Meta-Analysis of Observational Studies in Epidemiology

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The relationship between magnesium and osteoarthritis of knee

A MOOSE guided systematic review and meta-analysis

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Abstract

The impact of magnesium on risk of knee osteoarthritis (KOE) is still under investigation. This meta-analysis evaluated the relationship between magnesium and risk of KOE.

A comprehensive search was performed to identify retrospective cohort study or cross-sectional study of the association between magnesium and KOE from the Cochrane library, PubMed, and Embase. The search time limit was from the establishment of the database to December 2018. Two evaluators selected the literature, extracted the data, and evaluated the quality of the literature according to the inclusion and exclusion criteria, independently. Meta-analysis was performed using RevMan 5.3 software and publication bias was assessed using Begg and Egger test and funnel plot.

Finally, 6 studies were included with a total of 15,715 participants. Although higher daily intake of magnesium was associated with a significantly reduced risk of fracture in patients with KOE (OR = 0.66, 95%CI: 0.56, 0.78; $P < .00001$), it was not significant for lowering the risk of KOE (OR = 0.80; 95% CI: 0.61, 1.04; $P = .1$). Meta-analysis also showed that population with higher serum magnesium levels had significantly lower risk of KOE (odds ratio (OR) = 0.84; 95% confidence interval (CI): 0.72, 0.98; $P = .03$). Further subgroup analysis showed that the relationship between serum magnesium level and KOE risk was significantly affected by serum magnesium level ($P = .006$ for quartiles 4 vs 1).

Higher level of magnesium intake was not associated with lower risk of KOE. However, higher daily intake of magnesium may be inversely associated with risk of fracture in KOE patients.

Abbreviations: CI = confidence interval, HR = hazard ratio, KOA = knee osteoarthritis, MOOSE = meta-analyses of observational studies in epidemiology, NOS = Newcastle-Ottawa scale, OR = odds ratio, TGF-β = transforming growth factor beta.

Keywords: epidemiology, fracture, knee osteoarthritis, magnesium, meta-analysis

1. Introduction

Knee osteoarthritis (KOA) is a common disease in middle-aged and elderly population, which seriously affects the quality of these patients and imposes a heavy finial burden on patients and society.[1,2] In the United States, it is the second cause of men's incapacity to work over 50 years old.[3] As the aging population in the world becomes more, this problem needs to be highlighted.

Although researchers around the world have done a lot of experimental and clinical researches on the pathogenesis of osteoarthritis, its occurrence and development are still not totally understood.[4–6] Researchers have proposed various mechanisms. One of them is protease degradation.[7,8] Matrix metalloproteinases promote the degradation of cartilage matrix and induce the apoptosis of articular chondrocytes.[9] The expression and activity of local matrix metalloproteinases are regulated by tissue-derived matrix metalloproteinases in vivo.[9] The dynamic imbalance between the 2 aspects affects the occurrence of osteoarthritis.[10] The next one is cytokine theory. Cytokines are considered to be important factors in the occurrence and development of osteoarthritis, such as Interleukin 17,[11] tumor necrosis factor,[12] and they are significantly increased in osteoarthritis, eventually leading to the damage of articular cartilage tissue and causes inflammation and pain.[13] The growth factors, such as transforming growth factor beta (TGF-β), have been shown to protect against articular cartilage degradation.[14,15] However, they are found to be imbalanced in this disease.

At present, there are no effective drugs that can prevent KOA from happening, change or reverse the progress of the disease.[16,17] Most of the treatments are limited to controlling the symptoms of patients and improving the level of joint function. Therefore, it is important to find measures that prevent the occurrence of KOA and reverse the progress of patients. Many nutritional supplements have been used to treat patients with significant symptoms of KOA,[18] but there is not sufficient data to support the efficacy and safety of these treatments. It has been reported that supplementation with magnesium in elderly

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All the data are included in the manuscript and supplemental data.

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patients with high risk of KOA may be a viable mean of reducing risk of KOA. For patients with KOA, supplementation with magnesium could improve the symptoms and progress of the disease.

However, there has been no meta-analysis based on large population in the world to assess the effects of magnesium supplementation on KOE, so we performed this meta-analysis of eligible studies to assess the relationship between magnesium and KOA.

2. Materials and methods

This meta-analysis was performed according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) and the Cochrane handbook 5.1. This study is not registered. As this study was a meta-analysis, the ethical approval was not necessary.

2.1. Literature search

Databases including the Cochrane library, Embase, and PubMed were searched using a combination of the following terms: "Knee osteoarthritis", "knee arthritis", "KOA", "magnesium", and "Mg" until December 2018. The language of the studies was restricted to English and/or Chinese.

