

· 论 著 ·

硒水平与慢性肾脏病关联的Meta分析

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摘要: **目的** 系统评价人体硒水平与慢性肾脏病 (CKD) 发病风险, 为CKD的防治提供依据。**方法** 检索中国知网、万方数据知识服务平台、PubMed和Web of Science, 收集建库至2022年7月28日发表的关于硒水平与CKD的研究文献。采用Stata 16.0软件进行Meta分析, 以标准化均数差 (SMD) 及其95%CI描述。采用亚组分析和Meta回归分析异质性来源; 采用留一法进行敏感性分析; 采用漏斗图、Egger检验和Begg检验评估发表偏倚, 并采用剪补法评估结果的稳定性。**结果** 共检索文献2 990篇, 最终纳入63篇, 其中横断面研究18篇, 病例对照研究40篇, 队列研究2篇和随机对照试验3篇; CKD病例5 099例, 对照组6 334人。Meta分析结果显示, CKD病例硒水平低于对照组 ($SMD=-1.828$, $95\%CI: -2.132\sim-1.523$, $P<0.001$)。亚组分析结果显示, 亚洲、欧洲与混合不同地区人群的CKD病例硒水平低于对照组 ($P<0.05$); CKD病例血硒水平低于对照组 ($P<0.05$); 保守治疗、血液透析和腹膜透析病例硒水平低于对照组 ($P<0.05$); 横断面研究、病例对照研究和随机对照试验中CKD病例硒水平低于对照组 ($P<0.05$)。不同研究年份、样本量、文献质量评分均显示CKD病例硒水平低于对照组 ($P<0.05$)。敏感性分析显示结果稳健。漏斗图、Begg检验和Egger检验提示存在发表偏倚, 进一步用剪补法发现结果稳定。**结论** 硒水平与CKD的发生可能存在关联。

关键词: 慢性肾脏病; 硒; 关联; Meta分析

中图分类号: R692 **文献标识码:** A **文章编号:** 2096-5087 (2023) 08-0669-08

Correlation between selenium and chronic kidney disease: a meta-analysis

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Abstract: Objective To systematically evaluate the correlation between selenium in the body and the risk of chronic kidney disease (CKD), so as to provide insights into CKD prevention and control. **Methods** Publications pertaining to the correlation between selenium level and CKD were retrieved from electronic databases, including CNKI, WanFang Data, PubMed and Web of Science from inception until July 28, 2022. Meta-analysis was performed using the software Stata 16.0, and all measures were expressed with standardized mean difference (SMD) and its 95%CI. The source of heterogeneity was analyzed using subgroup analysis and meta-regression, and sensitivity analysis was performed using the leave-one-out method. In addition, the publication bias was evaluated with d funnel plot, Egger's test and Begg's test, and the robustness of the result was evaluated using the trim and filling method. **Results** A total of 2 990 publications were screened, and 63 eligible publications were included in the final analysis, including 18 cross-sectional studies, 40 case-control studies, 2 cohort studies and 3 randomized controlled trials (RCTs), which covered 5 099 CKD patients and 6 334 controls. Meta-analysis showed lower selenium levels in CKD patients than in controls ($SMD=-1.828$, $95\%CI: -2.132$ to -1.523 , $P<0.001$). Subgroup analysis showed lower selenium levels among CKD patients than among controls from Asia, Europe and multiple continents ($P<0.05$), and lower selenium levels were detected in patients undergoing conservative treatment, hemodialysis and peritoneal dialysis than in controls ($P<0.05$), while the selenium levels were significantly lower in CKD patients than in controls in cross-sectional studies, case-control studies and RCTs ($P<0.05$). The selenium level was significantly lower among CKD patients than among controls regardless of the study year, sample size and score for quality of publications ($P<0.05$). Sensitivity analysis showed robustness of this

DOI: 10.19485/j.cnki.issn2096-5087.2023.08.006

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meta-analysis. Publication bias was identified by funnel plot, Begg's test and Egger's test, and the robustness of the result was found using the trim-and-fill method. **Conclusion** There may be a possible correlation between selenium and the risk of CKD.

