Review

Obesity and the Risk of Developing Kidney Stones: A Systematic Review and Meta-analysis

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Obesity is a growing problem that causes various metabolic disorders and organ dysfunction. The present systematic review and meta-analysis examined the impact of obesity on the risk of kidney stones. This meta-analysis was designed according to PRISMA guidelines. This extensive search was conducted on June 6, 2022, using relevant keywords in databases including PubMed, Web of Science, EMBASE, and Scopus. The data collected from observational studies were recorded in a datasheet. Odds Ratio (OR) and their 95% confidence intervals (CI) evaluated the overall effect size. The Cochran Q test and the statistic I^2 were used to evaluate the heterogeneity of studies. Egger's and Begg's tests assessed potential publication bias. We included 15 observational studies published between 2005 to 2022 in this analysis. Compared to non-obese individuals, the OR for developing kidney stones in obese participants was 1.35 (95% CI: 1.20 to 1.52, P < .001). Considering geographical location, the OR for the risk of developing kidney stones in obese individuals was 1.51 (95% CI: 1.11 to 2.05, P = .009) in North America, 1.33 (95% CI: 1.16 to 1.51, P < .001) in Europe, and 1.18 (95% CI: 1.08 to 1.29, P < .001) in Asia. Begg's test results (P = .625) demonstrated no publication bias. However, Egger's test results (P = .005) indicated publication bias. Based on the results, obesity increases the risk of kidney stone development. Therefore, community health programs should be implemented to reduce the incidence of obesity and lower the risk of kidney stones.

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INTRODUCTION

Obesity is a multifactorial and complex condition that affects individuals of all ages and is associated with several non-communicable diseases.[1,2] Many environmental factors, including epigenetics, socioeconomic status, racial-ethnic identity, cultural and social factors, are associated with obesity.[3] The prevalence of obesity has dramatically increased globally in recent years.[4] Body mass index (BMI) is used frequently in assessing overweight and obese individuals in epidemiological studies.[4,5] In addition, a high BMI is correlated with the development of fatal and disabling disorders, including cardiovascular disease, hypertension, stroke, cancer, diabetes mellitus, and musculoskeletal disorders. This can significantly decrease an individual's quality of life and life expectancy.[3,6,7] Additional research shows that an increased BMI is associated with abnormalities in urine chemistry. This can point to the development of kidney stones, irregular urinary sodium-creatinine ratios and calcium, sodium, oxalate, magnesium, phosphate, and citrate changes in urine. In addition, there are changes in urine pH, causing hypercalciuria.[8-11]

Kidney stones can be excruciatingly painful if they obstruct the urinary system or when they pass through it. They can impair kidney function and may require non-invasive treatment or surgical intervention.[12,13] Kidney stones are associated with a higher risk of development of chronic kidney disease, which can progress to end-stage kidney failure. There is also a relationship between kidney stones, diabetes mellitus, cardiovascular diseases, and hypertension.[14] Given the frequent overlap of diseases associated with a high BMI and kidney stones, understanding the impact of obesity and the risk of developing kidney stones is imperative.

Various conventional and herbal medications are used to treat kidney stones.[15-18] Reducing the risk factors for kidney stones is a priority for communities and health services. Previous investigations of the pathophysiological causes have linked kidney stone formation with obesity. All these studies confirmed that additional research is needed to generate convincing and justifiable conclusions that solidify the relationship between the variables linked to higher risk.[19-21] Therefore, this systematic review and meta-analysis were conducted to determine the association between obesity and the risk of developing kidney stones.

MATERIAL AND METHODS

Data Sources and Search Strategy

This systematic review followed PRISMA guidelines (http://prisma-statement.org/prismastatement/Checklist.aspx). Per the directives, we undertook an extensive search on June 6, 2022, using PubMed, EMBASE, Web of Science, and Scopus databases. Keywords used for the electronic search included: (“kidney stone” OR “renal stone” OR “nephrolithiasis” OR “renal calculi” OR “urolithiasis”) AND (“obesity” OR “obese” OR “overweight”).