2.2. Inclusion and exclusion criteria

According to the Cochrane Handbook and our study question, the patients were defined as those who were at risk of KOE, or diagnosed with KOE, the exposure factor was magnesium intake level or serum magnesium concentration. The comparisons were differences of the risk of developing KOA, and/or happening fracture in patients with KOA. The outcomes of interest were the relationship between magnesium intake level or serum level and risk of KOA, and KOA related fracture. The relevant data can be extracted from the original literature. The methods and results of the literature were consistent.

The literature were excluded if they had small number of samples or poor credibility; had unclear diagnosis of KOA or the standard of magnesium detection; were other kinds of studies, such as animal experiments, reviews, case studies, and short comments.

2.3. Data extraction and quality assessment

A previously designed form was used to document data. Two reviewers screened the literature according to inclusion and exclusion criteria, extracted the first author, publication year, age, gender, study sample size, exposure factors, region, magnesium intake level or serum magnesium concentration, hazard ratio (HR) or OR values related to KOA, independently. As indicated by the original studies, the baseline information of the participants was comparable. After the information was cross-checked, the methodological quality of the literature was evaluated according to NOS.[19] If there was any disagreement, discuss and solve it. Assessment of study quality was performed, including blinding of quality evaluators and stratification on risk of KOA.

2.4. Statistical analysis

The count data was represented by OR and its 95% CI. The heterogeneity between the results of each study was analyzed using the $\chi 2$ test, and the test level was set to $\alpha = 0.10$. If there was no statistical or clinical heterogeneity between the studies ($P > .1$, $I^2 < 50\%$), a fixed effect model was used for the combined analysis; if there was moderate or higher statistical heterogeneity among the results ($P \leq .1$, $I^2 \geq 50\%$), indicating there was significant clinical difference, and the subgroup analysis or sensitivity analysis was performed. If there was no obvious heterogeneity source, a random effects model was used for the combined analysis. Meta-analysis and Begg funnel plots were performed using RevMan 5.3 software, and published bias was assessed using Egger method.

If the literature already provided risk ratio (RR) or HR values and their 95% CI, the natural logarithm of RR or HR and its 95% CI could be calculated directly. If the RR or HR value was not provided in the literature and the incidence of KOA in different groups was provided, the number of cases in each group was calculated and the point value was estimated for RR or HR. If the combined RR or HR and its 95% CI were <1, suggesting magnesium content was a beneficial factor for the prevention of KOA. If RR or HR or its 95% CI included 1, it was considered that magnesium levels were not suggested to be associated with reduced risk of KOA.

3. Results

3.1. Literature search results and basic characteristics of the included studies

The literature screening process is shown in Figure 1. After the initial search, 147 relevant articles were detected. Most of them were discarded after reading title and abstracts, and 6 articles were finally included, with a total of 15,715 patients. The agreement rate of literature screening by 2 reviewers was 100%. There were 5 studies excluded due to "insufficient data". Insufficient data means lacking data of either dietary intake of magnesium or serum level of magnesium and risk of KOA, as well as fracture risk in KOA patients. All the studies were reported in English language. The basic characteristics of the included studies are shown in Table 1. The participants included population with high risk of developing KOA and patients had been diagnosed with KOA. Magnesium concentrations included serum level and dietary intake level. The reference value was the lowest level or quintile of magnesium. Four studies used dietary magnesium intake to determine the association between magnesium and prevalence of KOA. Three studies used serum magnesium concentration to explore the relationship between magnesium and risk of KOA related diseases, such as fracture in KOA patients.

3.2. Methodological quality evaluation of the included studies

The methodological quality evaluation results are shown in Table 2. In general, the eligible studies were of higher quality. However, most of the included studies did not mention the "Description of the sample size calculation principle".

3.3. Findings from the meta-analysis

Out of 8 studies[20–27] that were included in the systematic review, we excluded 2 study[25,27] from the meta-analysis: that was conducted on patients with structures forming knee joint. Finally, 6 studies[20–24,26] were included in the final analysis: three studies that had evaluated the correlation between magnesium intake

