be seen in Appendix Table 3. We downgraded this outcome from high to low or very low quality for possible bias, inconsistency, or imprecision. Overall assessment for evidence quality was seen in Table 1.

Table 1 Quality ratings for comparison of different interventions

Comparison	Quality of direct evidence	Quality of indirect evidence	Quality of network meta-analysis evidence
Se vs. placebo	Low*,†	Low*,#	Low*,†
Se salt vs. placebo	Low*,†	Low*,#,	Low*,†
Se+VC vs. placebo	Moderate*	Low*,#	Moderate*
Se+VE vs. placebo	Very low*,†,‡	Low*,#	Low*,#
Se yeast vs. placebo	Moderate*	Low*,#	Moderate*
VC vs. placebo	Moderate*	Low*,#	Moderate*
Se salt vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se+VC vs. Se	Moderate*	Low*,‡	Moderate*
Se+VE vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se	Moderate*	Very low*,‡,¶	Moderate*
VC vs. Se	Moderate*	Low*,¶	Moderate*
Se+VC vs. Se salt	Low*,‡	Low*,¶	Low*,¶

Se+VE vs. Se salt	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶
Se yeast vs. Se salt	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶
VC vs. Se salt	Low*,‡	Very low*,‡,¶,¶¶	Low*,¶
Se+VE vs. Se+VC	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶
Se yeast vs. Se+VC	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶
VC vs. Se+VC	Moderate*	Very low*,‡,¶,¶¶	Moderate*
Se yeast vs. Se+VE	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶
VC vs. Se+VE	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶
VC vs. Se yeast	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶

*Limitations (risk of bias). †Inconsistency. ‡Imprecision. #Inconsistency for indirect evidence: prediction intervals for treatment effect include effects that would have different interpretations. ¶Indirectness: no convincing evidence for the plausibility of the transitivity assumption. Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Intervention-control pair-wise meta-analyses

All RCTs reported repair rate of metaphyseal lesions on X-ray films. The individual study data used in the analyses were listed in appendix Table 4. Follow-up duration of included RCTs were varied. We extracted data to the nearest 12 months to estimate the overall OR. When compared to placebo, the pooled OR (random effects model) of X-ray improvement was in favor of Se (OR 5.0, 95% CI: 3.21 - 7.78, $P < 0.001$, $I^2 = 70\%$), Se salt (OR 7.6, 95% CI: 2.34 - 24.67, $P = 0.001$), Se enriched yeast (OR 3.75, 95% CI: 1.76 - 8.02, $P = 0.001$), and Se + VE (OR 11.05, 95% CI: 2.61 - 46.80, $P = 0.03$, $I^2 = 60\%$) respectively, which indicated that repairing rate of metaphyseal lesions on X-ray films was significantly higher for these drugs than placebo (See Appendix figure) . Summary of findings for each selenium supplements compare to placebo was seen in Table 2. A few RCTs reported direct comparisons among active interventions. There were two RCTs compared Se with VC, the pooled OR of two RCTs also showed no significant difference existed (OR 1.15, 95% CI: 0.51 – 2.63,

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4 P=0.93, $I^2 = 0\%$)^{23,33}. There was only one RCT for Se vs. Se yeast²⁶, Se vs. Se +VC³¹, Se salt
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6 vs. Se + VC³¹, Se salt vs. VC³¹, respectively. OR of X-ray improvement was significantly
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8 higher in Se salt group compared with Se + VC (OR 6.00, 95% CI: 1.81 - 19.93, P=0.003)
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10 and VC alone (OR 4.24, 95% CI: 1.39 - 12.90, P=0.011). There were no significant differ-
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12 ences noted in other active interventions comparisons (See Table 3).
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Table 2 Summary of findings for each intervention in comparison to placebo

Patient or population: Children with Kashin-Beck disease Outcomes: Improvement of metaphyseal lesions on X-ray Intervention: Se, Se salt, Se yeast, Se + VE, Se + VC, VC Comparison: placebo						
Intervention/ Comparison:	Anticipated absolute effects* (95% CI)		Relative effect (95% CI) (based on net- work meta- analysis)	SUCRA	No of partic- ipants (studies with direct evidence)	Quality of the evidence based on network me- ta-analysis (GRADE)
	Repair rate with placebo	Repair rate with Se				
Se salt vs. placebo	34 per 100	87 per 100 (60 to 97)	OR 12.37 (2.81 to 54.41)	86.0%	59 (1 RCT)	⊕⊕○○ LOW ^{a,c}
Se+VE vs. placebo	45 per 100	90 per 100 (72 to 97)	OR 10.72 (3.14 to 36.57)	82.8%	145 (2 RCTs)	⊕⊕○○ LOW ^{a,c}
Se yeast vs. placebo	38 per 100	78 per 100 (51 to 93)	OR 5.81 (1.70 to 19.89)	62.5%	120 (1 RCT)	⊕⊕⊕○ MODERATE ^a
Se vs. placebo	42 per 100	77 per 100 (69 to 84)	OR 4.68 (2.99 to 7.34)	52.5%	2427 (11 RCTs)	⊕⊕○○ LOW ^{a,b}
Se+VC vs. placebo	34 per 100	63 per 100 (38 to 83)	OR 3.26 (1.14 to 9.28)	35.7%	54 (1 RCT)	⊕⊕⊕○ MODERATE ^a
VC vs. place- bo	34 per 100	61 per 100 (40 to 79)	OR 3.05 (1.29 to 7.20)	30.1%	124 (2 RCTs)	⊕⊕⊕○ MODERATE ^a

*The repair rate in the intervention group (and its 95% confidence interval) is based on the assumed rate in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Limitations (risk of bias): no studies described adequate methods regarding the sequence of randomization and reported allocation concealment. Some studies did not use of a blinding method and ITT analysis.

b. Inconsistency: small sample size or have a higher I², or both.

c. Imprecision: the effects are large but the overall sample size are low.

Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ;

Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Table 3 Results of pair-wise and network meta-analyses of repairing rate of metaphyseal lesions on X-ray films

OR (95%CI) #	Placebo	Se	Se salt	Se + VC	Se + VE	Se yeast
Se	4.68 (2.99 to 7.34)* 5.00 (3.21 to 7.78)	-	-	-	-	-
Se salt	12.37 (2.81 to 54.41)* 7.60 (2.34 to 24.67)	2.64 (0.59 to 11.84)	-	-	-	-
Se + VC	3.26 (1.14 to 9.28)* 1.27 (0.42 to 3.83)	0.70 (0.25 to 1.97) 1.30 (0.57 to 2.94)	0.26 (0.06 to 1.20) 0.17 (0.05 to 0.55)	-	-	-
Se + VE	10.72 (3.14 to 36.57)* 11.05 (2.61 to 46.80)	2.29 (0.62 to 8.43)	0.87 (0.13 to 5.93)	3.29 (0.65 to 16.53)	-	-
Se yeast	5.81 (1.70 to 19.89)* 3.75 (1.76 to 8.02)	1.24 (0.36 to 4.25) 1.92 (0.90 to 4.00)	0.47 (0.07 to 3.16)	1.78 (0.37 to 8.66)	0.54 (0.10 to 3.08)	-
VC	3.05 (1.29 to 7.20)* 2.02 (0.98 to 4.17)	0.65 (0.28 to 1.53) 0.95 (0.51 to 1.79)	0.25 (0.06 to 1.06) 0.24 (0.08 to 0.72)	0.94 (0.34 to 2.56) 0.87 (0.38 to 1.96)	0.28 (0.06 to 1.27)	0.52(0.12 to 2.27)

ORs represent odds of repair in row-treatment versus column-treatment. ORs larger than 1 denote higher repair rate in row-treatment than column-treatment. In each cell, the first line represents the result of network meta-analyses, and the second row represents the result of pair-wise meta-analyses. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Results of network meta-analyses and consistency test

The pooled OR and 95% CI of X-ray improvement for active treatment compared with placebo was 4.68 (2.99 to 7.34) for Se, 12.37 (2.81 to 54.41) for Se salt, 5.81 (1.70 to 19.89) for Se enriched yeast, 10.72 (3.14 to 36.57) for Se + VE, and 3.26 (1.14 to 9.28) for Se + VC respectively, which indicated a significant difference in efficacy. For the comparison between active treatments, no significant differences were found. More details were presented in Table 3. In Figure 3, we presented the OR for the network estimates along with 95% CI and PrI.

There was no inconsistency between direct and indirect evidences according to the design-by-treatment interaction model ($P=0.88$), implying that direct and indirect evidence were mainly consistent (Fig 4). However, the results of the comparison of Se + VC and VC versus placebo showed some degree of inconsistency. Actually, the lower CI for X-ray improvement were nearly equal to 1 (1.13 for Se + VC and 1.27 for VC), showing a trend to coincide with direct results.

Table 2 and Fig 5 displayed the distribution of probabilities for each treatment being ranked for their efficacy in KBD according the SUCRA values.

Discussion

Principal findings

Our network meta-analysis of all 15 available RCTs in 2931 patients with KBD showed that all five kinds of selenium supplementation (including Se, Se salt, Se enriched yeast, Se + VE, Se + VC) were superior to placebo/no treatment in repairing metaphyseal lesions. There was uncertainty around the difference between two active treatments. However, the probabilistic ranking of interventions showed that Se salt was ranked the most effective, followed by Se + VE, Se enriched yeast, Se and then Se + VC.

Relation to other studies

Studies have proposed that selenium deficiency is the underlying factor that predisposes the target cells (chondrocytes) to oxidative stress from free-radical carriers³⁵. In most highly endemic area, the level of total soil selenium concentrations is typically low. A meta-analysis of the correlation between selenium and KBD reported that selenium levels in water, soil, cereal, and corn in endemic regions were lower than regions without high rates of KBD³⁶. Furthermore, most of the inhabitants living in areas with KBD have a low selenium nutritive status, which is reflected by low selenium contents in their blood serum, red blood cell, urine, and hair.

The effectiveness of various methods of selenium supplementation for children has been demonstrated by many studies including Se salt³⁷, Se enriched yeast²⁶, oral sodium selenite tablet¹⁵, spraying Se on crops³⁸, and Se enriched fertilizer³⁹. Selenium supplementation was associated with a simultaneous decrease in the prevalence of KBD, along with an increased selenium content in the hair of inhabitants living in areas with KBD. It was reported that the incidence of radiographic evidence of metaphysical lesions of the hands was 44.8% in 1990 at Cuimu town of the Shaanxi province in children aged 7~12 years. After implementation of comprehensive prevention measures of KBD, especially using Se salt, the incidence these x-ray findings decreased to 0.3% in 2010⁴⁰. The low incidence of KBD also may explain why there has not been any studies about Se treatment for KBD published in recent years.

Se salt was produced by adding 0.833 g of sodium selenite powder into every 50 kg of source salt and then expanding it to 1:60,000 Se salt. Although administration of Se tablet is effective for preventing and treating KBD in children^{14,15}, it is very difficult for millions of children living in endemic areas to adhere to a long-term medication. However, salt is a nec-

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4 essary part of daily life and food intake. The compliance can be more effectively guaranteed.
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6 A limitation to the findings about Se salt is that due to the difficulty of carrying out a RCT
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8 comparing Se salt with placebo or other active drugs, only one RCT has been done³¹. Howev-
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10 er, one meta-analysis involving 11 non-RCTs (2652 participants) also showed that supple-
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12 ment Se salt was effective for preventing and treatment for KBD in Children³⁷. Since Se salt
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14 is the most economical way for low-income families, it is anticipated that continuous use of
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16 Se salt and other comprehensive prevention measures may help to eliminate the KBD carti-
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18 lage damages in Children⁴¹.

21 Despite the evidence in our meta-analysis, there remains some controversy around sele-
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23 nium supplementation in relationship with iodine deficiency. In a cross sectional study in Ti-
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25 bet area, Moreno-Reyes and his colleges found no association between individual selenium
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27 status and KBD, whereas iodine deficiency was a risk factor⁴². Similarly, the only RCT³²
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29 published in English in our review showed only 1 case of improvements in X-ray in sodium
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31 selenite group. The negative findings of the above studies should, however, be interpreted
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33 with caution. These studies were all conducted in Tibet where selenium and iodine are both
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35 deficient in the diet. Selenium and iodine deficiency are both risk factors of KBD³⁵. In animal
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37 experiments, growth retardation was observed in rats fed with a low selenium diet⁴³, and im-
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39 paired bone development was observed with an iodine deficient diet⁴⁴. We do not exclude the
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41 possibility that selenium supplementation may not counterbalance the negative effects of
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43 long-term iodine deficiency. So KBD seems unlikely to be due to only one cause. Other ge-
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45 netic and environmental factors may confer either a relatively protective effect or accelerate
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47 the disease.