Study Selection

Considering the relevant keywords and inclusion (observational studies on the relationship between obesity and the risk of kidney stones) and exclusion criteria (articles not retrieved as full text, non-English language articles, and studies related to metabolic syndrome and diabetes mellitus) the related articles were retrieved and imported into EndNote X9 (July 31, 2018, Thomson Reuters).

Two researchers independently reviewed the full text of articles retrieved for the purposes of the study, removed duplicates, screened the records, and assessed the titles and abstracts based on the study inclusion criteria.

The two researchers resolved their disagreements by discussion, if there were any. In cases where agreement could not be reached, another team member joined the team until consensus was achieved.

Data Extraction

We entered data from the selected articles into an Excel spreadsheet. The collected data included the first author’s name, article publication date, country/region, gender, age, sample size, obesity criteria (e.g., BMI), length of the follow-up, and statistical data, including odds ratio (OR) or hazard ratio (HR) and/or risk ratio (RR) with 95% confidence intervals (CI) which were calculated to estimate the connection between obesity and formation of kidney stones.

Evaluating the Quality of the Studies

To assess the quality of the selected non-randomized studies, researchers used the three criteria section Newcastle-Ottawa Scale (NOS),[22] which incorporates selection of the study groups, the comparability of the groups, and the ascertainment of exposure/outcome of interest for case-control and cohort studies. This systematic review and meta-analysis study considered a score of at least seven as high quality.

Statistical Analysis

The odds ratios measured the relationship between obesity and the chance of kidney stones and reported the effect size of the association between study exposure and the outcome with 95% confidence intervals (CI). In studies where the effect size was calculated and suggested separately, such as for time, seasonal variation, and other distinct categories, a total effect size was calculated from the presented values and considered in the meta-analysis. In studies where the effect size was not reported, but information related to exposure and outcome was available, the effect size and 95% CI were estimated. Random-effects models for the meta-analysis were used in overall summary estimations. Forest plots were used to illustrate the results and any individual odds ratio. Subgroup analysis was performed based on geographical location (e.g., North America, Europe, and Asia), study sample size (> 10,000 vs. ≤ 10,000), study design (e.g., case-control, cross-sectional, and cohort), study period (2005 to 2014, and 2015 to 2022), and duration of follow-up (> 7 years or ≤ 7 years). Adjustments for confounding variables in the study indicated Yes (multivariable analysis) or No (univariate analysis) and included the Newcastle-Ottawa Scale (NOS) category (< 7 and ≥ 7).

The exploration of heterogeneity in the studies was assessed using the Cochran chi-square (reported by chi-square and $P < .1$ was significant); and the statistic I^2 was calculated. A series of sensitivity analysis assessed the heterogeneity robustness. In addition, the analysis evaluated the effect of individual studies on the summary estimates. A sensitivity analysis was performed using the pooled estimates which were recalculated after each run and subsequently excluding studies. Finally, a meta-regression analysis was performed to determine the difference in the observed effect size among studies.

Potential publication bias was calculated by using Begg's and Egger's tests. All statistical analyses were performed by using Stata 14.0 (Stata LLC, College Station, TX, USA). A $P < .05$ was considered statistically significant.