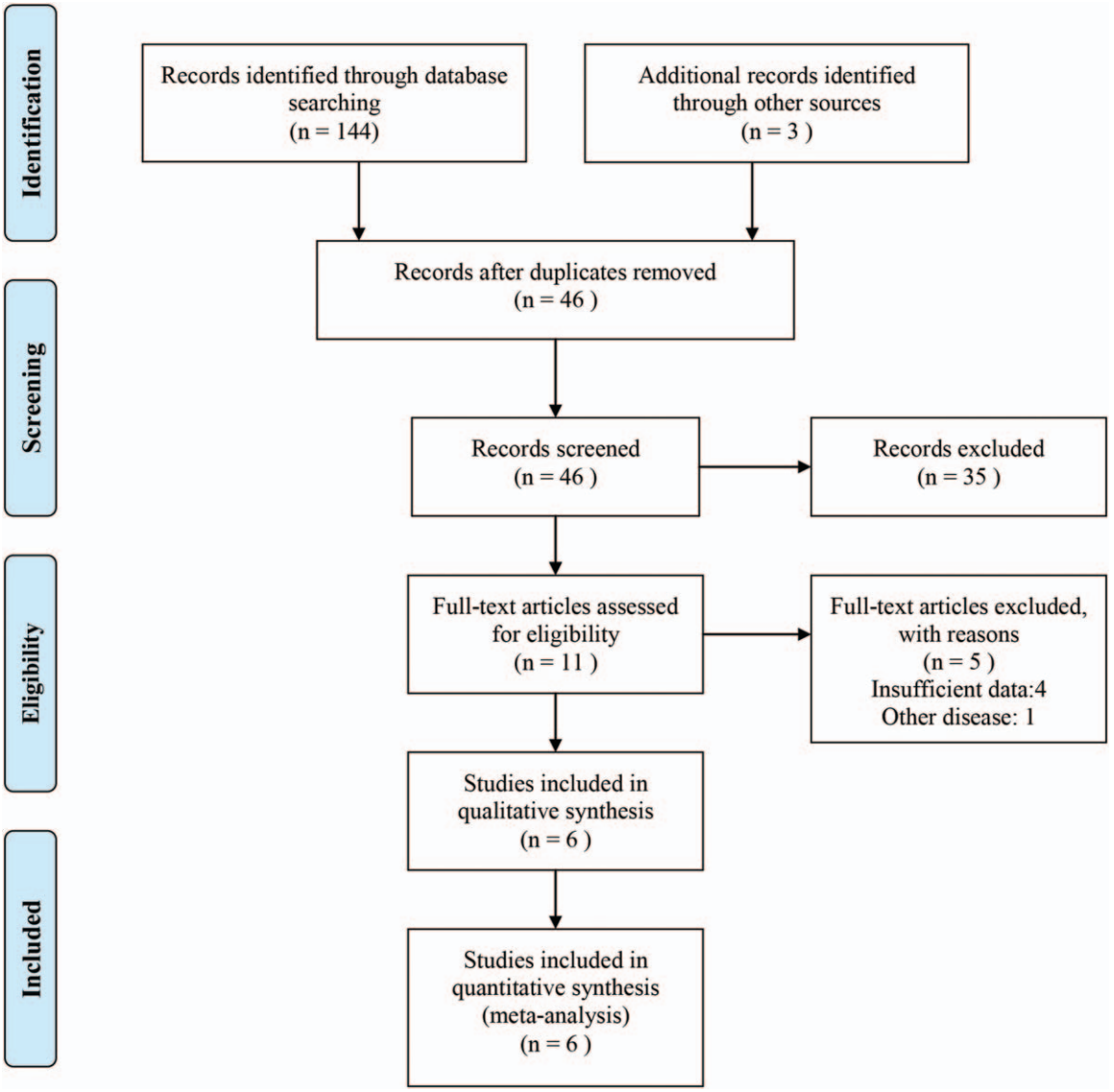

Figure 1. Process of identifying eligible studies for meta-analysis.

and risk of KOA, 2 studies that had examined the association between serum magnesium level and fracture in patients with KOA and 1 study that had tested the relationship between serum magnesium level and prevalence of KOA.

3.4. Prevalence of KOA

The combined prevalence of KOA across included studies was 30.8% (2032/6593). Combining three effect sizes from 2 studies,[20,22] a non-significant correlation between magnesium intake and incidence of KOA was observed (pooled OR = 0.80; 95% CI: 0.61, 1.04; $P = .1$), with a significant across-study heterogeneity ($I^2 = 62\%$; $P = .002$; Fig. 2). Subgroup analysis based on magnesium intake level was done and findings are shown in Figure 2. It revealed no alteration in the findings across these subgroups.