Keywords: chronic kidney disease; selenium; correlation; meta-analysis

慢性肾脏病 (chronic kidney disease, CKD) 是指各种原因导致的肾结构和功能改变的慢性进展性疾病^[1]。CKD 全球患病率为 9.1%，截至 2017 年，全球约有 6.795 亿 CKD 患者，其中我国有 1.323 亿^[2]。CKD 每年导致全球约 120 万人死亡^[2]，预计到 2040 年将成为全球第五大死因^[3]。硒是一种微量元素，在人体内主要依靠 25 种硒蛋白发挥生物学功能，健康人血浆硒的浓度为 0.5~2.5 $\mu\text{mol/L}$ ^[4]。研究发现，硒蛋白可通过抗氧化、抗炎、调节免疫反应、下调细胞生长因子表达和抑制肾小管上皮细胞转分化等作用改善肾功能^[5]。目前已有不少关于低硒水平与 CKD 发生风险关联的研究，本研究采用 Meta 分析方法对这些研究进行系统评价，探讨人体硒水平与 CKD 发病的相关性，为 CKD 防治提供依据。

1 资料与方法

1.1 文献检索策略

检索中国知网、万方数据知识服务平台、PubMed 和 Web of Science 数据库从建库至 2022 年 7 月 28 日发表的关于硒与 CKD 发病风险的中英文文献。中文检索词：硒、硒补充、慢性肾脏病、终末期肾脏病、慢性肾功能不全、慢性肾衰竭。英文检索词：selenium、selenium supplement、CKD、CKF、CRF、CRD、chronic kidney disease、chronic kidney failure、kidney disease、kidney failure、kidney insufficiency、kidney dysfunction、chronic renal disease、renal disease、renal failure、renal insufficiency、renal dysfunction。

1.2 文献纳入和排除标准

纳入标准：(1) 研究类型为横断面研究、病例对照研究、队列研究或随机对照试验；(2) 疾病结局符合 CKD 诊断标准^[6]，即肾损伤或肾小球滤过率 < 60 mL/(min · 1.73 m²) 超过 3 个月；(3) 研究因素为人体内硒水平。排除标准：(1) 非英文、非中文文献；(2) 报告数据不完整或前后不一致的文献；(3) 来自同一人群但样本量较小的文献；(4) 无法检索到全文的文献；(5) 研究内容与暴露造成结局发生风险无关的文献。

1.3 文献筛选和数据提取

文献筛选由 2 名研究人员独立完成。剔除重复

文献后，通过阅读文献的标题和摘要，剔除明显不符合纳入和排除标准的文献。然后对筛选出的文献进行全文阅读，确定最终纳入研究的文献。若 2 名研究人员产生分歧，则咨询第 3 名研究人员意见，讨论后确定。文献筛选结束后，2 名研究人员独立进行资料提取，包括第一作者、发表年份、研究类型、研究对象、硒样本来源、硒含量、肾功能指标和治疗方法等。

1.4 文献质量评价

2 名研究人员独立进行文献质量评价。横断面研究、病例对照研究和队列研究采用纽卡斯尔-渥太华量表 (Newcastle-Ottawa Scale, NOS)^[7] 进行质量评分，包括“研究对象的选择”“组件可比性”“结果的测量”3 个方面，横断面研究满分为 10 分，病例对照研究和队列研究满分为 9 分， ≥ 7 分为高质量文献， < 7 分为低质量文献。随机对照试验采用 Jadad 量表^[8] 从随机、盲法和失访/退出 3 个方面进行评分，满分为 5 分， ≥ 3 分为高质量文献， < 3 分为低质量文献。