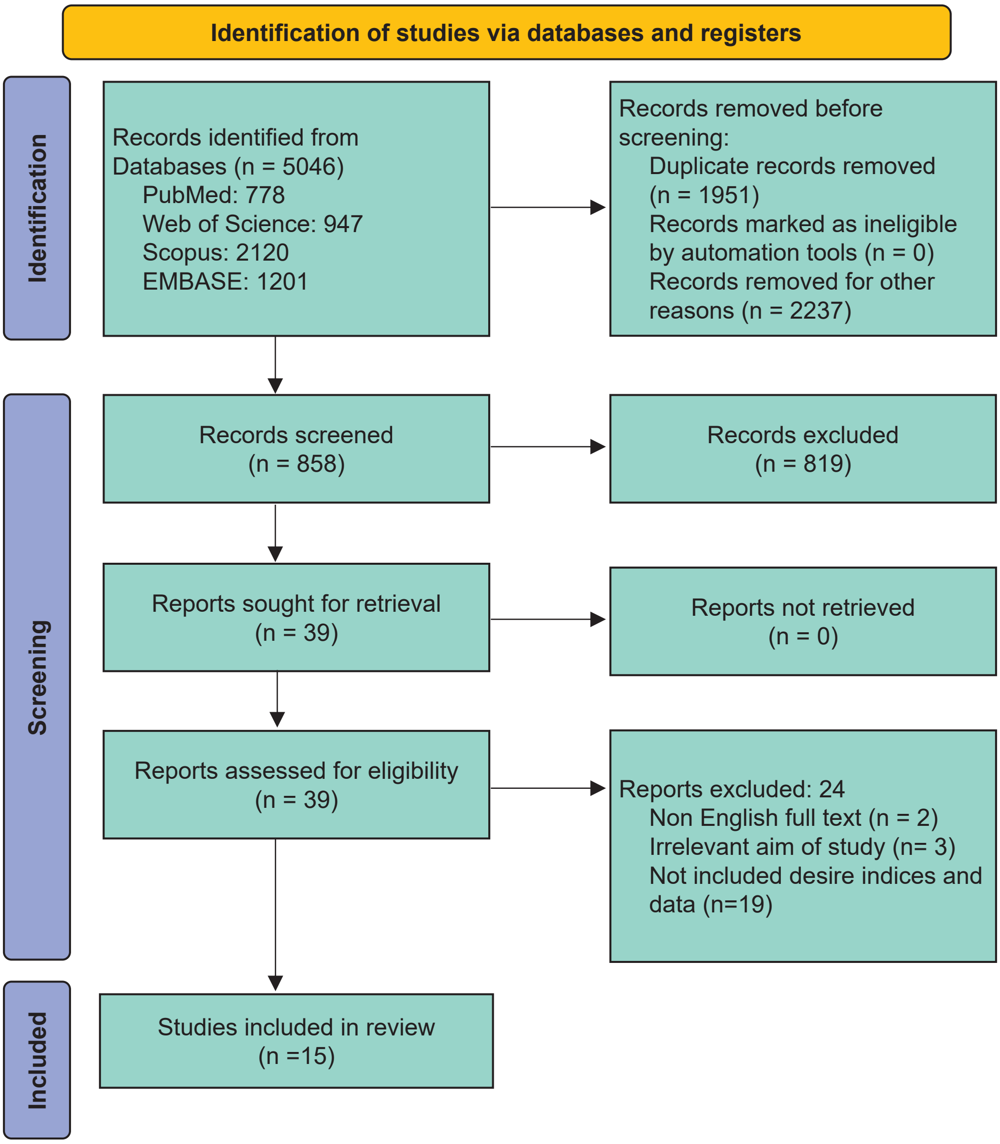

Figure 1. The Flowchart of the Studies Included in the Meta-analysis

RESULTS

Search Results, Characteristics of Selected Studies

Figure 1 illustrates the study selection processes represented by the PRISMA flow diagram. In the initial search of the four databases (PubMed, EMBASE, Web of Science, and Scopus), 5046 titles/abstracts were retrieved. 1951 duplicated articles were removed, and 24 titles/abstracts were also excluded since two of them were published in non-English language[23,24] and others were irrelevant to our research.[8-10,25] The goal was only to include appropriate indices and data.[3,9,26-42] After review, a total of 15 articles were included in this systematic review and meta-analysis study.[43-57] The included studies were cohort (n = 5),[43,50,52,56,57] case-control (n = 4),[44,47-49] and cross-sectional (n = 6).[45,46,51,53-55] There were five studies from North America,[43,45,46,49,50] eight from Asia,[44,47,48,51-55] and two from Europe.[56,57] The mean age of participants was less than 30 years in four studies,[46,47,49,52] and greater than or equal to 30 years in the other 11 studies,[43-45,48,50,51,53-57] The data of these studies were available from 936,005 participants from the selected articles used in the meta-analysis. There were 320,159 (34.20%) individuals from North America, 537,807 (57.45%) from Europe, and 78,039 (8.33%) from Asia (Table 1).