Next, we examined the relationship between serum level and prevalence of KOA. Based on 3 effect sizes from 1 study,[21] a significant association between serum magnesium level and reduced risk of KOA was found (pooled OR = 0.84; 95% CI: 0.72, 0.98; $P = .03$), with an evidence of non-significant heterogeneity between these studies ($I^2 = 23\%$; $P = .27$) (Fig. 3). To detect the impact of different levels of magnesium on incidence of KOA, we performed subgroup analysis. The results showed that patients with the highest serum level of magnesium had the lowest risk of developing KOA (OR = 0.72, 95%CI: 0.57, 0.91; $P = .006$). Based on different serum magnesium level, for patients with low or moderate level of serum magnesium, trends towards decreased risk of KOA were observed without significance (OR = 0.90, $P = .38$ for quartiles 2 vs 1, OR = 0.92, $P = .48$ for quartiles 3 vs 1) (Fig. 3).

3.5. Fracture risk in patients with KOA

Two studies[24,26] with 4 effect sizes had assessed the association between magnesium intake and risk of fractures in patients at high risk of KOA. The overall effect of higher magnesium intake was associated with significantly decreased risk of fracture in

Table 1

Baseline characteristics of included studies.

Author	Year	Number	Age	Male (%)	Region	Study type	Disease	Diagnosis	Define of KOA	Levels of Magnesium	Prevalence of KOA (%)	Observation	Control	Outcomes
Qin	2012	2112	≥ 45	696 (32.95)	American	RT	KOA	K-L scale	K-L grade of at least 2 in at least one knee	129.8–523.9 mg/d	36.27	dietary Mg intake	lowest intake	Incidence of KOA, Mg intake and risk of OA
Zeng	2015-A	2855	52.26 ± 7.16	1623 (56.86)	Asian	CR	KOA	K-L scale	K-L grade of at least 2 in at least one knee	0.84–1.00 mmol/L	30	serum Mg level	lowest level	Incidence of KOA, serum Mg level and risk of KOA
Zeng	2015-B	1626	50.9 ± 9.5	963 (53.58)	Asian	RT	KOA	K-L scale	K-L grade of at least 2 in at least one knee	170.3–672.2 mg/d	25.2	dietary Mg intake	lowest intake	Incidence of KOA, Mg intake and risk of KOA
Li	2016	936	51.8 ± 6.9	656 (70.1)	Asian	CR	KOA	K-L scale	at least one knee joint was graded as K-L 1 or 2	244.67–533.15 mg/d	NA	serum Mg level	lowest level	serum Mg level, Mg intake and risk of KOA, CRP and risk of KOA
Veronese	2017-B	4421	61.3 ± 9.2	1857 (42.0)	American	CR	KOA	K-L scale	K-L grade of at least 2 in at least one knee	NA	NA	dietary Mg intake	lowest intake	Mg intake and Osteoporotic Fractures index
Veronese	2017-A	3765	60.6 ± 9.1	1577 (41.89)	Europe	PR	KOA	K-L scale	K-L grade of at least 2 in at least one knee	161.0–491.0 mg/d	NA	dietary Mg intake	lowest intake	Incidence of Fracture, Mg intake and Fracture risk

CR = cross-sectional study, K-L scale = Kellgren-Lawrence scale, KOA = knee osteoarthritis, Mg = magnesium, RT = retrospective study, NA = not available, PR = prospective study.

Table 2

Methodological quality evaluation of included studies according to NOS scale.

Author Name	Year	Selection	Comparability	Outcome
Qin	2012	☐☐☐	☐☐	☐☐☐
Zeng	2015-A	☐☐☐	☐☐	☐☐
Zeng	2015-B	☐☐☐	☐☐	☐☐☐
Li	2016	☐☐	☐☐	☐☐☐
Veronese	2017-B	☐☐☐	☐☐	☐☐☐
Veronese	2017-A	☐☐	☐☐	☐☐☐

NOS = Newcastle-Ottawa scale.

patients with KOA (OR = 0.66, 95%CI: 0.56, 0.78; $P < .00001$) (Fig. 4), without significant between-study heterogeneity ($I^2 = 15\%$; $P = .30$). The findings were not significantly altered after examining the impact of different quintiles of magnesium ($P < .05$ for all). We also evaluated the impact of gender on the risk of fracture. As reported by 2 studies,[24,26] low intake of magnesium was associated with significantly reduced risk of fracture in male patients with KOA ($P < .05$ for quartiles 3, 2 vs 1, respectively), but this effect was not consistently significant in female KOA patients.

3.6. Publication bias

The data about magnesium intake along with serum magnesium level and risk of KOA were used to perform the publication bias assessment. As illustrated in Figure 5, the funnel plots were even, suggesting low risk of publication bias.