51 ***Limitations of the trials included in this review***

52 Overall, the methodological quality of the included trails was low. The method of ran-
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4 domization and allocation concealment were not described in all the included trials. Double-
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6 blinding was reported in 8 trials and details of the blinding methods were reported in 3 trials.
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8 Withdrawal rates of participants were less than 20% in 8 trials. Only Six trials performed in-
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10 tention to treat analysis.
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13 After assessment of the overall quality of the evidence, we downgraded our primary
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15 outcomes from high to low or very low quality, because of the high risk of bias due to unclear
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17 sequence generation and allocation concealment. In addition, we also found in some trials
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19 that there were very small sample sizes and higher levels of statistical heterogeneity, which
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21 caused serious inconsistency between the included trials.
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23 ***Strengths and weaknesses***

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25 The present NMA integrated evidence from direct and indirect comparisons. The litera-
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27 ture search strategy was extensive, which makes it unlikely that we missed any relevant trial.
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29 Trial selection and data extraction including quality assessments were done independently by
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31 two authors to minimize bias and transcription errors. In this NMA, we applied the GRADE
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33 system to NMAs based on the GRADE working group to rate the quality of the evidence.
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37 Potential limitations to this review exist. Firstly, the duration of follow-up diverse wide-
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39 ly which varied from 6 to 36 months. However, follow-up period of most studies are concen-
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41 trated in 12 months. So the data in our review were extracted to the nearest 12 months. Even
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43 so, the best beneficial duration of therapy period remains unclear for KBD. Conferring with
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45 other RCT about osteoarthritis, 36 months of therapy duration may be appropriate for observ-
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47 ing X-ray repairing changes of KBD. Secondly, the sample sizes of our included RCTs were
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49 all small. Sample size calculations were not mentioned in any of the studies. Thirdly, despite
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51 our exhaustive search, only 15 RCTs conducted in China were included in this review. North
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53 Korea and Russia also have a high incidence of KBD; some trials may have been published
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4 in local journals that were missed in our search. Finally, the heterogeneity in this meta-
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6 analysis was somewhat high, which could be explained by a lack of concealment of alloca-
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8 tion, failure to perform an ITT analysis, small sample sizes of the studies included and differ-
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10 ences between different preparations of selenium. As with heterogeneity between trials, in-
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12 consistency between direct and indirect comparisons was also near zero. Although we cannot
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14 rule out clinically relevant inconsistency, we have no indication that clinical characteristics of
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16 included patients or other trial characteristics confounded the indirect comparisons.
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19 **Conclusions**

20 *Implications for clinical practice*

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22 Based on this NMA, it appears that all types of Se supplementation were more effective
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24 than placebo for the treatment of KBD in children. Ranking on efficacy indicated that Se salt
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26 were highest, followed by Se + VE, Se enriched yeast, Se, Se + VC, VC, and placebo/no
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28 treatment. Since the overall quality of the evidence was low or very low, the SUCRA values
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30 may be misleading and should be considered jointly with the GRADE confidence in the esti-
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32 mates for each comparison. The quality of the evidence is insufficient to draw a conclusion
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34 about what method of selenium supplementation is most effective. Se salt can be an econom-
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36 ical and convenient strategy for controlling KBD in endemic areas. However, selenium over-
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38 dose is toxic. Therefore, suitable dosages should be strictly controlled and content of seleni-
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40 um should be closely monitored in order to avoid harmful effects on health.
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48 *Implications for research*

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50 Since KBD among children has almost disappeared, we believe it unlikely that future tri-
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52 als will involve a RCT to demonstrate the clinically relevant benefit of any selenium supple-
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54 mentation for children with KBD. At present, there are no effective clinical measures to re-
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4 pair the cartilage damage of KBD in adults. Tissue engineering and gene therapy approaches
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6 may become the potential treatment strategy that can applied to the treatment of the KBD car-
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8 tilage damages.
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12 13 **Contributors**

14
15 Dongmei Xie and Yulin Liao conceived the review question, reviewed studies for inclusion,
16
17 assessed the included studies, extracted data, completed the first draft, and edited the review.
18
19 Jirong Yue and Chao Zhang analyzed the data, did the literature search, advised and coordi-
20
21 nated the review development, performed part of the writing and editing of the review, ap-
22
23 proved the final version of the review prior to submission, and is also a guarantor. Yanyan
24
25 Wang, Chuanyao Deng and Ling Chen contributed to the development of the review ques-
26
27 tion, edited and provided intellectual contributions to the review.
28
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32 **Funding Statement:** This research was funded by China National Science & Technology
33
34 Pillar Program (2007BA125B04).
35

36
37 **Conflict of interest:** We declare that we have no conflicts of interest.
38

39 **Role of the funding source:** The sponsors of the study had no role in study design, data col-
40
41 lection, data analysis, data interpretation, or writing of the report. The corresponding author
42
43 had full access to all the data in the study and had final responsibility for the decision to sub-
44
45 mit for publication.
46

47 **Acknowledgments:** Dr. Joseph H. Flaherty is especially acknowledged for editorial review
48
49 and language assistance.
50

51
52 **Data sharing statement:** No additional data are available.
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55 **Reference:**
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For peer review only

Figure Legends

Fig 1 Flow diagram of included study

Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD

The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment. Two-arm study n=11; Three-arm study n=3 (Cui 1984²³, Guo 1986²⁶, Chen 2003³³); Four-arm study n=1 (Zhou 1991³¹)

OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% prediction intervals (red extensions)

OR = Odds ratio, CI = Confidence intervals, PrI = prediction intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 4 Consistency test in the network Meta-analysis

IF= inconsistency factor, OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

The x-axis is Log OR, and the vertical line is 0. IF is the absolute inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at zero indicate no significant difference of inconsistency.

Fig 5 SUCRA for the cumulative probabilities

SUCRA=surface under cumulative ranking

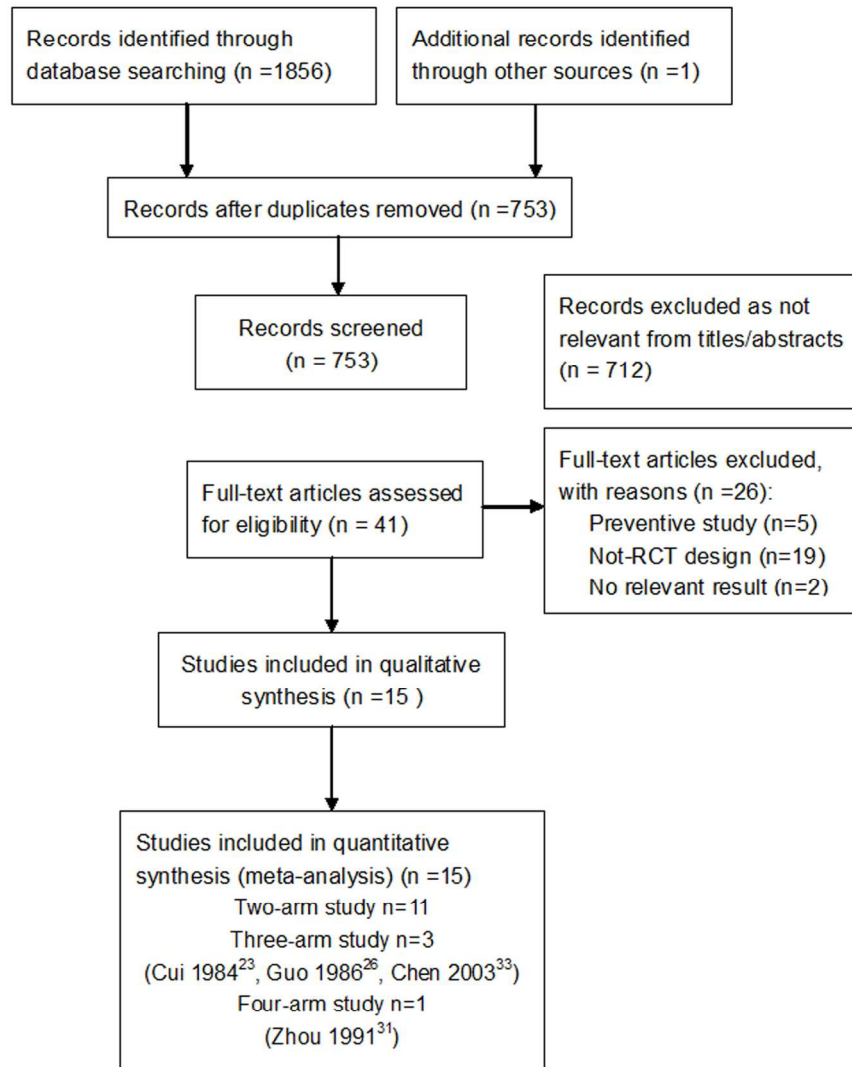


Fig 1 Flow diagram of included study

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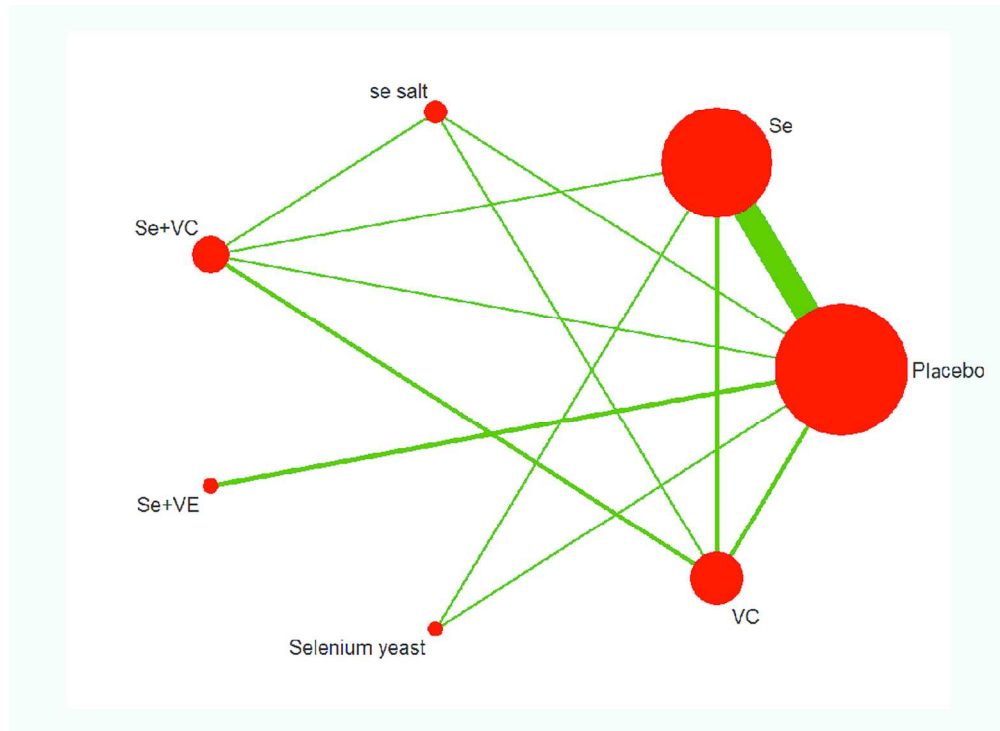


Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD. The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment. Two-arm study $n=11$; Three-arm study $n=3$ (Cui 1984, Guo 1986, Chen 2003); Four-arm study $n=1$ (Zhou 1991)_T. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