Subsequently, each individual study was included in the meta-analysis and used to estimate the connection between obesity and the possibility of kidney stones. Some data required adjustment to the role of the variables by using statistical techniques adjusted confounding variables. Table 2 outlines the variables that were adjusted for each study.

Association Between Obesity and Risk of Developing Kidney Stones

Compared to non-obese individuals, the OR of kidney stones in obese participants was 1.35 (95% CI: 1.20 to 1.52, $P < .001$). The OR determined for the link between obesity and kidney stones are illustrated in Figure 2. There was significant heterogeneity in the results from the meta-analysis [chi-square = 316.87, (df = 14), $P \leq .001$, $I^2 = 95.6\%$].

The Meta-regression and Sensitivity Analysis

To explore the sources of heterogeneity, a meta-regression model was developed that considered different variables, including year, study design, follow-up duration, sample size, study period, study quality, geographical location, and the adjustment of confounding variables. The meta-regression analysis revealed no significant source of heterogeneity ($P > .20$).

In addition, a sensitivity analysis was conducted by excluding each study from the analysis one by one. However, the estimated OR did not change significantly, indicating the robustness of the meta-analysis results (Table 3 and Figure 3).

Subgroup Analysis

A subgroup analysis was performed to investigate

Table 1. Characteristics of Studies Reviewed for the Assessment of the Association Between Obesity and the Risk of Developing Kidney Stones

Publication Lead Author	Year	Study Setting	Study Design	Sample Size	Age (mean)	OR	95% CI		Follow-up (months)	NOS
Taylor [43]	2005	United States	Cohort	139746	NA	1.67	1.07	2.61	552	9
Semins [45]	2010	United States	Cross-sectional	95,598	48.55	2.19	1.92	2.49	60	5
Kim [46]	2011	United States	Cross-sectional	506	11.01	0.84	0.63	1.12	84	7
Lee [44]	2008	South Korea	Case-control	714	43.3	2.57	1.38	4.79	54	5
Oda [48]	2014	Japan	Case-control	2718	51.9	1.01	0.92	1.10	48	7
Sorensen [50]	2014	United States	Cohort	84,225	63.55	1.84	1.64	2.07	96	7
Roddy [49]	2014	United States	Case-control	84	15.3	1.11	0.58	2.11	60	7
Sancak [51]	2015	Turkey	Cross-sectional	574	51.2	1.08	1.03	1.13	12	5
Yoshimura [52]	2016	Japan	Cohort	4074	31	1.41	1.01	1.96	228	7
Khalili [53]	2021	Iran	Cross-sectional	9932	49.94	1.3	1.14	1.48	NA	6
Choi [54]	2022	South Korea	Cross-sectional	34,294	50.72	1.29	1.19	1.39	84	9
Lee [55]	2022	Taiwan	Cross-sectional	25,268	50.99	1.027	1.019	1.034	144	7
Selimoğlu [47]	2013	Turkey	Case-control	465	4.9	3.28	1.68	6.41	NA	6
UKBB (UK Biobank) [56]	2015	United Kingdom	Cohort	361,194	60	1.4	1.16	1.69	> 60	8
FinnGen [57]	2021	Finland	Cohort	176613	50	1.26	1.05	1.51	-	8

Abbreviation: NA, Not applicable.

Table 2. Adjusted Variables in Assessment of the Association Between Obesity and the Risk of Developing Kidney Stones