1.5 统计分析

采用 Stata 16 软件进行 Meta 分析。采用标准化均数差 (standard mean difference, SMD) 及其 95%CI 描述。采用 Q 检验和 I^2 值评估异质性，若 $P > 0.10$ 且 $I^2 < 50\%$ ，提示研究间存在的异质性较小或不存在异质性，采用固定效应模型；若 $P \leq 0.10$ 且 $I^2 \geq 50\%$ ，提示研究间存在较大的异质性，采用随机效应模型。采用固定或随机效应模型合并 SMD 并绘制森林图。采用亚组分析和 Meta 回归分析异质性来源， $P < 0.05$ 提示存在组内异质性。采用漏斗图、Begg 检验和 Egger 检验评估发表偏倚；若存在发表偏倚，进一步采用剪补法评估研究结果的稳定性。采用留一法进行敏感性分析。检验水准 $\alpha = 0.05$ 。

2 结果

2.1 纳入文献基本情况

共检索 2 990 篇文献，最终纳入 63 篇文献^[9-71]，文献筛选流程见图 1。纳入 CKD 病例 5 099 例，对照组 6 334 人。研究对象来自亚洲 25 篇，来自欧洲 31 篇，来自美洲 5 篇，混合 2 篇。横断面研究 18 篇，病例对照研究 40 篇，队列研究 2 篇，随

机对照试验 3 篇。高质量文献 15 篇，低质量文献 48 篇。

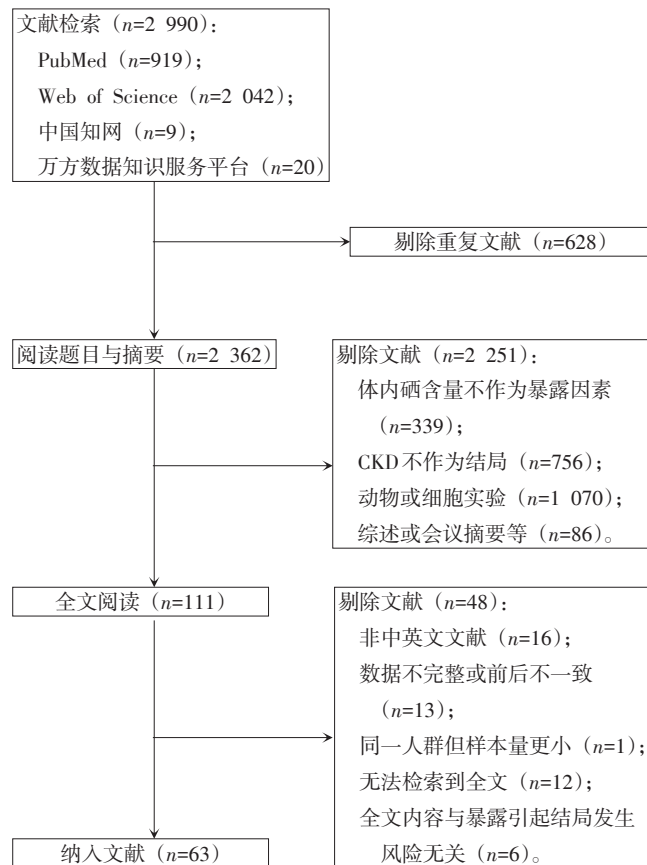


图 1 文献筛选流程

Figure 1 Flow chart of publication selection

2.2 Meta 分析结果

63 篇文献的异质性检验结果显示存在异质性 ($P < 0.001$, $I^2 = 96.6\%$), 故采用随机效应模型进行合并。CKD 病例的硒水平低于对照组 ($SMD = -1.828$, $95\%CI: -2.132 \sim -1.523$, $P < 0.001$)。见图 1。

2.3 亚组分析

亚洲、欧洲和混合不同地区来源的 CKD 病例硒水平低于对照组 ($P < 0.05$), 而美洲 CKD 病例硒水平与对照组差异无统计学意义 ($P > 0.05$)。CKD 病例血硒水平低于对照组 ($P < 0.05$), 尿液、头发、指甲等其他样本来源的硒水平在两组人群中差异无统计学意义 ($P > 0.05$)。保守治疗、血液透析和腹膜透析病例硒水平均低于对照组 ($P < 0.05$), 肾移植病例的硒水平与对照组差异无统计学意义 ($P > 0.05$)。横断面研究、病例对照研究和随机对照试验中 CKD 病例硒水平低于对照组 ($P < 0.05$), 队列研究中两组人群硒水平差异无统计学意义 ($P > 0.05$)。不同研究年份、样本量、文献质量评分的研究显示, CKD 病例硒水