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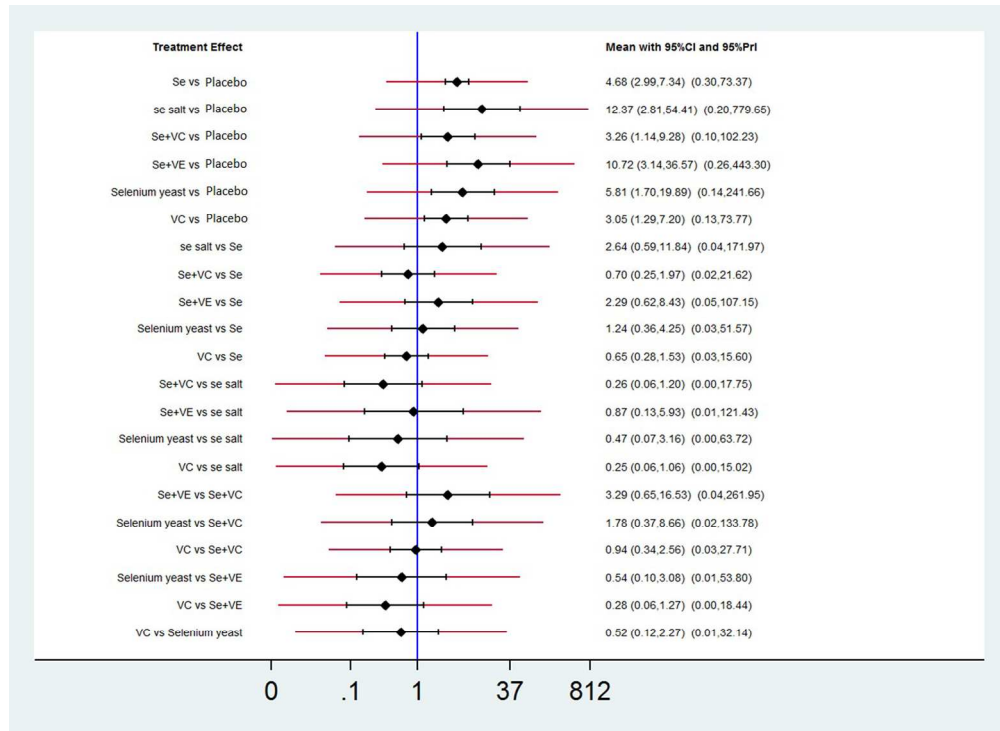
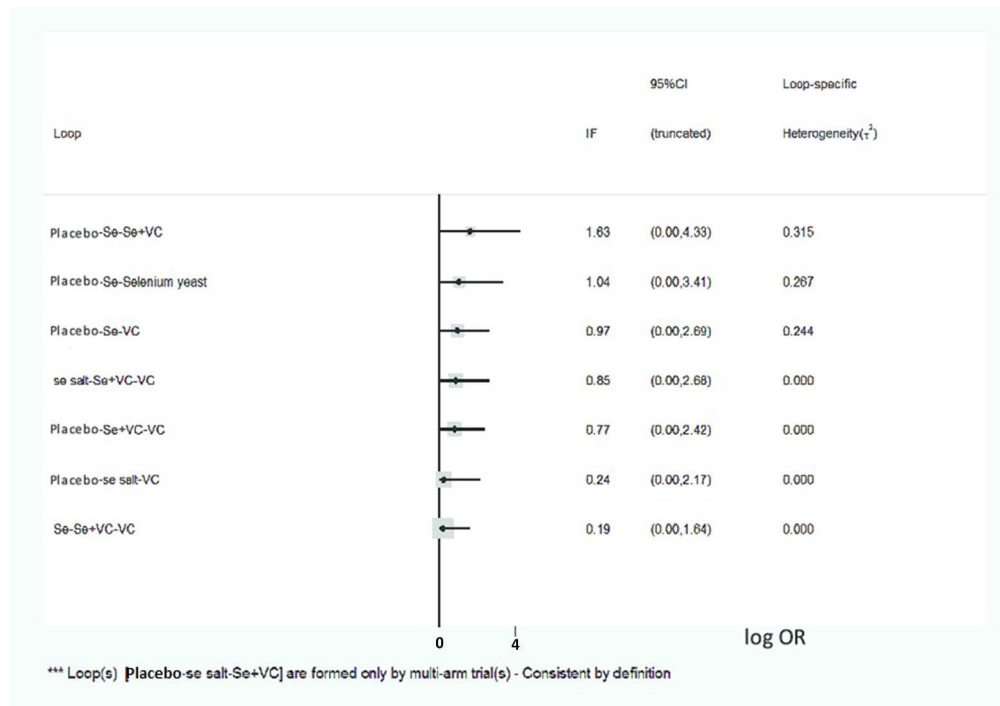


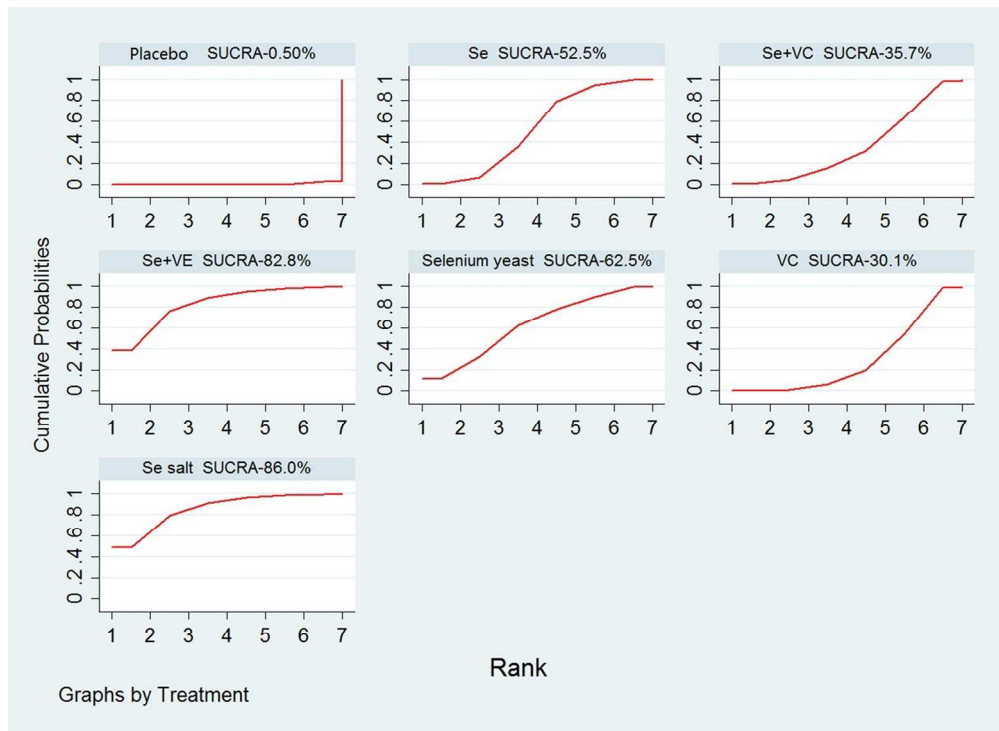
Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% prediction in-tervals (red extensions)† . OR = Odds ratio, CI = Confidence intervals, PrI = prediction intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.†

454x330mm (300 x 300 DPI)



30 Fig 4 Consistency test in the network Meta-analysis. † IF= inconsistency factor, OR = Odds ratio, CI =
 31 Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the
 32 combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin
 33 E, Se yeast = selenium enriched yeast.† The x-axis is Log OR, and the vertical line is 0. IF is the absolute
 34 inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence
 35 for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at
 36 zero indicate no significant difference of inconsistency.†

37 308x217mm (300 x 300 DPI)



450x328mm (300 x 300 DPI)

Appendix table 1 Characteristics of excluded studies(ordered by study ID)

Study	Reason for exclusion
Ding 1985	No relevant result
Fan 1986	Not a RCT
Guo 1990	Not a RCT
Han 2013	Not a RCT
He 1988	Not a RCT
Huang 1959	Not a RCT
Li 1986	Not a RCT
Li 2004	Preventive study
Liang 1986	Preventive study
Ma 1996	Not a RCT
Sun 2008	Not a RCT
Suolang 2008	Not a RCT
Wang 1983	Preventive study
Wang 1988	Not a RCT
Wang 1989	Preventive study
Wu 1991	Preventive study
Yang 2009	Not a RCT
Yang 2010	Not a RCT
Yi 2006	Not a RCT
Yu 2016	Not a RCT
Zhang 1989	Not a RCT
Zhang 1996	No relevant result
Zhang 2006	Not a RCT
Zhang 2009	Not a RCT
Zhong 1986	Not a RCT
Zhou 1998	Not a RCT

Appendix table 2 Characteristics of included trials

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Niu 1981 ²⁰	27	29	6~13	6~13	Se + VE: Se tablet 2mg/week +VE 15mg/day	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
YSSG 1982 ²¹	166	159	3~13	3~13	Se tablet, 1 mg/week (3-10 yrs), 2 mg/week (11-13 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
Wang 1983 ²²	47	42	5~15	5~15	Se + VC: Se tablet 2mg/week +VE 15mg/day	No treatment	11	Improvement of metaphyseal lesions on X-ray
Cui 1984 ^{23*}	30	30/30	7~19	7~19	Se tablet, 1 mg/week (7-10 yrs), 2 mg/week (11-19 yrs)	①VC 200 mg 3 times/day; ②Placebo/week	6~12	Improvement of metaphyseal lesions on X-ray
Niu 1984 ²⁴	56	59	6~13	6~13	Se tablet first week: 1.0 mg/day (< 10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/week (< 10 yrs), 2.0 mg/week (> 11 yrs)	Placebo/week	24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films
Guo 1985 ²⁵	50	50	5~15	5~15	Se tablet, 1 mg/week (<5 yrs), 2 mg/week (>5 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome	
	I	C	I	C					
Guo 1986 ^{26*}	60/60	60	5~14	5~14	①Se tablet, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs); ②Se yeast, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs);	Placebo/week	13	Improvement of metaphyseal lesions on X-ray	metaphyseal lesions on X-ray
Niu 1986 ²⁷	285	277	6~13	6~13	Se tablet, 1 mg/week (<10 yrs), 2 mg/week (>10 yrs)	Placebo/week	12~24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	metaphyseal lesions on X-ray
Wu 1986 ²⁸	171	177	5~16	5~16	Se tablet, 1 mg/week (< 10 yrs), 2 mg/week (> 10 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray	metaphyseal lesions on X-ray
Deng 1988 ²⁹	43	46	2~13	2~13	Se tablet, no details	No treatment	36	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	metaphyseal lesions on X-ray

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome	
	I	C	I	C					
Niu 1990 ³⁰	210	228	6~13	6~13	Se tablet, first week: 0.5 mg/day (< 5 yrs), 1.0 mg/day (6-10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/month (< 5 yrs), 2.0 mg/month (6-10 yrs), 4.0 mg/month (> 11 yrs)	Placebo/month	12	Improvement of lesions on X-ray	metaphyseal
Zhou 1991 ^{31#}	25/30	35/29	4~12	4~12	①Se + VC: Se tablet 1mg/10day+ VC 100mg/day; ②Se salt (sodium selenite: salt = 1:60,000) /10day	③VC, 300mg/day; ④No treatment	12	Improvement of lesions on X-ray	metaphyseal
Moreno-Reyes 2003 ³²	113	95	10±0.28	10±0.3	Se tablet, 1 mg/week	Placebo/week	12	Improvement of lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	metaphyseal
Chen 2003 ^{33*}	50/50	50	6~11	6~11	①Se tablet 1mg/week; ② Se + VC: Se tablet 1mg/week+ VC 300 mg 2 times/day	VC 300mg bid	12	Improvement of lesions on X-ray	metaphyseal

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Cai 2005 ³⁴	31	31	7~13	7~13	Se tablet, 2mg/10 days (7-10 yrs), 3 mg/10 days (11-13 yrs)	No treatment	18	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films

I= intervention, C = control, YSSG = Yongshou scientific survey group of Kashin-Beck Disease, yrs = years, Se = Sodium selenite, Se salt =selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast. * Three arms study, # Four arms study

Appendix table 3 Risk of Bias of Included Studies

Study	Balanced allocation	Allocation concealment	Blinding	Completeness of outcome	Selective outcome reporting	Other Bias	overall assessment*
Niu 1981 ²⁰	Unclear	Unclear	Double-blind	Low	Low	Low	Unclear
YSSG 1982 ²¹	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear
Wang 1983 ²²	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Cui 1984 ²³	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1984 ²⁴	Unclear	Unclear	Double-blind	Low, No dropout	Low	High, no ITT analysis	High
Guo 1985 ²⁵	Unclear	Unclear	Not Used	High, dropouts >20%	Low	High, no ITT analysis	High
Guo 1986 ²⁶	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1986 ²⁷	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear

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3	Wu 1986 ²⁸	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High, no ITT analysis	High
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6								
7								
8	Deng 1988 ²⁹	Unclear	Unclear	Unclear	Low, drop out <10%	Low	High, no ITT analysis	High
9								
10								
11								
12	Niu 1990 ³⁰	Unclear	Unclear	Single-blind	Low, No dropout	Low	Low	Unclear
13								
14								
15	Zhou 1991 ³¹	Unclear	Unclear	Unclear	Low, No dropout	Low	Low	Unclear
16								
17								
18	Moreno-Reyes 2003 ³²	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High no ITT analysis	High
19								
20	Chen 2003 ³³	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
21								
22								
23								
24								
25								
26	Cai 2005 ³⁴	Unclear	Unclear	Not Used	Low, No dropout	Low	Low	Unclear
27								
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29 *: Overall Score: Low risk of bias = no bias detected in any domain; Unclear risk of bias = one category or more is potentially at risk of bias; High risk of bias = one
30 category or more is at high risk of bias.