4. Discussion

The results of this meta-analysis show that the overall incidence of KOA across the included participants is around 30%. Patients with higher level of magnesium intake was not associated with the lower risk of KOA, and higher daily intake of magnesium may be inversely associated with risk of fracture in KOA. In addition, high serum magnesium level was significantly associated with reduced risk of KOA only in patients whose median magnesium concentration was 1 mmol/l.

There is limited number of evidence about the association between magnesium level and prevalence of KOA. In recent years, researches are focusing on the impact of supplementation of magnesium on prevalence of KOA.[20–26] As reported in the included studies, the incidence of KOA ranged from 25.2% to 36.27%, with an estimated overall incidence of 30.8% across these studies, indicating a large number of patients suffering from KOA. With regard to the preventing effect of magnesium on KOA, there are still debates. While some studies find positive link between magnesium and reduced risk of KOA, results of other studies are different.[20–26,28] In our study, we find dietary magnesium intake is not significantly associated with decreased risk of KOA, but associated with significantly decreased risk of fracture in patients with KOA ($P < .05$). A significant association between magnesium intake and reduced risk of KOA may be achieved after enrolling more participants. However, we do observe a significant connection between higher level of serum magnesium and lower risk of KOA only in patients whose median magnesium concentration was 1 mmol/l. Moreover, a recent study also suggests the serum magnesium concentration is

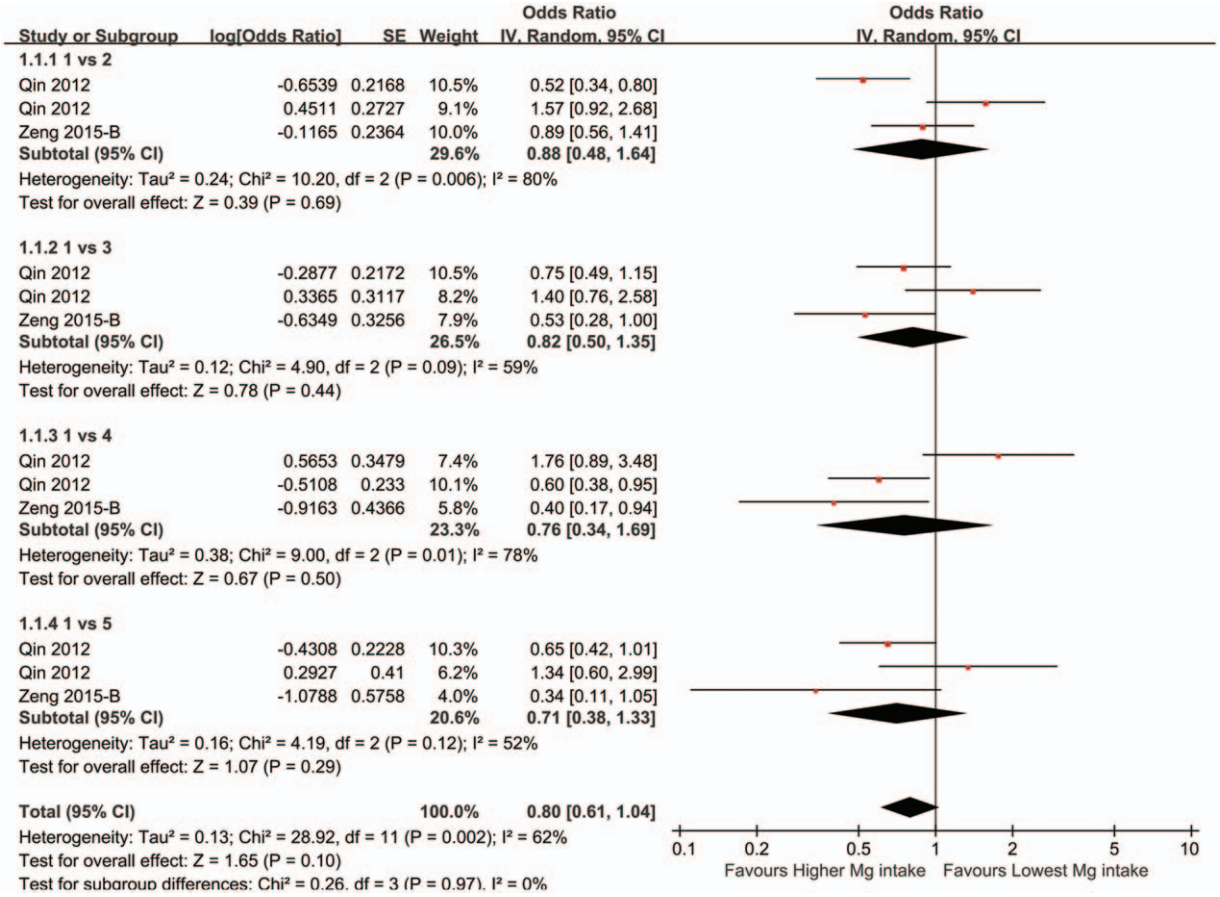

Figure 2. Forest plot of comparison: high vs low level of magnesium intake and risk of knee osteoarthritis.