First Author	Year	Adjusted Variables
Taylor [43]	2005	Age, fluid intake, dietary factors, and thiazide use
Semins [45]	2010	NA
Kim [46]	2011	American race, Medicaid payer status
Lee [44]	2008	NA
Oda [48]	2014	Age, antidiabetic and/or antihyperlipidemic drug use, antihypertensive, current smoking, physical activity, daily alcohol drinking, and histories of stroke and coronary heart disease
Sorensen [50]	2014	Age (continuous); history of diabetes; race (category); hormone replacement therapy (category); use of calcium supplement; region (category); income (dichotomized); and quintile intake of water, animal protein, sodium, and dietary calcium.
Roddy [49]	2014	Creatinine and weight, potassium, citrate, pH, sodium, and oxalate
Sancak [51]	2015	NA
Yoshimura [52]	2016	Age, cardiorespiratory fitness, systolic blood pressure, alcohol consumption, and cigarette smoking.
Khalili [53]	2021	NA
Choi [54]	2022	Age, and sex
Lee [55]	2022	Age, sex, alcohol consumption, smoking, exercise habits, diastolic blood pressure, history of hypertension, systolic blood pressure, history of diabetes history of dyslipidemia, uric acid, hemoglobin, eGFR, albumin, Hemoglobin A1c, fasting glucose, and triglyceride
Selimoğlu [47]	2013	NA
UKBB [56]	2015	NA
FinnGen [57]	2021	NA

Abbreviations: NA, Not applicable; eGFR, estimated glomerular filtration rate.