平均低于对照组 ($P < 0.05$)。Meta 回归未发现异质性来源。见表 1。

2.4 敏感性分析和发表偏倚评估结果

敏感性分析显示, 合并估计的方向并未随每项研究的依次删除而发生明显变化, 数据未受到任何 1 项研究的过度影响, 提示 Meta 分析结果稳健。漏斗图显示不对称, Begg 检验 ($Z = 4.110$, $P < 0.001$) 和 Egger 检验 ($t = -3.863$, $P < 0.001$) 提示存在发表偏倚; 进一步用剪补法发现结果一致 ($P < 0.001$)。

3 讨论

本研究共纳入 63 篇文献, Meta 分析结果显示 CKD 患者硒水平低于对照组, 提示体内低硒水平可能与 CKD 发生有关。硒主要以硒蛋白的形式在人体中发挥生物学作用, 在与硒生物学功能密切相关的 25 种硒蛋白中, 大多数以抗氧化酶的形式为人们所熟知, 硒缺乏会增加氧化应激易感性。肾是除甲状腺外含硒量最大的器官, 谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px) 等含硒酶在肾中发挥重要的抗氧化作用, 当 GSH-Px 活性降低, 氧化应激增强, 炎症状态加重, 可导致肾损伤。所以, 硒与 CKD 发生相关的机制可能是当机体处于低硒状态时, 肾的抗氧化功能减弱, 氧化应激易感性增加, 导致肾的结构和功能损伤, 持续较长时间会导致 CKD 发生风险升高。此外, 一项研究通过小鼠模型发现硒缺乏可能导致细胞外基质的累积和基质金属蛋白酶表达的变化, 并引起 Wnt/ β -连环蛋白信号通路分子上调, 导致肾纤维化, 进一步导致 CKD 发生、发展^[72]。硒可影响免疫系统, 例如硒蛋白可促进 T 细胞和 B 细胞的激活, 而硒水平增高可诱导巨噬细胞活化为抗炎表型, 增加 NK 细胞活性与细胞毒性。总之, 较高水平的硒可促进人体免疫功能, 防止感染, 促进肾脏疾病进展, 预防 CKD 发生。

本研究通过亚组分析发现 CKD 病例血硒水平明显低于对照组, 而非血液样本来源 (如尿液、头发、指甲以及其他组织) 的研究并未发现 CKD 病例与对照人群硒水平存在差异, 可能是因为人体硒主要来源于膳食摄入, 通过血液输送至其他组织, 而尿液、头发与指甲中的硒含量主要用于评估硒排泄水平, 且有文献指出, 相较于尿液、头发、指甲等, 血浆与血清是评估硒水平最有效的样本来源^[73]。此外, 研究人群来源分组中美洲、治疗方法分组中的肾移植、研究方法分组中的队列研究也未发现 CKD 病例体内硒水平与对照组差异存在统计学意义。然而 Meta 回归并