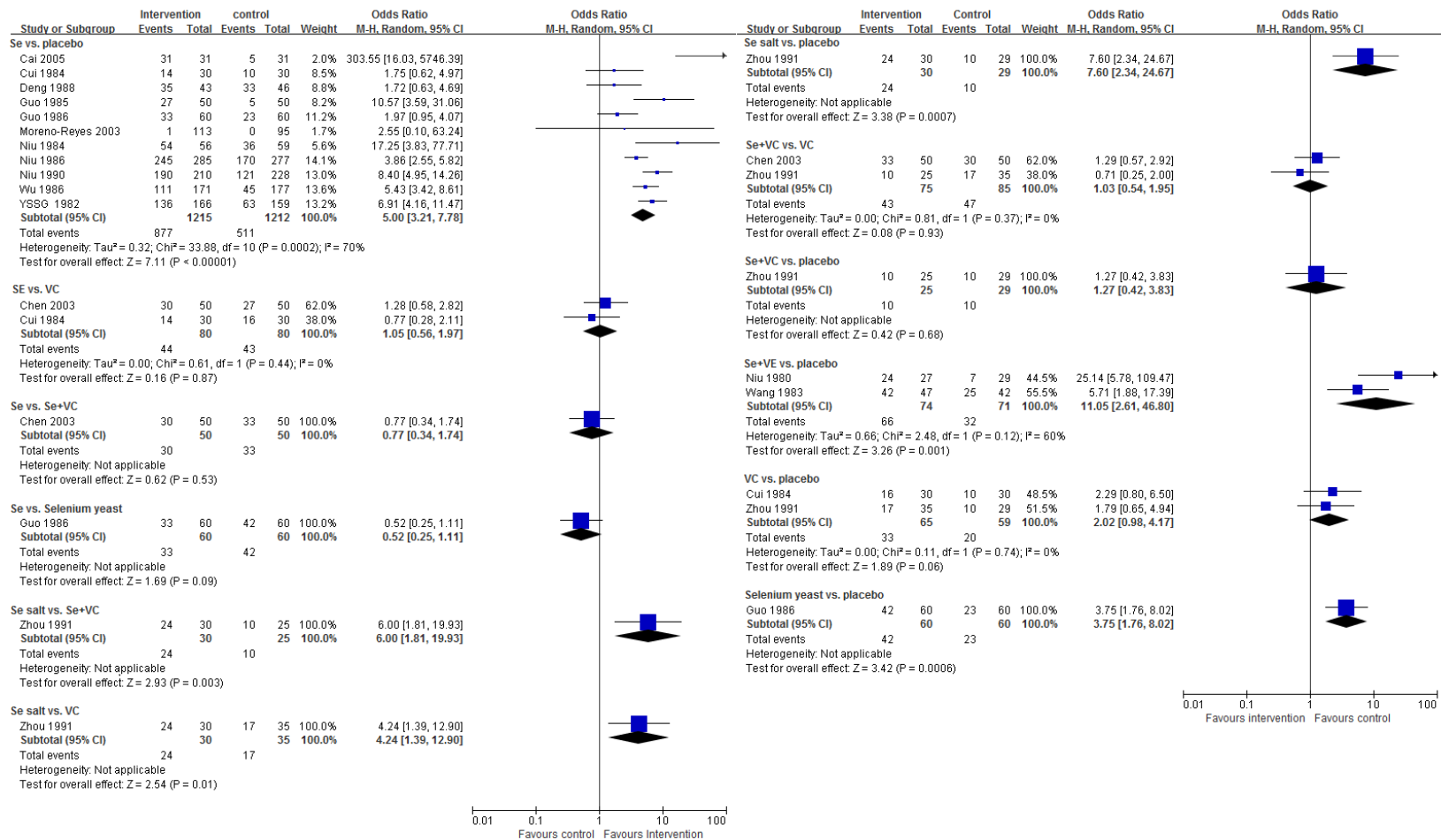
31 ITT = intention to treat

Appendix table 4 Data from included studies

Author	Treatment	Group 1		Group 2			Group 3			Group 4		
		Case No.	Total No.	Treatment	Case No.	Total No.	Treatment	Case No.	Total No.	Treatment	Case No.	Total No.
Niu 1981 ²⁰	Se +VE	24	27	Placebo	7	29						
YSSG 1982 ²¹	Se	136	166	Placebo	63	159						
Wang 1983 ²²	Se+VE	42	47	Placebo	25	42						
Cui 1984 ²³	Se	14	30	VC	16	30	Placebo	10	30			
Niu 1984 ²⁴	Se	54	56	Placebo	36	59						
Guo 1985 ²⁵	Se	27	50	Placebo	5	50						
Guo 1986 ²⁶	Se	33	60	Se yeast	42	60	Placebo	23	60			
Niu 1986 ²⁷	Se	245	285	Placebo	170	277						
Wu 1986 ²⁸	Se	111	171	Placebo	45	177						
Deng 1988 ²⁹	Se	35	43	Placebo	33	46						
Niu 1990 ³⁰	Se	190	210	Placebo	121	228						
Zhou 1991 ³¹	Se salt	24	30	VC	17	35	Se+ VC	10	25	Placebo	10	29
Moreno-Reyes 2003 ³²	Se	1	113	Placebo	0	95						
Chen 2003 ³³	Se	30	50	VC	27	50	Placebo	33	50			
Cai 2005 ³⁴	Se	31	31	Placebo	5	31						

Se = Sodium selenite, Se salt =selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

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Appendix figure: Forest plot for intervention-control pairwise meta-analyses of repairing rate of metaphyseal lesions on X-ray films.

Appendix box 1 Ovid search strategy

#1 exp kashin-beck disease/
#2 kashin-beck disease.tw.
#3 kashin-bek disease.tw.
#4 big bone disease.tw.
#5 endemic osteoarthritis.tw.
#6 Urov disease.tw.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 sodium selenite.tw.
#9 selenium .tw.
#10 Se salt.tw.
#11 enriched yeast
#12 8 or 9 or 10 or 11
#13 7 AND 12
#14 randomized controlled trial.pt.
#15 controlled clinical trial.pt.
#16 randmoized.ab.
#17 placebo.ab.
#18 randomly.ab.
#19 trial.ab.
#20 groups.ab.
#21 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 13 and 21
#23 limit #22 to human

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review
Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Page 5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Page 6 Registration number: CRD42016051874
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	Page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6-8
12				
13				
14	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Page 9 & Fig 2
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10
22				
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24				
25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Page 8-9
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	Page 8-9
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 8-9
41				
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43				
44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 10
45				
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	Page 7-9
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RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9 & Fig 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Page 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 10 & Appendix table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 10 & Appendix table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Page 10-11 & Appendix table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Page 10-11 & Table 2
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Page 11 & Fig 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 11 & Fig 4
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Page 11 Table 4 Fig 4 Fig 5

DISCUSSION

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2	Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).
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6	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>
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14	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
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18	FUNDING		
19	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.
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PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

BMJ Open

Effects of Five Types of Selenium Supplementation for Treatment of Kashin-Beck disease in children: A Systematic Review and Network Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017883.R4
Article Type:	Research
Date Submitted by the Author:	16-Jan-2018
Complete List of Authors:	Xie, Dongmei; West China Hospital, Sichuan University, Department of Geriatrics Liao, Yulin; West China Hospital, Sichuan University, Department of Geriatrics Yue, Jirong; West China Hospital, Sichuan University, Department of Geriatrics Zhang, Chao; Taihe Hospital, Hubei University of Medicine, Center for Evidence-based Medicine and Clinical Research Wang, Yanyan; West China Hospital, Sichuan University, Department of Geriatrics Deng, Chuanyao; West China Hospital, Sichuan University, Department of Geriatrics Chen, Ling; West China Hospital, Sichuan University, Department of Geriatrics
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Complementary medicine, Evidence based practice, Medical management, Nutrition and metabolism
Keywords:	Kashin-Beck disease, Selenium supplementation, Network meta-analysis, Randomized controlled trial

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5 **of Kashin-Beck disease in children: A Systematic Review and**
6 **Network Meta-analysis**
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10 **Running title: Selenium Supplementation for Treatment of KBD**

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Abstract

Objective: To compare the effectiveness of five kinds of selenium supplementation for the treatment of patients with Kashin-Beck disease (KBD), and rank these selenium supplementation based on their performance.

Design: We searched for all publications between January 1, 1966 and March 31, 2017 using seven electronic databases. GRADE system to NMAs was applied to rate the quality of the evidence. We conducted a random effects model network meta-analysis in STATA to determine comparative effectiveness of each intervention. Rankings were obtained by using the surface under the cumulative ranking curve (SUCRA) values and mean ranks.

Results: A total of 15 randomized controlled trials involving 2931 patients were included. After assessment of the overall quality of the evidence, we downgraded our primary outcomes from high to low or very low quality. Network meta-analyses showed that all five kinds of selenium supplementation had higher metaphysis X-ray improvement which were superior to placebo. Ranking on efficacy indicated that selenium salt was ranked the highest, followed by sodium selenite + vitamin E, selenium enriched yeast, sodium selenite and then sodium selenite + vitamin C.

Conclusions: Based on the results of network meta-analysis, all five types of selenium supplements are more effective than placebo and so that selenium supplementation is of help in repairing metaphyseal lesions. Since the overall quality of the evidence was low or very low, the SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison. The quality of the evidence is insufficient to draw a conclusion about what method of selenium supplementation is most effective.

Trial registration number: CRD42016051874

Keywords: Kashin-Beck disease; Selenium supplementation; Network meta-analysis; Randomized controlled trial

Strengths of this study:

- The present NMA integrated evidence from direct and indirect comparisons. We applied GRADE system to NMAs based GRADE working group to rate the quality of the evidence.
- We comprehensively summarized all RCTs of selenium supplements for KBD.

Potential limitations:

- Despite our exhaustive search, only 15 RCTs conducted in China were included in this review. Some trials may have been published in local journals that were missed in our search.
- The overall quality of the evidence was low or very low. The SUCRA values may be misleading and should be considered jointly with the GRADE confidence in the estimates for each comparison.

Introduction

Kashin-Beck disease (KBD) is an endemic, chronic, disabling degenerative disorder of peripheral joints and spine^{1,2}. It is present primarily among people in southeast Siberia, north Korea, and China³. KBD is prevalent in 377 counties of 14 provinces in China, with 0.64 million cases⁴. KBD occurs in childhood and includes alterations in the epiphyseal plate and metaphysis. This leads to a variety of complications, such as bony deformity, joints enlargement, growth retardation and functional impairment in multiple joints, which is a significant human and social economically problem for all individuals involved. Moreover, KBD can also cause disruptive cartilage metabolism, lipid peroxidation, and disturb the metabolism of selenium and sulfur^{5,6}. Because of the incomplete ability of the cartilage to repair itself, only few therapies are available to treat KBD. For example, non-steroidal anti-inflammatory drugs⁷, sodium hyaluronate⁸, physical therapy⁹, and chondroitin sulfate combined with glucosamine are an option¹⁰. Moreover, orthopaedists have demonstrated that surgery to repair joint defects is beneficial^{11,12}.

Although the etiology of KBD is multifactorial, one of the major environmental risk factors is selenium deficiency¹³. Since the 1970s, selenium was administered in several severely endemic regions. A meta-analysis study consisting of 5 randomized control trials (RCTs) as well as 10 non-RCTs demonstrated benefits of selenium administration in preventing KBD in children¹⁴. Another systematic review suggested that sodium selenite (Se) was effective for the treatment of patients already affected with KBD¹⁵. Besides Se tablet, there are other selenium supplements used for treating KBD, including selenium salts (Se salt), selenium enriched yeast (Se yeast), combining sodium selenite and vitamin E (Se + VE), as well as combining sodium selenite and vitamin C (Se + VC). At the time of our review, there were few head-to-head comparisons of different types of selenium supplement for treatment of KBD.

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4 In light of the need for government policy makers and clinical care workers to know the ef-
5
6 fects of a set of alternative options, a systematic review and network meta-analysis (NMA)
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8 was performed. This study aimed at comparing the effectiveness of administration of seleni-
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10 um in treating KBD patients, and rank these selenium supplementation based on their per-
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12 formance.
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16 17 **Method**

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19 In this study, a protocol was devised according to PRISMA guidelines. The protocol was
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21 registered on PROSPERO, and the trial registration number was CRD42016051874.
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23

24 *Search strategy*

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26 We searched all the literature from January 1, 1966 to March 31, 2017. In our study we
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28 used electronic databases, included EMBASE, MEDLINE, The Cochrane Database of Sys-
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30 tematic Reviews, The Cochrane Central Register of Controlled Trials, The Chinese Biomed-
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32 ical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technique
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34 Journals Database, and the Wan Fang database. Key words used in our search criteria includ-
35
36 ed: Kashin-Beck disease, big bone disease, Urov disease, endemic osteoarthritis, as well as:
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38 selenium, sodium selenite, and Se. Appendix box 1 presents the Ovid search strategy used.
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40 For identification of additional studies of interest, references from publications were manual-
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42 ly screened.
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45 *Eligibility criteria*

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47 We included all randomized, controlled trials (RCTs) that used Se tablet and other types
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49 of selenium supplements including Se salt, Se yeast, Se + VE, as well as Se + VC for KBD
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51 patients. The control groups included placebo or no treatment controls, or other active medi-
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53 cines. The diagnostic criteria used for KBD was based on the Diagnosis Criteria for Kashin-
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4 Beck Disease (GB16003-1995), which was developed by the National Health and Family
5
6 Planning Commission of China¹⁶. We excluded the following studies: (1) studies with small
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8 sample sizes (numbers of patients less than 20 in each treatment group); (2) preventive stud-
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10 ies; (3) studies without available information of interest. The studies in which individuals
11
12 with and without KBD were enrolled only if the therapeutic effect data could be extracted.
13
14 Outcome of interest to this review was the rate of repair of metaphyseal lesions using X-ray
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16 film. Typically, repair was defined as being cured basically or improved significantly of met-
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18 aphyseal lesions according to the latest judgment standard of X-ray for treatment effect of
19
20 KBD¹⁷.