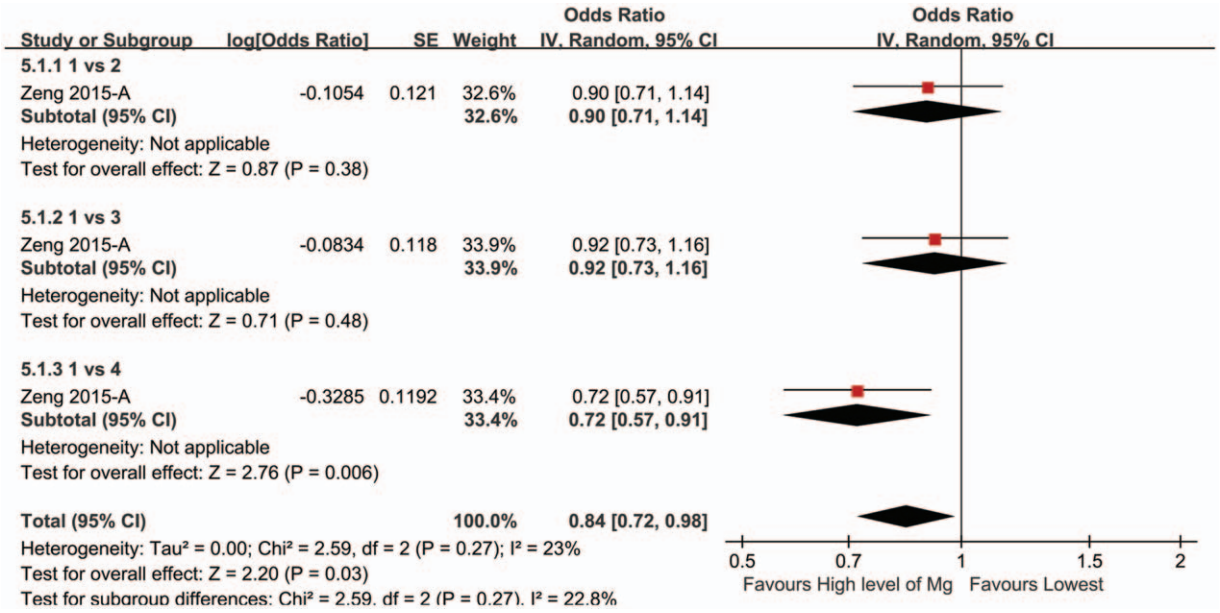

Figure 3. Forest plot of comparison: high vs low level of serum magnesium and risk of knee osteoarthritis.