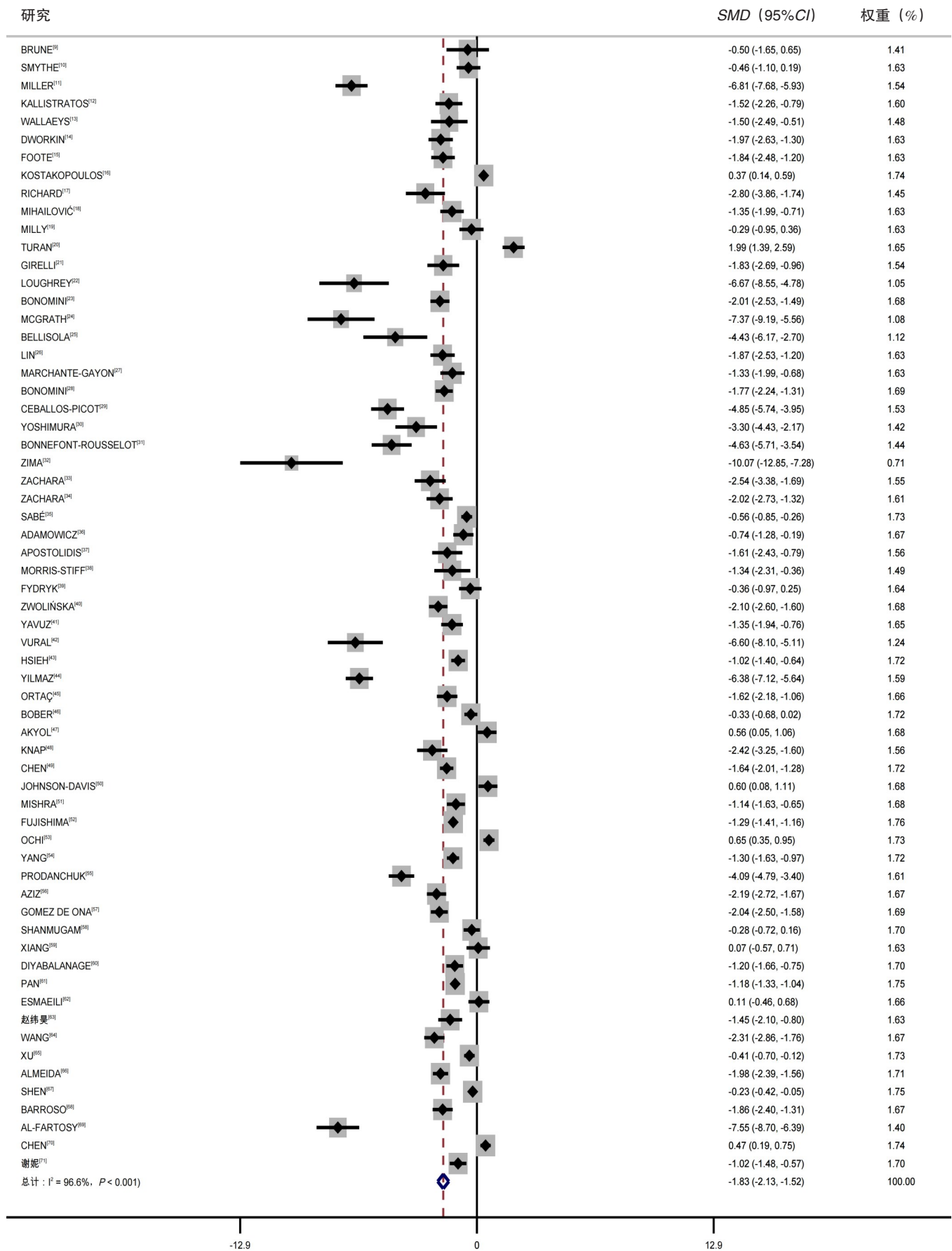


图 2 硒水平与慢性肾脏病关联的 Meta 分析森林图

Figure 2 Forrest plot showing the correlation between selenium and CKD

表 1 硒与 CKD 关联的亚组分析结果
Table 1 Subgroup analysis of the correlation between selenium and CKD