21 22 23 ***Data extraction and quality evaluation***

24
25 Two authors (Y. L & D. X) independently screened all citations identified by the searches.
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27 Full-text articles of potential studies were obtained and assessed according to the aforemen-
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29 tioned inclusion criteria. The data extraction form included publication (first author, year of
30
31 publication), demographics (sample size and age), interventions (dose, administration route,
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33 and length of therapy), the follow-up period, as well as outcomes. To determine the overall
34
35 odds ratio (OR), data was extracted to the closest 12 months because this time point was re-
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37 ported in all included RCTs. Two reviewers independently evaluated the methodological
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39 quality of individual study according the Cochrane risk-of-bias tool¹⁸. In our review, we ap-
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41 plied the GRADE system to our NMA based on the GRADE working group¹⁹. The methods
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43 of rating the quality of direct comparison are the same for GRADE in traditional meta-
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45 analysis. Evidence was downgraded by one level from “high quality” for significant (or by
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47 two levels for very significant), study limitations (risk of bias), indirect of evidence, incon-
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49 consistency, imprecision of effects, or potential bias in publication. The rating of quality of indi-
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51 rect estimates was based on the ratings of the two pair-wise estimates that contributes to the
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4 indirect estimate of the comparison of interest. The lower rating score of direct comparisons
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6 comprise the confidence score of indirect comparison. When direct and indirect evidence
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8 were available, the highest score was used as a quality score for NMA assessment¹⁹. In addi-
9
10 tion, we needed to consider the intransitivity among different groups and the inconsistency
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12 between direct comparison and indirect comparison. Furthermore, we used the GRADE pro-
13
14 filer to help us create "Summary of findings" tables. In case of a discrepancy, an additional
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16 experienced rater was consulted (J.Y).

17 18 19 ***Statistical analysis***

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21 As the repair rate of metaphyseal lesions on X-ray film, the outcome of interest in this
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23 text, was a discontinuous statistics, we calculated the OR and its 95% confidence intervals
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25 (CI) as the effect estimates. The reason why OR were used instead of Risk Ratios (RR) was
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27 as follows: the inferential fallacies by using RR in indirect comparison offers the possibility
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29 for abuse regarding choice when outlining outcomes and confound the decision making pro-
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31 cess in which both data sets are shown. ORs can overcome this misconception, and dependa-
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33 bly interprets regarding treatment effect direction in indirect comparisons²⁰. Initially, we per-
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35 formed standard pair-wise meta-analyses for all available direct comparisons using a random
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37 effects model in Revman 5.3. Statistical heterogeneity of treatment effects across studies was
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39 assessed by the Cochrane Q test, and the extent of between-study heterogeneity was quanti-
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41 fied by I^2 , of which with a value >50% indicates significant heterogeneity. Then, to estimate
42
43 the efficiency of each intervention, a random effects model NMA was performed in STATA
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45 by conducting a network command and self-programmed STATA, which can be found at
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47 <http://www.mtm.uoi.gr>. We present the mean effect sizes for the network estimates (OR)
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49 along with their 95% confidence intervals (CI) and prediction intervals (PrI). The PrI shows
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51 the predicted parameter around estimated treatment effects in the future study.
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4 To evaluate consistency within a network, a 'design-by-treatment' model was used, as per-
5 formed by Higgins et al., by using the network meta command in STATA. This approach ac-
6 counted for several causes of inconsistency, which may have occurred when studies with dif-
7 ferent designs (two-arm trials vs. three-arm trials) give different results as well as disagree-
8 ment between direct and indirect evidence²¹. In this study, the chi-square test was used to de-
9 termine any inconsistency within the network, and $P > 0.05$ indicated that the direct and indi-
10 rect comparisons within the network were consistent.
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19 We also estimated the ranking probabilities for all treatment methods at each possible rank.
20 Rankings were obtained by the surface under the cumulative ranking curve (SUCRA) values
21 as well as mean ranks. SUCRA could be presented as a percentage of effectiveness of a
22 treatment method that would be ranked first without hesitation. To derive these SUCRA val-
23 ues we used the ranking probabilities estimated from the mvmeta command.
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30 **Results**

31 *Study inclusion and characteristics*

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33 Initial searches yielded 1686 citations. Of these, 1645 duplicate or irrelevant records were
34 excluded and full-text articles of the remaining 41 studies were retrieved for further assess-
35 ment according to the inclusion criteria. A total of 15 studies²²⁻³⁶ containing 2931 patient were
36 included eventually in our meta-analysis (Fig 1). We excluded 26 trials for the reasons docu-
37 mented in the Characteristics of excluded studies table (Appendix Table 1).
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45 A total of seven interventions were evaluated: Se, Se salt, Se yeast, Se + VE, Se + VC, VC,
46 and placebo. Figure 2 shows the network of all treatment comparisons included in this review.
47 The age of participants range from 2 to 16 years old and the duration of follow-up varied
48 from 6 months to 36 months. The main characteristics of the included studies were similar,
49 and the characteristics (e.g. interventions dosage, route of administration, duration of treat-
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ment, the follow-up period, and outcomes) are presented in the online supplementary Appendix Table 2.

Overall assessment for evidence quality

All included trials were reported to be RCTs. The quality of included studies was overall low. Study quality for each study can be seen in Appendix Table 3. We downgraded this outcome from high to low or very low quality for possible bias, inconsistency, or imprecision. Overall assessment for evidence quality was seen in Table 1.

Table 1 Quality ratings for comparison of different interventions

Comparison	Quality of direct evidence	Quality of indirect evidence	Quality of network meta-analysis evidence
Se vs. placebo	Low*,†	Low*,#	Low*,†
Se salt vs. placebo	Low*,†	Low*,#,	Low*,†
Se+VC vs. placebo	Moderate*	Low*,#	Moderate*
Se+VE vs. placebo	Very low*,†,‡	Low*,#	Low*,#
Se yeast vs. placebo	Moderate*	Low*,#	Moderate*
VC vs. placebo	Moderate*	Low*,#	Moderate*
Se salt vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se+VC vs. Se	Moderate*	Low*,‡	Moderate*
Se+VE vs. Se	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se	Moderate*	Very low*,‡,¶	Moderate*
VC vs. Se	Moderate*	Low*,¶	Moderate*
Se+VC vs. Se salt	Low*,‡	Low*,¶	Low*,¶
Se+VE vs. Se salt	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se salt	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se salt	Low*,‡	Very low*,‡,¶	Low*,¶
Se+VE vs. Se+VC	—	Very low*,‡,¶	Very low*,‡,¶
Se yeast vs. Se+VC	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se+VC	Moderate*	Very low*,‡,¶	Moderate*
Se yeast vs. Se+VE	—	Very low*,‡,¶	Very low*,‡,¶
VC vs. Se+VE	—	Very low*,‡,¶	Very low*,‡,¶

VC vs. Se yeast	—	Very low*,‡,¶,¶¶	Very low*,‡,¶,¶¶
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*Limitations (risk of bias). †Inconsistency. ‡Imprecision. #Inconsistency for indirect evidence: prediction intervals for treatment effect include effects that would have different interpretations. ¶Indirectness: no convincing evidence for the plausibility of the transitivity assumption.

Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Intervention-control pair-wise meta-analyses

All RCTs reported repair rate of metaphyseal lesions on X-ray films. The individual study data used in the analyses were listed in appendix Table 4. Follow-up duration of included RCTs were varied. We extracted data to the nearest 12 months to estimate the overall OR. When compared to placebo, the pooled OR (random effects model) of X-ray improvement was in favor of Se (OR 5.0, 95% CI: 3.21 - 7.78, $P < 0.001$, $I^2 = 70\%$), Se salt (OR 7.6, 95% CI: 2.34 - 24.67, $P = 0.001$), Se enriched yeast (OR 3.75, 95% CI: 1.76 - 8.02, $P = 0.001$), and Se + VE (OR 11.05, 95% CI: 2.61 - 46.80, $P = 0.03$, $I^2 = 60\%$) respectively, which indicated that repairing rate of metaphyseal lesions on X-ray films was significantly higher for these drugs than placebo (See Appendix figure) . Summary of findings for each selenium supplements compare to placebo was seen in Table 2. A few RCTs reported direct comparisons among active interventions. There were two RCTs compared Se with VC, the pooled OR of two RCTs also showed no significant difference existed (OR 1.15, 95% CI: 0.51 – 2.63, $P=0.93$, $I^2 = 0\%$)^{25,35}. There was only one RCT for Se vs. Se yeast²⁸, Se vs. Se +VC³³, Se salt vs. Se + VC³³, Se salt vs. VC³³, respectively. OR of X-ray improvement was significantly higher in Se salt group compared with Se + VC (OR 6.00, 95% CI: 1.81 - 19.93, $P=0.003$) and VC alone (OR 4.24, 95% CI: 1.39 - 12.90, $P=0.011$). There were no significant differences noted in other active interventions comparisons (See Table 3).

Table 2 Summary of findings for each intervention in comparison to placebo

Patient or population: Children with Kashin-Beck disease Outcomes: Improvement of metaphyseal lesions on X-ray Intervention: Se, Se salt, Se yeast, Se + VE, Se + VC, VC Comparison: placebo						
Intervention/ Comparison:	Anticipated absolute effects* (95% CI)		Relative effect (95% CI) (based on net- work meta- analysis)	SUCRA	No of partic- ipants (studies with direct evidence)	Quality of the evidence based on network me- ta-analysis (GRADE)
	Repair rate with placebo	Repair rate with Se				
Se salt vs. placebo	34 per 100	87 per 100 (60 to 97)	OR 12.37 (2.81 to 54.41)	86.0%	59 (1 RCT)	⊕⊕○○ LOW ^{a,c}
Se+VE vs. placebo	45 per 100	90 per 100 (72 to 97)	OR 10.72 (3.14 to 36.57)	82.8%	145 (2 RCTs)	⊕⊕○○ LOW ^{a,c}
Se yeast vs. placebo	38 per 100	78 per 100 (51 to 93)	OR 5.81 (1.70 to 19.89)	62.5%	120 (1 RCT)	⊕⊕⊕○ MODERATE ^a
Se vs. placebo	42 per 100	77 per 100 (69 to 84)	OR 4.68 (2.99 to 7.34)	52.5%	2427 (11 RCTs)	⊕⊕○○ LOW ^{a,b}
Se+VC vs. placebo	34 per 100	63 per 100 (38 to 83)	OR 3.26 (1.14 to 9.28)	35.7%	54 (1 RCT)	⊕⊕⊕○ MODERATE ^a
VC vs. place- bo	34 per 100	61 per 100 (40 to 79)	OR 3.05 (1.29 to 7.20)	30.1%	124 (2 RCTs)	⊕⊕⊕○ MODERATE ^a

*The repair rate in the intervention group (and its 95% confidence interval) is based on the assumed rate in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Limitations (risk of bias): no studies described adequate methods regarding the sequence of randomization and reported allocation concealment. Some studies did not use of a blinding method and ITT analysis.

b. Inconsistency: small sample size or have a higher I², or both.

c. Imprecision: the effects are large but the overall sample size are low.

Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ;

Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Table 3 Results of pair-wise and network meta-analyses of repairing rate of metaphyseal lesions on X-ray films

OR (95%CI) #	Placebo	Se	Se salt	Se + VC	Se + VE	Se yeast
Se	4.68 (2.99 to 7.34)* 5.00 (3.21 to 7.78)	-	-	-	-	-
Se salt	12.37 (2.81 to 54.41)* 7.60 (2.34 to 24.67)	2.64 (0.59 to 11.84)	-	-	-	-
Se + VC	3.26 (1.14 to 9.28)* 1.27 (0.42 to 3.83)	0.70 (0.25 to 1.97) 1.30 (0.57 to 2.94)	0.26 (0.06 to 1.20) 0.17 (0.05 to 0.55)	-	-	-
Se + VE	10.72 (3.14 to 36.57)* 11.05 (2.61 to 46.80)	2.29 (0.62 to 8.43)	0.87 (0.13 to 5.93)	3.29 (0.65 to 16.53)	-	-
Se yeast	5.81 (1.70 to 19.89)* 3.75 (1.76 to 8.02)	1.24 (0.36 to 4.25) 1.92 (0.90 to 4.00)	0.47 (0.07 to 3.16)	1.78 (0.37 to 8.66)	0.54 (0.10 to 3.08)	-
VC	3.05 (1.29 to 7.20)* 2.02 (0.98 to 4.17)	0.65 (0.28 to 1.53) 0.95 (0.51 to 1.79)	0.25 (0.06 to 1.06) 0.24 (0.08 to 0.72)	0.94 (0.34 to 2.56) 0.87 (0.38 to 1.96)	0.28 (0.06 to 1.27)	0.52(0.12 to 2.27)

ORs represent odds of repair in row-treatment versus column-treatment. ORs larger than 1 denote higher repair rate in row-treatment than column-treatment. In each cell, the first line represents the result of network meta-analyses, and the second row represents the result of pair-wise meta-analyses. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast

Results of network meta-analyses and consistency test

The pooled OR and 95% CI of X-ray improvement for active treatment compared with placebo was 4.68 (2.99 to 7.34) for Se, 12.37 (2.81 to 54.41) for Se salt, 5.81 (1.70 to 19.89) for Se enriched yeast, 10.72 (3.14 to 36.57) for Se + VE, and 3.26 (1.14 to 9.28) for Se + VC respectively, which indicated a significant difference in efficacy. For the comparison between active treatments, no significant differences were found. More details were presented in Table 3. In Figure 3, we presented the OR for the network estimates along with 95% CI and PrI.

There was no inconsistency between direct and indirect evidences according to the design-by-treatment interaction model ($P=0.88$), implying that direct and indirect evidence were mainly consistent (Fig 4). However, the results of the comparison of Se + VC and VC versus placebo showed some degree of inconsistency. Actually, the lower CI for X-ray improvement were nearly equal to 1 (1.13 for Se + VC and 1.27 for VC), showing a trend to coincide with direct results.

Table 2 and Fig 5 displayed the distribution of probabilities for each treatment being ranked for their efficacy in KBD according the SUCRA values.

Discussion

Principal findings

Our NMA of all 15 available RCTs in 2931 patients with KBD showed that all five kinds of selenium supplementation (including Se, Se salt, Se enriched yeast, Se + VE, Se + VC) were superior to placebo/no treatment in repairing metaphyseal lesions. There was uncertainty around the difference between two active treatments. However, the probabilistic ranking of interventions showed that Se salt was ranked the most effective, followed by Se + VE, Se enriched yeast, Se and then Se + VC.

Relation to other studies

Studies have proposed that a deficiency in selenium is key in disposing target cells, such as chondrocytes, to oxidative stress³⁷. In most highly endemic area, the level of total soil selenium concentrations is typically low. In a previous study, it was demonstrated that in endemic regions, selenium concentrations in water, soil, cereal, and corn were reduced compared to regions without high rates of KBD³⁸. Furthermore, the majority of individuals who live in areas with KBD have a low selenium nutritive status, as is indicated by the low levels of selenium in their serum, red blood cell, urine, and hair.

The effectiveness of various methods of selenium supplementation for children has been demonstrated by many studies including Se salt³⁹, Se enriched yeast²⁸, oral sodium selenite tablet¹⁷, spraying Se on crops⁴⁰, and Se enriched fertilizer⁴¹. Selenium supplementation was related to a reduced KBD prevalence, along with an increased selenium content the hair of individuals who living in areas with KBD. It was reported that the incidence of radiographic evidence of metaphysical lesions of the hands was 44.8% in 1990 at Cuimu town of the Shaanxi province in children aged 7~12 years. After implementation of comprehensive prevention measures of KBD, especially using Se salt, the incidence these x-ray findings decreased to 0.3% in 2010⁴². The low incidence of KBD also may explain why there has not been any studies about Se treatment for KBD published in recent years.

Se salt was produced as follows: a total of 0.833 g sodium selenite powder was added to 50 kg source salt and expanded to 1:60,000 of Se salt. Although administration of Se tablet is effective for prevention and treatment of KBD in children^{16,17}, it is very difficult for many children who reside in endemic areas to adhere to any type of long-term medication. However, salt is a necessary part of daily life and food intake. The compliance can be more effec-

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4 tively guaranteed. A limitation to the findings about Se salt is that due to the difficulty of car-
5 rying out a RCT comparing Se salt with placebo or other active drugs, only one RCT has
6 been done³³. However, one meta-analysis involving 11 non-RCTs (2652 participants) also
7 showed that supplement Se salt was effective for preventing and treatment for KBD in Chil-
8 dren³⁹. Since Se salt is the most economical way for low-income families, it is anticipated
9 that continuous use of Se salt and other comprehensive prevention approaches could be bene-
10 ficial in eliminating KBD cartilage damages in children⁴³.

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19 Despite the evidence in our meta-analysis, there remains some controversy around sele-
20 nium supplementation in relationship with iodine deficiency. In a previous study that was
21 performed in the Tibet area, Moreno-Reyes et al. did not find a relation between KBD ad se-
22 lenium deficiency, whereas they did identify iodine deficiency as a risk factor⁴⁴. Similarly, the
23 only RCT³⁴ published in English in our review showed only 1 case of improvements in X-ray
24 in sodium selenite group. The above studies should, however, be interpreted with caution.
25 These studies were all performed in the Tibet area where selenium and iodine are both defi-
26 cient in the diet. Moreover, both Selenium and iodine deficiency are risk factors of KBD³⁷.
27 Previous studies have shown growth retardation in rats that were fed a diet containing low
28 selenium levels⁴⁵. In addition, impaired development of the bone was demonstrated when rats
29 were fed a iodine deficient diet⁴⁶. Supplementation with selenium may not counterbalance the
30 negative effects of long-term iodine deficiency. Thus, it does not seem very likely that KBD
31 has only one cause. Additional factors (both genetic and environmental) may be a protective
32 or show disease acceleration.

33 ***Methodological quality of included trials***

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52 Overall, the methodological quality of the included trails was low. In all the included tri-
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4 double-blinding was described, whereas specifics of the methods of blinding were described
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6 in 3 trials. Withdrawal rates of participants were less than 20% in 8 trails. Only Six trials per-
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8 formed intention to treat analysis.
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10 After evaluation, we downgraded the evidence quality of primary outcomes from high to
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12 low or very low, because of the high risk of bias due to unclear sequence generation and allo-
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14 cation concealment. Moreover, we observed very small sample sizes in several trials com-
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16 bined with higher levels of heterogeneity that showed significant inconsistency between trials.
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19 ***Strengths and weaknesses***

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21 In the current NMA, evidence was integrated from both direct and indirect comparisons.
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23 The literature search strategy was extensive, and it was unlikely that relevant trials were
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25 missed. The selection of trials as well as the extraction of data and quality assessments were
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27 performed by two investigators to minimize bias and transcription errors. In this NMA, we
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29 applied the GRADE system to NMAs based on the GRADE working group to rate the quality
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31 of the evidence.
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34 Although the results are promising, this study has several limitations. First, the length of
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36 follow-up varied greatly, and varied from 6 to 36 months. However, follow-up period of most
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38 studies are concentrated in 12 months. Therefore, the data in our review were extracted to the
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40 nearest 12 months. Even so, the best beneficial duration of therapy period remains unclear for
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42 KBD. When compared with other RCTs in osteoarthritis, 36 months of therapy might be ap-
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44 propriate for detecting X-ray-related alterations of KBD. Secondly, the sample size of the
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46 RCTs included in our NMA was limited. Thirdly, despite our extensive research, we were on-
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48 ly able to include 15 RCTs in our NMA that were performed in China. Apart from China,
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50 both North Korea and Russia have a high KBD incidence, and it is likely that in our search,
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52 trials that were published in local journals may have been missed. Finally, in this study, the
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4 heterogeneity was relatively high that may be explained by a lack of allocation concealment,
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6 limited number of samples, and alterations between selenium preparations. Similar as with
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8 heterogeneity between trials, inconsistency between direct and indirect comparisons was
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10 close to zero. Clinically relevant inconsistency cannot be ruled out, therefore there is no indi-
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12 cation that clinical characteristics of enrolled subjects or additional features of the trial con-
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14 founded indirect comparisons.
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16 **Conclusions**

17 *Implications for clinical practice*

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20 Based on the current NMA, all types of Se supplementation were of higher efficiency
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22 compared to the placebo in treating KBD in children. Ranking on efficacy indicated that Se
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24 salt were highest, followed by Se + VE, Se enriched yeast, Se, Se + VC, VC, and placebo/no
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26 treatment. Since the overall assessment quality was relatively low (or very low), the SUCRA
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28 values may be misleading and should be considered jointly with the GRADE confidence in
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30 the estimates for each comparison. Evidence quality is insufficient to draw a conclusion
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32 about what method of selenium supplementation is most effective. Se salt can be an econom-
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34 ical and convenient strategy for controlling KBD in endemic areas. However, selenium over-
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36 dose is toxic. Therefore, suitable dosages should be strictly controlled and content of seleni-
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38 um should be closely monitored to prevent detrimental health-related issues.
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45 *Implications for research*

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47 Since KBD among children has almost disappeared, it is highly unlikely that upcoming
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49 trials involve RCT to demonstrate the clinically relevant benefit of any selenium supplemen-
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51 tation for children with KBD. Currently, no effective therapy exists to correct KBD-related
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53 cartilage damage in adults. Novel approaches, including gene therapy and tissue engineering
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4 may become a potential treatment strategy that can be used for treating KBD-related cartilage
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6 damages.
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10 **Contributors**

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12 Dongmei Xie and Yulin Liao conceived the review question, reviewed studies for inclusion,
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14 assessed the included studies, extracted data, completed the first draft, and edited the review.
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16 Jirong Yue and Chao Zhang analyzed the data, did the literature search, advised and coordi-
17
18 nated the review development, performed part of the writing and editing of the review, ap-
19
20 proved the final version of the review prior to submission, and is also a guarantor. Yanyan
21
22 Wang, Chuanyao Deng and Ling Chen contributed to the development of the review question,
23
24 edited and provided intellectual contributions to the review.
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30 **Funding Statement:** This research was funded by China National Science & Technology
31
32 Pillar Program (2007BA125B04).
33

34 **Conflict of interest:** We declare that we have no conflicts of interest.
35

36
37 **Role of the funding source:** The sponsors of the study had no role in study design, data col-
38
39 lection, data analysis, data interpretation, or writing of the report. The corresponding author
40
41 had full access to all the data in the study and had final responsibility for the decision to sub-
42
43 mit for publication.
44

45 **Acknowledgments:** Dr. Joseph H. Flaherty is especially acknowledged for editorial review
46
47 and language assistance.
48

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50 **Data sharing statement:** No additional data are available.
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52 **Reference:**

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For peer review only

Figure Legends

Fig 1 Flow diagram of included study

Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD

The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment. Two-arm study n=11; Three-arm study n=3 (Cui 1984²⁵, Guo 1986²⁸, Chen 2003³⁵); Four-arm study n=1 (Zhou 1991³¹)
OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% prediction intervals (red extensions)

OR = Odds ratio, CI = Confidence intervals, PrI = prediction intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

Fig 4 Consistency test in the network Meta-analysis

IF= inconsistency factor, OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

The x-axis is Log OR, and the vertical line is 0. IF is the absolute inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at zero indicate no significant difference of inconsistency.