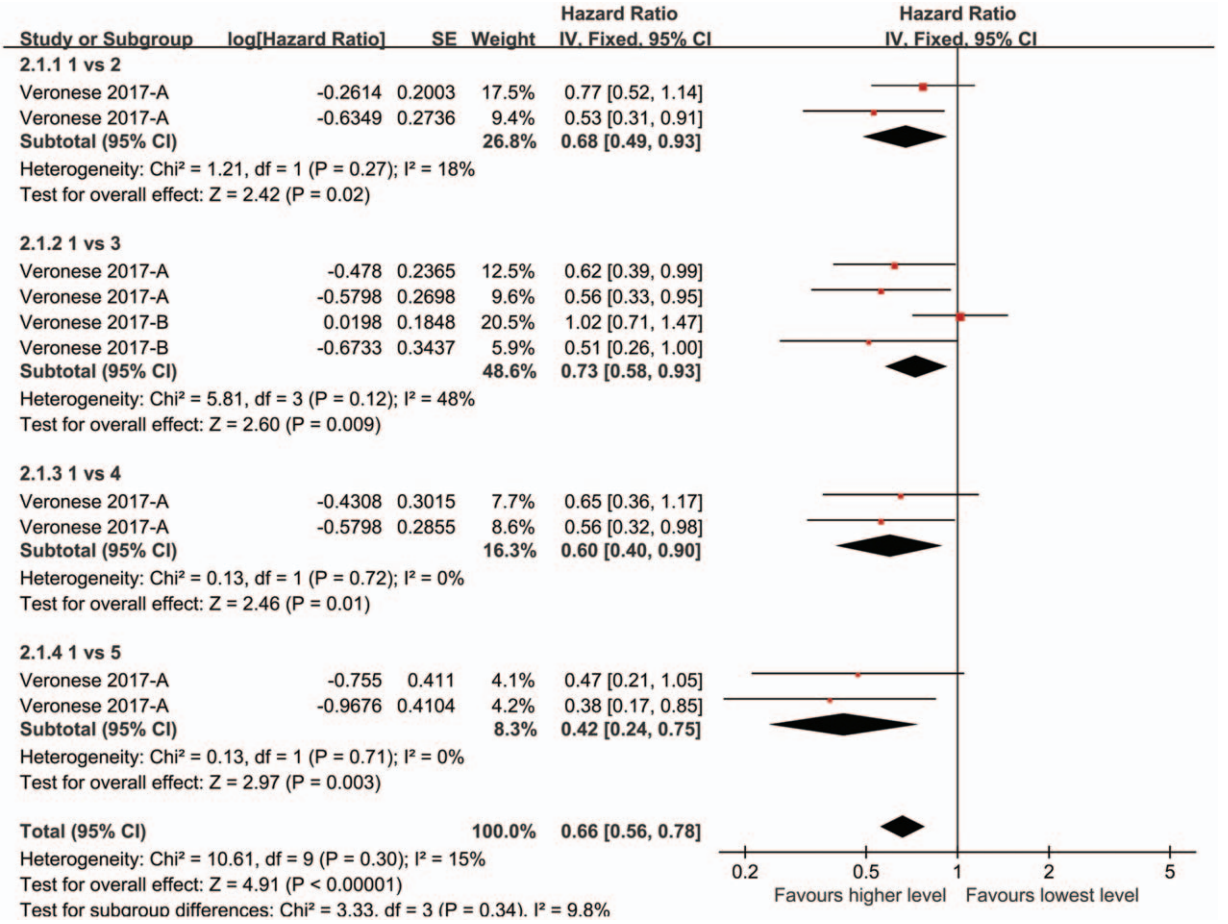

Figure 4. Forest plots of high vs low level of magnesium intake and risk of fracture in patients with KOA.

inversely correlated with the prevalence of metabolic syndrome, diabetes mellitus and hyperuricemia in patients with radiographic KOA.[28] These findings show a potential effect of serum magnesium against risks of KOA and related diseases. Further study is warranted to answer what is the optimal level of serum magnesium in these patients.

There is significant heterogeneity between included studies during evaluation of the relation between magnesium and risk of KOA, so the subgroup analyses are performed. The heterogeneity is minimized after subgroup analyses and determined by the $\chi 2$ test. We find the correlation between serum magnesium levels and the risk of KOA is independent of sex. However, we also notice that men have a better reduction in developing KOA compared to that of women, regardless of serum level of magnesium. This difference may be caused by several factors, such as hormones. This needs further investigation to fully understand the difference.

Previously, there is a meta-analysis[29] evaluating the correlation between magnesium intake and risk of fracture. After a systematical search, they identified 12 studies met their inclusion criteria. With the combined data, they found higher magnesium intake was not significantly associated with fracture ($P > .05$). However, the pooled result from our study determined a significant association between higher magnesium intake and lower risk of fracture. These controversial findings could be explained by the following reasons. First, we included participants at risk of developing KOA or already had KOA. The patients in the above meta-analysis had different kinds of bone related diseases. Second, we included more recent studies with positive and updated findings, eventually affecting the combined effect.

Although the study yielded positive results, there are still some limitations. First, the number of included studies is small, along with limited original data and potential risk of publication bias. Second, the cutoff values of serum magnesium levels vary between different included studies, as well as the intake levels. Besides, the baseline characteristics are different across included eligible studies. These raise the risk of selection bias. Thirdly, although we did a subgroup analysis, we failed to fully minimize the heterogeneity between the results. Fourth, there may be some potential factors not considered in the present study, such as region, education, and race. Nevertheless, the present meta-analysis may provide potential useful data for further research.

5. Conclusions

The association between magnesium and KOA and its related fraction is evaluated in this study, and the meta-analysis results suggest magnesium intake is not associated with reduced risk of KOA. However, decreased risk of fracture in KOA patients with higher daily intake of magnesium was observed. Due to limited data and partial positive findings, the results of this study should be considered with caution and further validation.