项目	文献数量	SMD (95%CI)	P 值	Q 检验 P 值	I ² 值/%	Meta 回归 P 值
研究对象来源						
亚洲	25	-1.446 (-1.923~-0.969)	<0.001	<0.001	97.4	0.609
欧洲	31	-2.241 (-2.732~-1.749)	<0.001	<0.001	95.2	
美洲	5	-2.048 (-4.141~0.045)	0.055	<0.001	98.2	
混合	2	-0.892 (-1.588~-0.195)	0.012	0.032	78.3	
硒样本来源						
血浆	29	-2.388 (-2.898~-1.878)	<0.001	<0.001	95.8	0.123
红细胞	10	-1.657 (-2.377~-0.937)	<0.001	<0.001	92.7	
血清	24	-1.402 (-1.836~-0.969)	<0.001	<0.001	96.9	
全血	11	-2.663 (-3.885~-1.440)	<0.001	<0.001	97.4	
白细胞	1	-1.389 (-1.987~-0.792)	<0.001	—	—	
尿	2	-4.267 (-13.018~4.485)	0.339	<0.001	96.8	
头发	3	-0.711 (-2.216~0.794)	0.355	<0.001	97.3	
指甲	1	0.105 (-0.318~0.528)	0.627	—	—	
其他组织	2	0.069 (-0.924~1.062)	0.891	0.016	82.9	
治疗方法						
保守治疗	39	-1.901 (-2.321~-1.481)	<0.001	<0.001	97.0	0.288
血液透析	36	-1.582 (-1.995~-1.168)	<0.001	<0.001	97.2	
腹膜透析	14	-1.743 (-2.482~-1.005)	<0.001	<0.001	95.2	
肾移植	4	-0.336 (-2.346~1.674)	0.743	<0.001	98.4	
血液透析或腹膜透析	3	-1.275 (-1.913~-0.638)	<0.001	0.020	74.5	
发表年份						
2000 年之前	24	-2.598 (-3.403~-1.793)	<0.001	<0.001	96.9	0.064
2000 年及之后	39	-1.481 (-1.807~-1.154)	<0.001	<0.001	96.5	
文献质量						
低	48	-1.950 (-2.372~-1.528)	<0.001	<0.001	96.3	0.735
高	15	-1.460 (-1.954~-0.967)	<0.001	<0.001	97.4	
样本量						
<100	39	-2.207 (-2.695~-1.718)	<0.001	<0.001	94.8	0.124
≥100	24	-1.373 (-1.800~-0.946)	<0.001	<0.001	97.8	
研究类型						
横断面研究	18	-1.355 (-1.928~-0.783)	<0.001	<0.001	97.0	0.428
病例对照研究	40	-2.104 (-2.505~-1.703)	<0.001	<0.001	96.4	
队列研究	2	-0.413 (-2.145~1.320)	0.641	<0.001	98.4	
随机对照试验	3	-2.414 (-4.260~-0.568)	0.010	<0.001	91.7	

注：“—”表示该亚组仅1篇文章，无法评估异质性。

未发现组内异质性，可能是对应的分组中文献数量较少，样本量较小，结果仍需更多大样本研究进一步验证。

本次 Meta 分析存在一定局限性：(1) 研究纳入文献所提供的因果关联证据等级不高，纳入的 63 篇

文献中仅有 2 篇队列研究和 3 篇随机对照试验，且这 5 篇研究仅有基线数据可纳入分析。(2) 纳入文献的质量总体偏低，仅有 15 篇文献为高质量文献。(3) 纳入文献存在一定的发表偏倚，但经剪补法发现结果稳定。

综上所述, 硒可能与 CKD 发生存在关联, 但考虑到纳入文献的证据等级与文献质量总体不高, 研究间异质性较大且存在发表偏倚, 后续还需开展更多大样本、高质量的队列研究和随机对照试验提供进一步证据。

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收稿日期: 2023-04-17 修回日期: 2023-06-10 本文编辑: 田田

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2023年优秀论文评选活动

《预防医学》杂志深入贯彻预防为主的新时期卫生工作方针, 坚持正确出版导向和价值取向, 聚焦学术前沿和卫生健康领域重大问题, 努力打造精品学术期刊品牌, 连续保持入选中国科技核心期刊(中国科技论文统计源期刊)、《中国学术期刊影响因子年报》统计源期刊, 连续5年位于预防医学与卫生学Q1区。2020年入选第二十七届北京国际图书博览会(BIBF)“中国精品期刊展”“防疫抗疫”主题精品期刊, 2021年获评第七届华东地区优秀期刊。

为繁荣学术, 响应“把论文写在祖国的大地上”号召, 隆重推出2023年优秀论文评选活动, 每期评出5~10篇月度优秀论文, 通过《预防医学》杂志官网和微信公众号同步推送, 提高作者学术影响力。评选年度优秀论文1篇, 奖励3000元; 创新奖10篇, 奖励1000元。

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