Fig 5 SUCRA for the cumulative probabilities

SUCRA=surface under cumulative ranking

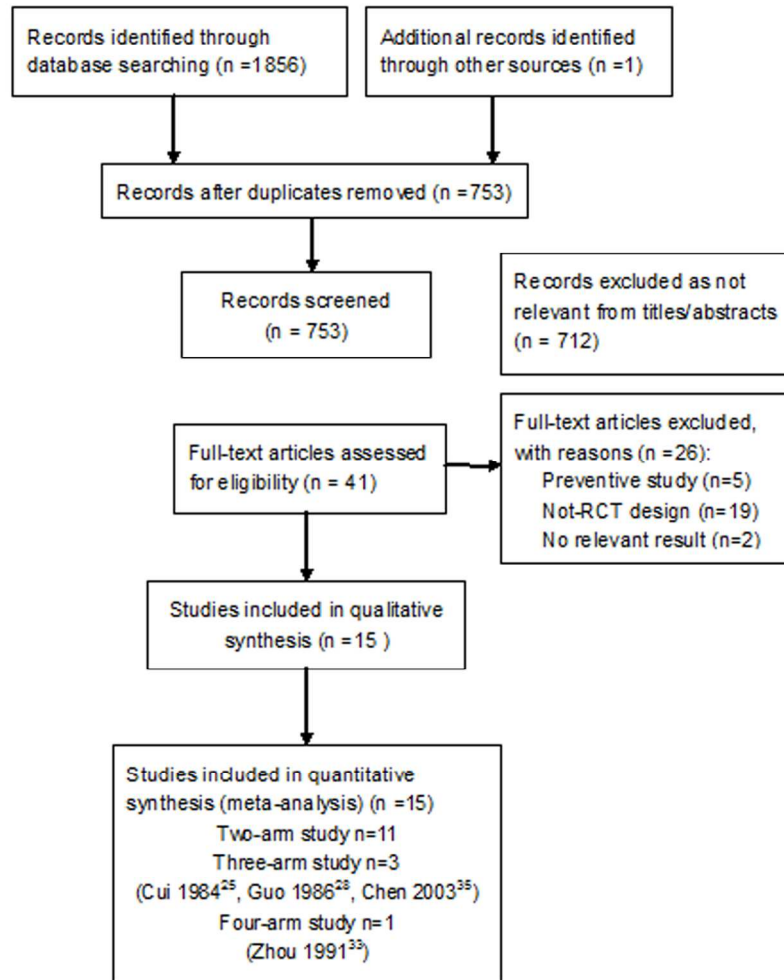


Fig 1 Flow diagram of included study

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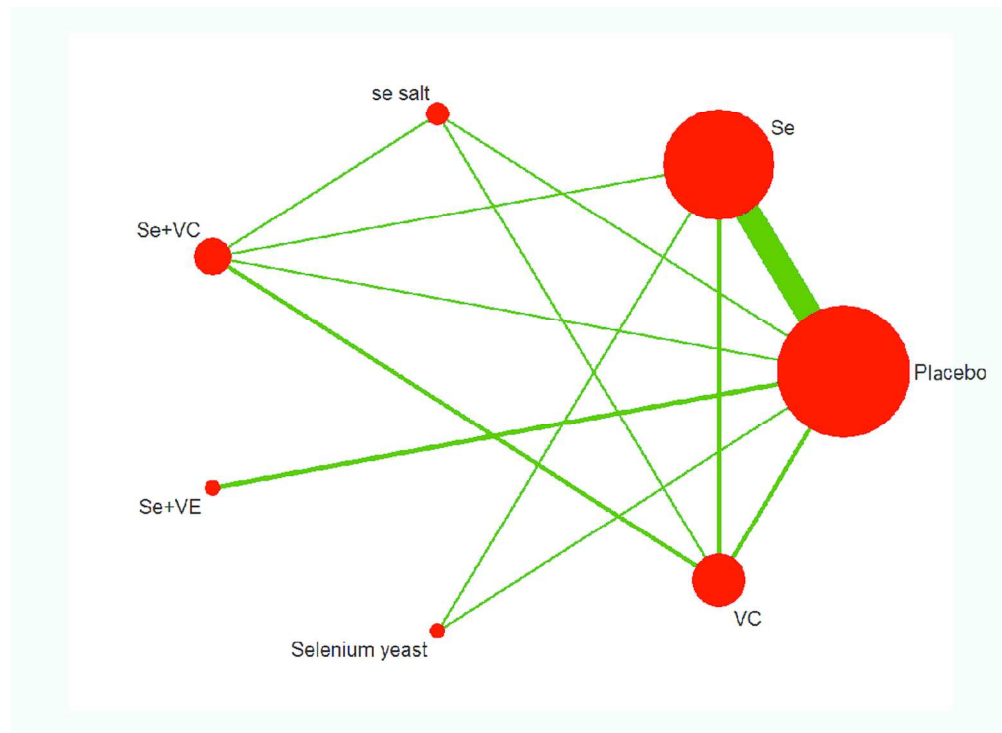


Fig 2 Network of eligible comparisons for treatment efficacy network meta-analysis for KBD. The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment. Two-arm study $n=11$; Three-arm study $n=3$ (Cui 1984, Guo 1986, Chen 2003); Four-arm study $n=1$ (Zhou 1991)_T. OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.

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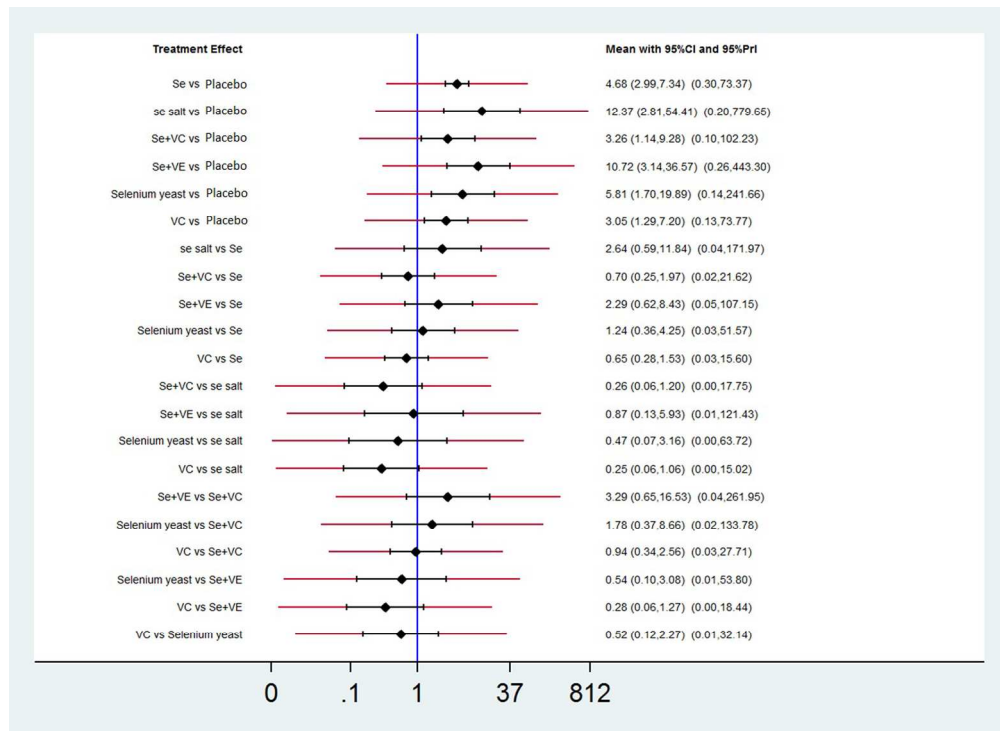


Fig 3 Network estimates of mean ORs, their 95% confidence intervals and 95% prediction in-tervals (red extensions)[†]. OR = Odds ratio, CI = Confidence intervals, PrI = prediction intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.[†]

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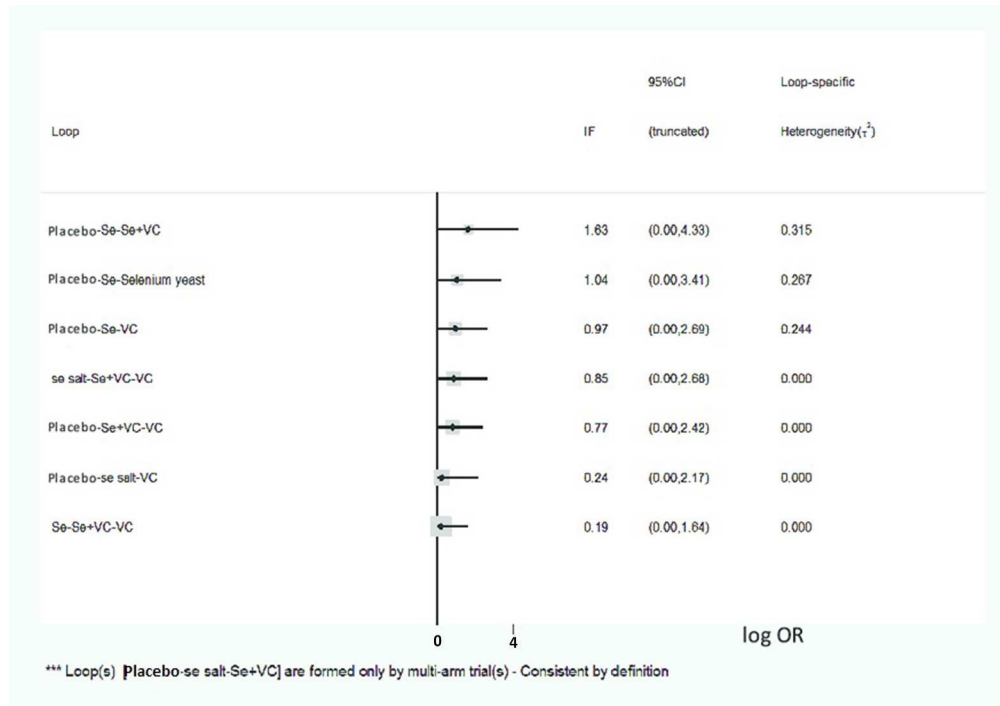


Fig 4 Consistency test in the network Meta-analysis. † IF= inconsistency factor, OR = Odds ratio, CI = Confidence intervals, Se = Sodium selenite, Se salt = selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.† The x-axis is Log OR, and the vertical line is 0. IF is the absolute inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence for each comparison loop. The absolute inconsistency factor values and confidence intervals are truncated at zero indicate no significant difference of inconsistency.†

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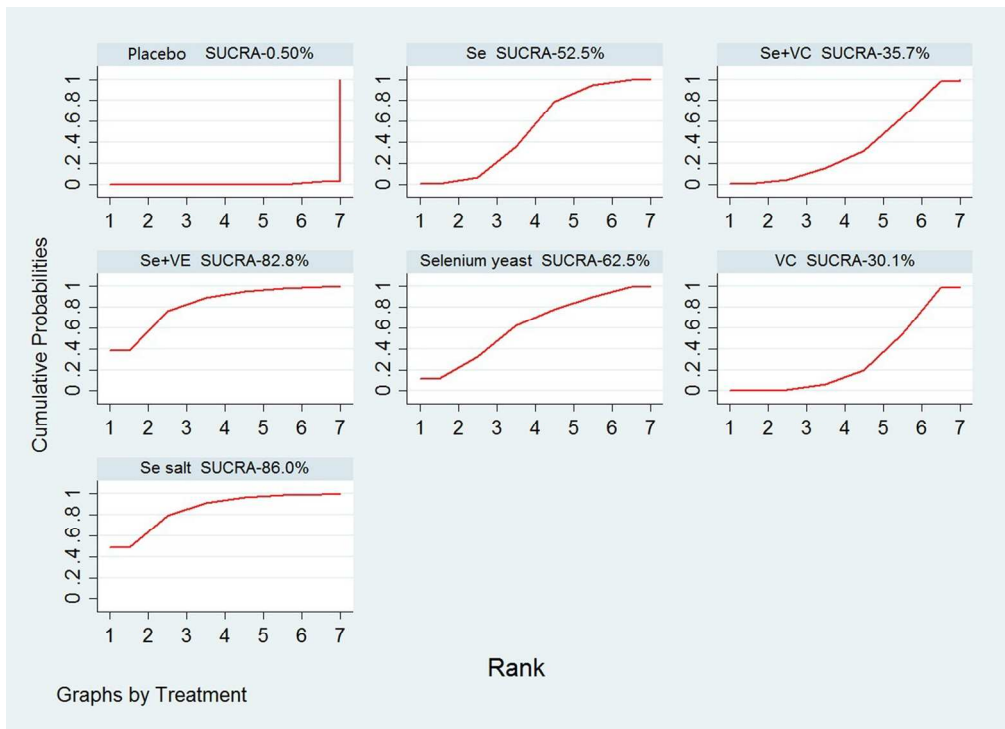


Fig 5 SUCRA for the cumulative probabilities† . SUCRA=surface under cumulative ranking†

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Pre-view only

Appendix box 1 Ovid search strategy

#1 exp kashin-beck disease/
#2 kashin-beck disease.tw.
#3 kashin-bek disease.tw.
#4 big bone disease.tw.
#5 endemic osteoarthritis.tw.
#6 Urov disease.tw.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 sodium selenite.tw.
#9 selenium .tw.
#10 Se salt.tw.
#11 enriched yeast
#12 8 or 9 or 10 or 11
#13 7 AND 12
#14 randomized controlled trial.pt.
#15 controlled clinical trial.pt.
#16 randmoized.ab.
#17 placebo.ab.
#18 randomly.ab.
#19 trial.ab.
#20 groups.ab.
#21 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 13 and 21
#23 limit #22 to human

Appendix table 1 Characteristics of excluded studies(ordered by study ID)