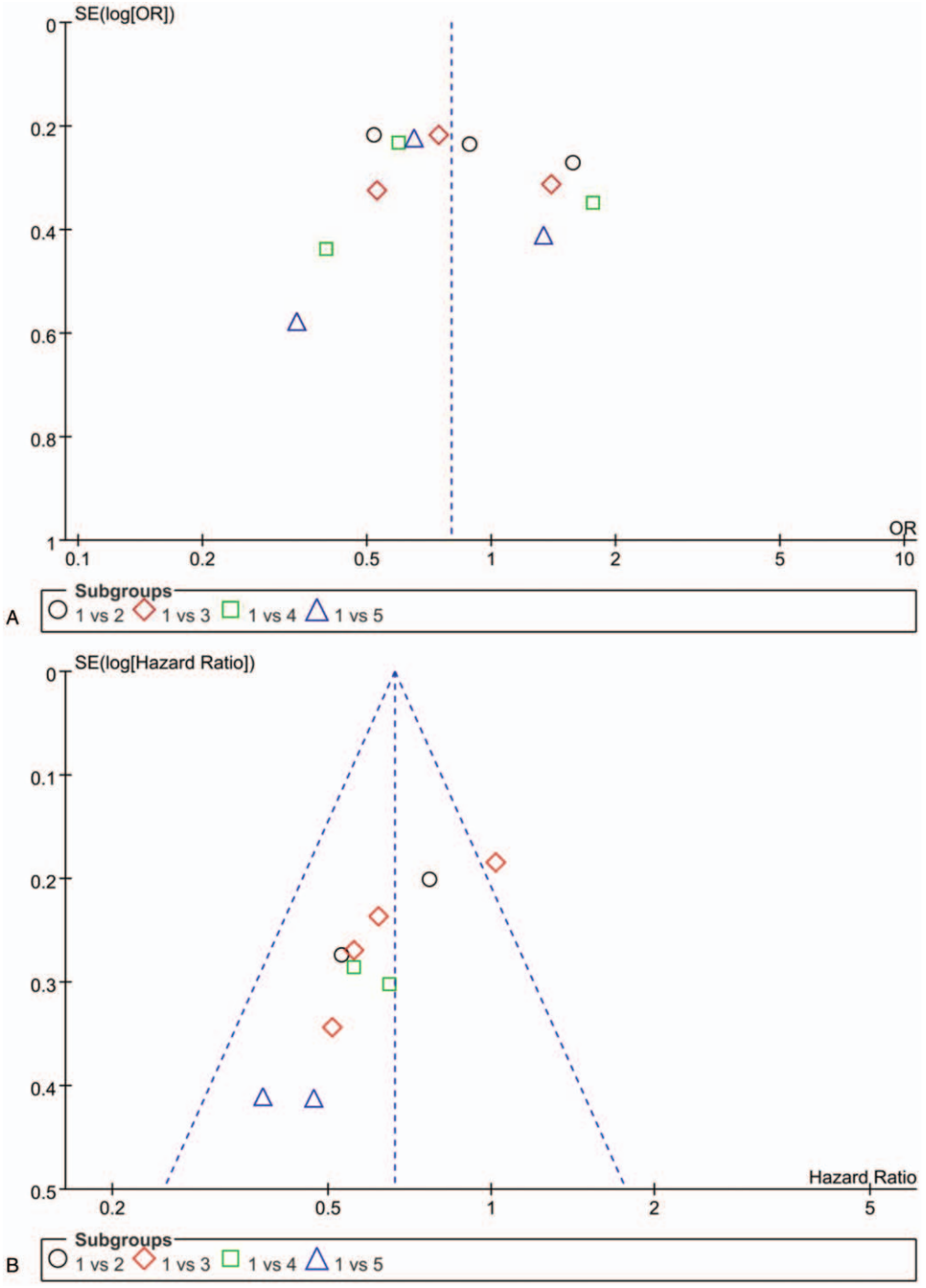

Figure 5. Funnel plot of comparison: A, high vs low intake of magnesium and risk of knee osteoarthritis; B, high vs low level of serum magnesium and risk of knee osteoarthritis.

Author contributions

Conceptualization: Zhiming Wu, Jiangtao Liu.
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Formal analysis: Zhiming Wu, Jiangtao Liu.
Methodology: Zhiming Wu, Kai Lian.
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Supervision: Zhiming Wu.
Validation: Juguang Yang.
Visualization: Juguang Yang.
Writing – original draft: Zhiming Wu.
Writing – review & editing: Zhiming Wu, Jiangtao Liu, Kai Lian.

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