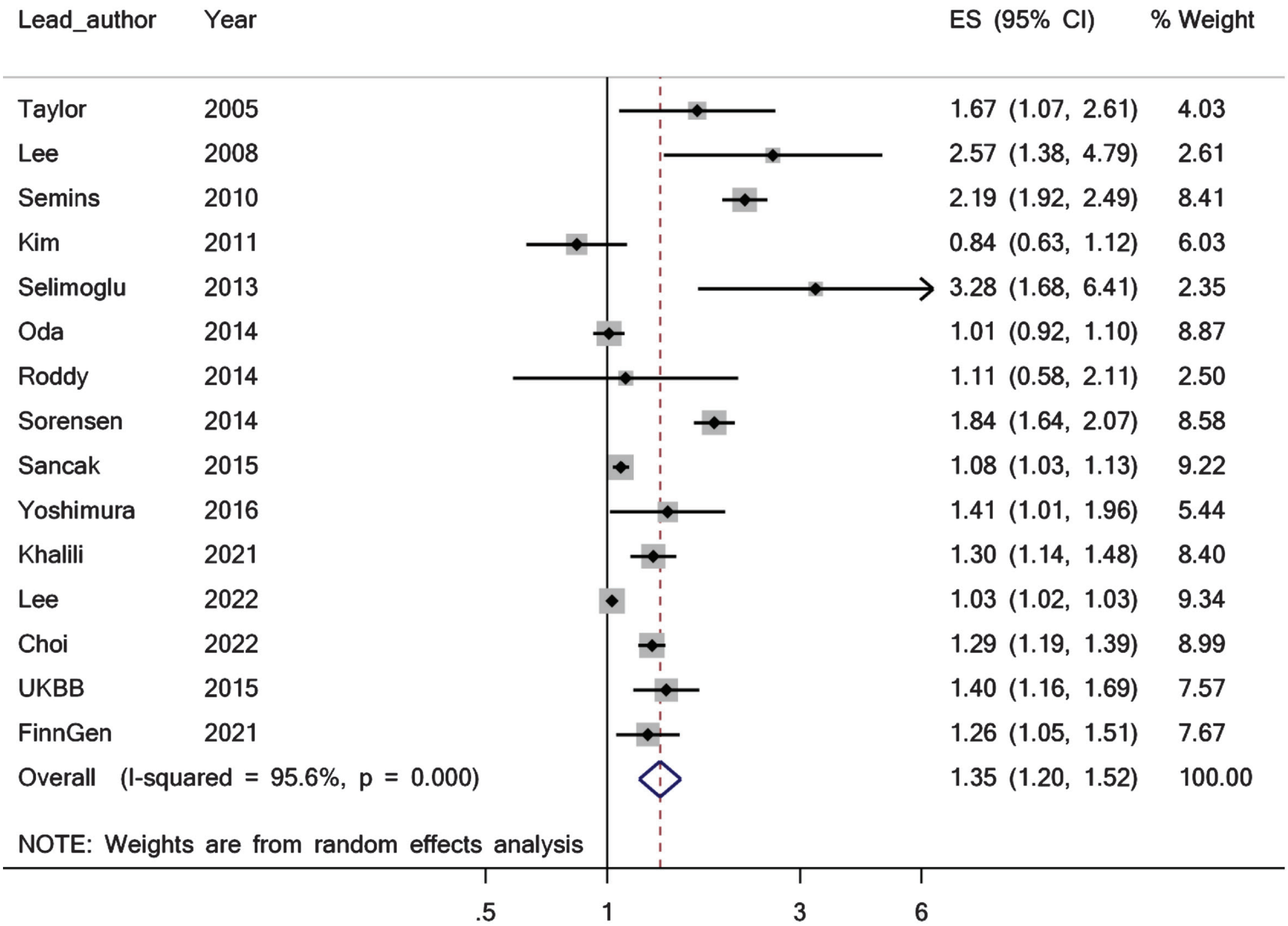

Figure 2. The Forest Plot of the Association Between Obesity and the Risk of Developing Kidney Stones

Table 3. Sensitivity Analysis for the Assessment of the Association Between Obesity and the Risk of Developing Kidney Stones

First author	Year	OR (95% CI)
Taylor	2005	1.34 (1.19 to 1.51)
Lee	2008	1.33 (1.18 to 1.50)
Semins	2010	1.27 (1.15 to 1.41)
Kim	2011	1.39 (1.23 to 1.58)
Selimoglu	2013	1.32 (1.17 to 1.49)
Oda	2014	1.39 (1.22 to 1.59)
Roddy	2014	1.36 (1.20 to 1.53)
Sorensen	2014	1.30 (1.17 to 1.45)
Sancak	2015	1.40 (1.20 to 1.64)
Yoshimura	2016	1.35 (1.19 to 1.52)
Khalili	2021	1.36 (1.20 to 1.54)
Lee	2022	1.40 (1.21 to 1.63)
Choi	2022	1.36 (1.20 to 1.54)
UKBB	2015	1.35 (1.19 to 1.52)
FinnGen	2021	1.36 (1.20 to 1.54)

correlation between obesity and kidney stones. The analysis evaluated study design, sample size, length of the follow-up period, study period, geographical location, and study quality based on the Newcastle-Ottawa Scale. The OR of developing kidney stones in obese individuals was 1.50 (95% CI: 1.25 to 1.80, $P < .001$). Further assessment of the cohort studies resulted in 1.25 (95% CI: 1.07 to 1.45, $P = .004$); for case-control studies, and in cross-sectional studies 1.68 (95% CI: 0.91 to 3.09, $P = .098$). Breaking the studies into geographical locations indicated that the OR for developing kidney stones in obese individuals was 1.51 (95% CI: 1.11 to 2.05, $P = .009$) in North America, 1.33 (95% CI: 1.16 to 1.51, $P < .001$) in Europe, and 1.18 (95% CI: 1.08 to 1.29, $P < .001$) in Asia (Table 4). The results of the subgroup analysis investigating other variables are tabulated in Table 4.

Evaluation of Publication Bias of Association Between Obesity and Risk of Developing Kidney Stones

Calculating the relationship between obesity and the risk of developing kidney stones resulted in Begg's ($P = .625$) test result, which confirmed no publication bias. However, the analysis from Egger's test was ($P = .005$) demonstrating publication bias, which is illustrated in Figure 4.