Study	Reason for exclusion
Ding 1985	No relevant result
Fan 1986	Not a RCT
Guo 1990	Not a RCT
Han 2013	Not a RCT
He 1988	Not a RCT
Huang 1959	Not a RCT
Li 1986	Not a RCT
Li 2004	Preventive study
Liang 1986	Preventive study
Ma 1996	Not a RCT
Sun 2008	Not a RCT
Suolang 2008	Not a RCT
Wang 1983	Preventive study
Wang 1988	Not a RCT
Wang 1989	Preventive study
Wu 1991	Preventive study
Yang 2009	Not a RCT
Yang 2010	Not a RCT
Yi 2006	Not a RCT
Yu 2016	Not a RCT
Zhang 1989	Not a RCT
Zhang 1996	No relevant result
Zhang 2006	Not a RCT
Zhang 2009	Not a RCT
Zhong 1986	Not a RCT
Zhou 1998	Not a RCT

Appendix table 2 Characteristics of included trials

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Niu 1981 ²²	27	29	6~13	6~13	Se + VE: Se tablet 2mg/week +VE 15mg/day	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
YSSG 1982 ²³	166	159	3~13	3~13	Se tablet, 1 mg/week (3-10 yrs), 2 mg/week (11-13 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray
Wang 1983 ²⁴	47	42	5~15	5~15	Se + VC: Se tablet 2mg/week +VE 15mg/day	No treatment	11	Improvement of metaphyseal lesions on X-ray
Cui 1984 ^{25*}	30	30/30	7~19	7~19	Se tablet, 1 mg/week (7-10 yrs), 2 mg/week (11-19 yrs)	①VC 200 mg 3 times/day; ②Placebo/week	6~12	Improvement of metaphyseal lesions on X-ray
Niu 1984 ²⁶	56	59	6~13	6~13	Se tablet first week: 1.0 mg/day (< 10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/week (< 10 yrs), 2.0 mg/week (> 11 yrs)	Placebo/week	24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films
Guo 1985 ²⁷	50	50	5~15	5~15	Se tablet, 1 mg/week (<5 yrs), 2 mg/week (>5 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray

Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome	
	I	C	I	C					
Guo 1986 ^{28*}	60/60	60	5~14	5~14	①Se tablet, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs); ②Se yeast, 0.5mg/week (<7 yrs), 1 mg/week (>8 yrs);	Placebo/week	13	Improvement of metaphyseal lesions on X-ray	
Niu 1986 ²⁹	285	277	6~13	6~13	Se tablet, 1 mg/week (<10 yrs), 2 mg/week (>10 yrs)	Placebo/week	12~24	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	
Wu 1986 ³⁰	171	177	5~16	5~16	Se tablet, 1 mg/week (< 10 yrs), 2 mg/week (> 10 yrs)	Placebo/week	12	Improvement of metaphyseal lesions on X-ray	
Deng 1988 ³¹	43	46	2~13	2~13	Se tablet, no details	No treatment	36	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome	
	I	C	I	C					
Niu 1990 ³²	210	228	6~13	6~13	Se tablet, first week: 0.5 mg/day (< 5 yrs), 1.0 mg/day (6-10 yrs), 2.0 mg/day (> 11 yrs); after: 1.0 mg/month (< 5 yrs), 2.0 mg/month (6-10 yrs), 4.0 mg/month (> 11 yrs)	Placebo/month	12	Improvement of metaphyseal lesions on X-ray	metaphyseal
Zhou 1991 ^{33#}	25/30	35/29	4~12	4~12	①Se + VC: Se tablet 1mg/10day+ VC 100mg/day; ②Se salt (sodium selenite: salt = 1:60,000) /10day	③VC, 300mg/day; ④No treatment	12	Improvement of metaphyseal lesions on X-ray	metaphyseal
Moreno-Reyes 2003 ³⁴	113	95	10±0.28	10±0.3	Se tablet, 1 mg/week	Placebo/week	12	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films	metaphyseal
Chen 2003 ^{35*}	50/50	50	6~11	6~11	①Se tablet 1mg/week; ② Se + VC: Se tablet 1mg/week+ VC 300 mg 2 times/day	VC 300mg bid	12	Improvement of metaphyseal lesions on X-ray	metaphyseal

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Study	Case No.		Age		Intervention	Control	Follow-up (months)	Outcome
	I	C	I	C				
Cai 2005 ³⁶	31	31	7~13	7~13	Se tablet, 2mg/10 days (7-10 yrs), 3 mg/10 days (11-13 yrs)	No treatment	18	Improvement of metaphyseal lesions on X-ray Repairing rate at the distal end of phalanges in hands on X-ray films

I= intervention, C = control, YSSG = Yongshou scientific survey group of Kashin-Beck Disease, yrs = years, Se = Sodium selenite, Se salt =selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast. * Three arms study, # Four arms study

Appendix table 3 Risk of Bias of Included Studies

Study	Balanced allocation	Allocation concealment	Blinding	Completeness of outcome	Selective outcome reporting	Other Bias	overall assessment*
Niu 1981 ²²	Unclear	Unclear	Double-blind	Low	Low	Low	Unclear
YSSG 1982 ²³	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear
Wang 1983 ²⁴	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Cui 1984 ²⁵	unclear	unclear	Double-blind	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1984 ²⁶	Unclear	Unclear	Double-blind	Low, No dropout	Low	High, no ITT analysis	High
Guo 1985 ²⁷	Unclear	Unclear	Not Used	High, dropouts >20%	Low	High, no ITT analysis	High
Guo 1986 ²⁸	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
Niu 1986 ²⁹	Unclear	Unclear	Double-blind	Low, No dropout	Low	Low	Unclear

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3	Wu 1986 ³⁰	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High, no ITT analysis	High
4								
5								
6								
7								
8	Deng 1988 ³¹	Unclear	Unclear	Unclear	Low, drop out <10%	Low	High, no ITT analysis	High
9								
10								
11								
12	Niu 1990 ³²	Unclear	Unclear	Single-blind	Low, No dropout	Low	Low	Unclear
13								
14								
15	Zhou 1991 ³³	Unclear	Unclear	Unclear	Low, No dropout	Low	Low	Unclear
16								
17								
18	Moreno-Reyes 2003 ³⁴	Unclear	Unclear	Double-blind	Unclear, No dropout < 20%	Low	High no ITT analysis	High
19								
20	Chen 2003 ³⁵	Unclear	Unclear	Unclear	High, dropouts >20%	Low	High, no ITT analysis	High
21								
22								
23								
24								
25								
26	Cai 2005 ³⁶	Unclear	Unclear	Not Used	Low, No dropout	Low	Low	Unclear
27								
28								

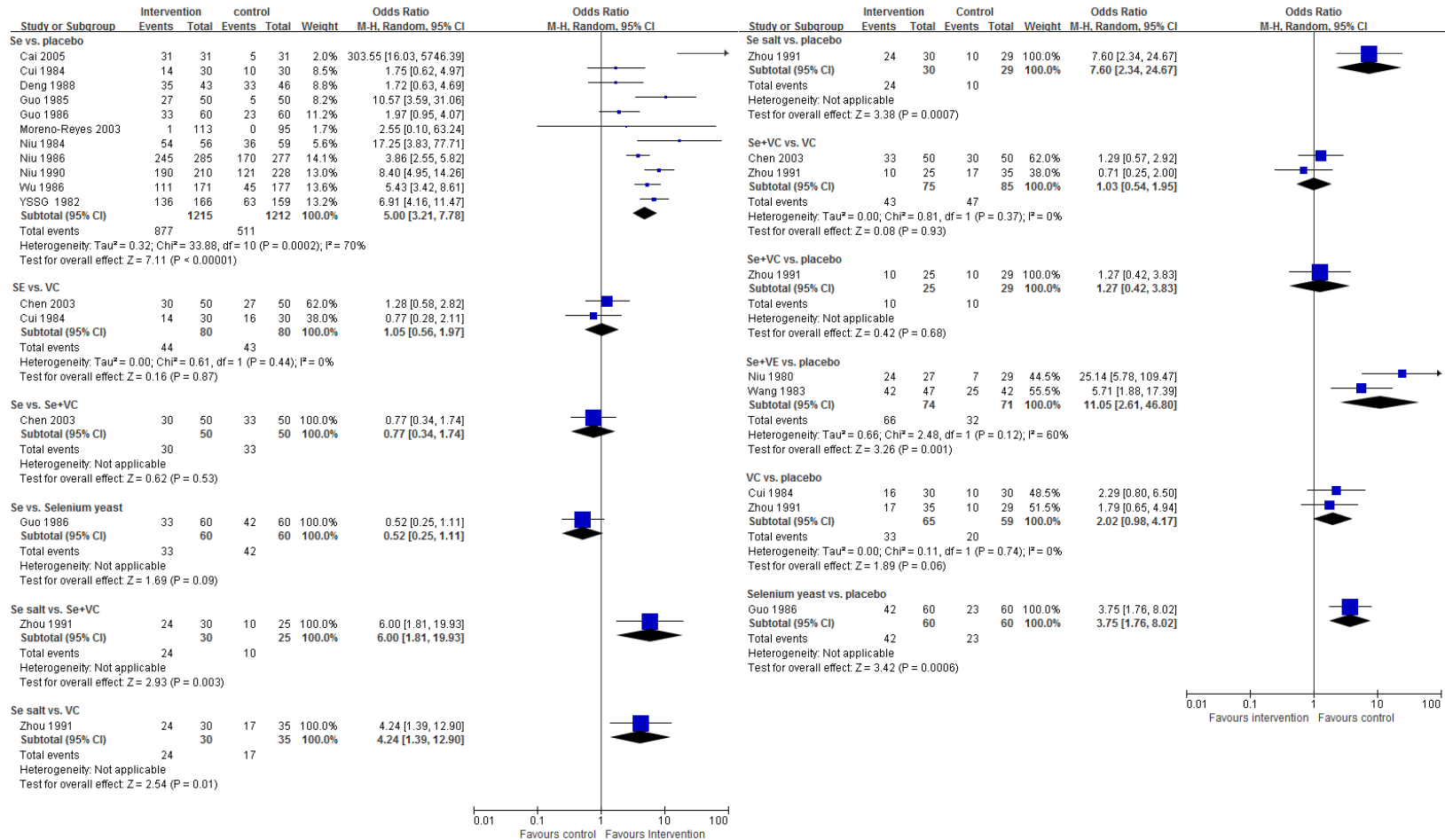
29 *: Overall Score: Low risk of bias = no bias detected in any domain; Unclear risk of bias = one category or more is potentially at risk of bias; High risk of bias = one
30 category or more is at high risk of bias.

31 ITT = intention to treat

Appendix table 4 Data from included studies

Author	Treatment	Group 1		Group 2			Group 3			Group 4		
		Case No.	Total No.	Treatment	Case No.	Total No.	Treatment	Case No.	Total No.	Treatment	Case No.	Total No.
Niu 1981 ²²	Se +VE	24	27	Placebo	7	29						
YSSG 1982 ²³	Se	136	166	Placebo	63	159						
Wang 1983 ²⁴	Se+VE	42	47	Placebo	25	42						
Cui 1984 ²⁵	Se	14	30	VC	16	30	Placebo	10	30			
Niu 1984 ²⁶	Se	54	56	Placebo	36	59						
Guo 1985 ²⁷	Se	27	50	Placebo	5	50						
Guo 1986 ²⁸	Se	33	60	Se yeast	42	60	Placebo	23	60			
Niu 1986 ²⁹	Se	245	285	Placebo	170	277						
Wu 1986 ³⁰	Se	111	171	Placebo	45	177						
Deng 1988 ³¹	Se	35	43	Placebo	33	46						
Niu 1990 ³²	Se	190	210	Placebo	121	228						
Zhou 1991 ³³	Se salt	24	30	VC	17	35	Se+ VC	10	25	Placebo	10	29
Moreno-Reyes 2003 ³⁴	Se	1	113	Placebo	0	95						
Chen 2003 ³⁵	Se	30	50	VC	27	50	Placebo	33	50			
Cai 2005 ³⁶	Se	31	31	Placebo	5	31						

Se = Sodium selenite, Se salt =selenium salt, VC = vitamin C, Se + VC = the combination of sodium selenite with vitamin C ; Se + VE = the combination of sodium selenite with vitamin E, Se yeast = selenium enriched yeast.



Appendix figure: Forest plot for intervention-control pairwise meta-analyses of repairing rate of metaphyseal lesions on X-ray films.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Page 5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Page 6 Registration number: CRD42016051874
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	Page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6

1	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6
2				
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4	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7
5				
6				
7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
8				
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11	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6-8
12				
13				
14	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Page 9 & Fig 2
15				
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21	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10
22				
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Page 8-9
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	Page 8-9
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 8-9
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 10
45				
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	Page 7-9
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RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9 & Fig 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Page 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 10 & Appendix table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 10 & Appendix table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Page 10-11 & Appendix table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Page 10-11 & Table 2
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Page 11 & Fig 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 11 & Fig 4
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Page 11 Table 4 Fig 4 Fig 5

DISCUSSION

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Page 11-12
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Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	Page 14
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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15-16
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FUNDING

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Page 16
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PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.