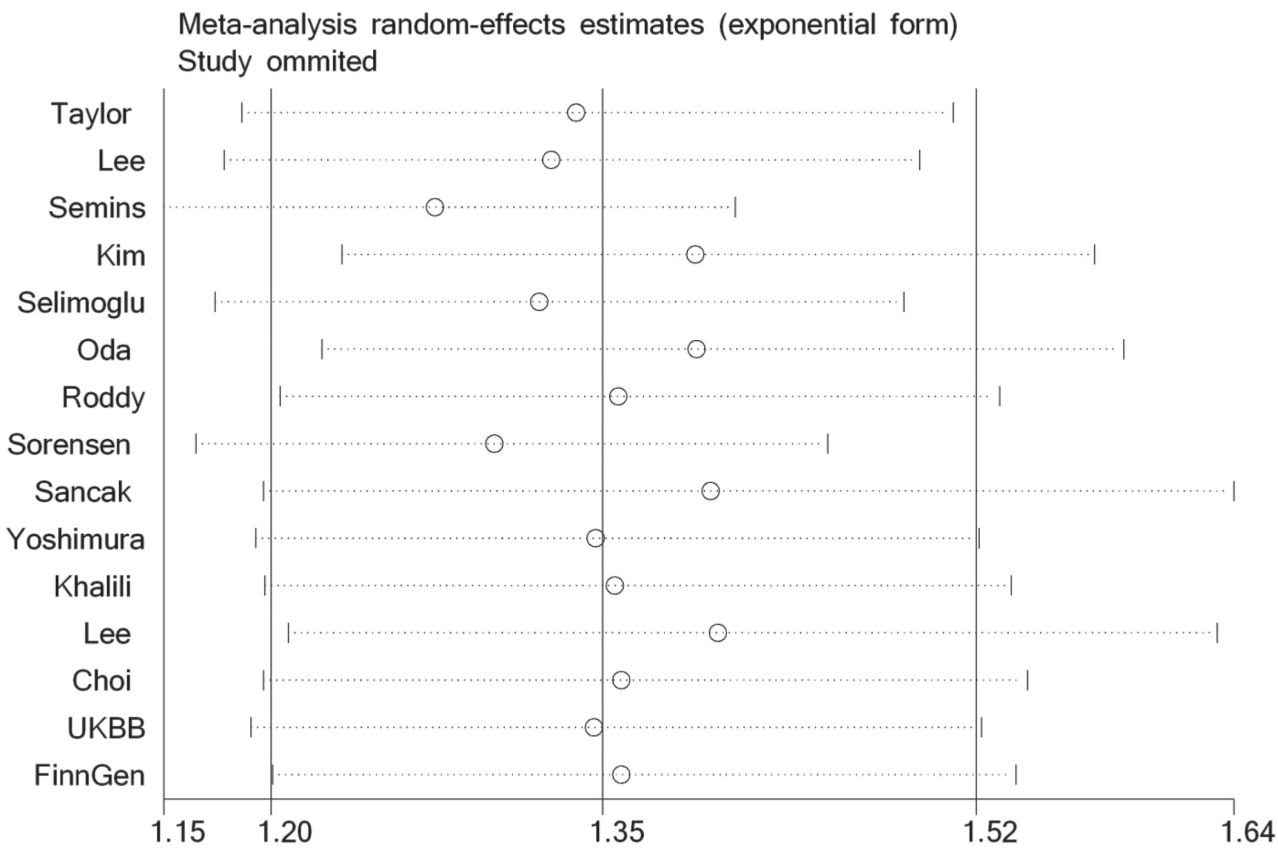

Figure 3. Sensitivity Analysis for the Assessment of the Association Between Obesity and the Risk of Developing Kidney Stones

Table 4. Subgroup Analysis of the Association Between Obesity and the Risk of Developing Kidney Stones

Characteristics	Study Number	OR (95% CI)	*P*
Study Type			
Cohort	5	1.50 (1.25 to 1.80)	< .001
Case-control	6	1.25 (1.07 to 1.45)	.004
Cross-sectional	4	1.68 (0.91 to 3.09)	.098
Study Location			
North America and Canada	5	1.51 (1.11 to 2.05)	.009
Asia	8	1.18 (1.08 to 1.29)	< .001
Europe	2	1.33 (1.16 to 1.51)	< .001
Study Period			
2005 to 2014	8	1.59 (1.15 to 2.20)	.005
2015 to 2022	7	1.20 (1.15 to 2.20)	< .001
Follow-up Period			
Less than seven years	7	1.49 (1.16 to 1.91)	.002
Seven years and more	8	1.30 (1.08 to 1.56)	.006
Sample Size			
> 10000	7	1.47 (1.15 to 1.88)	.006
≤ 10000	8	1.19 (1.04 to 1.37)	.014
Newcastle-Ottawa Scale (NOS)			
< 7	5	1.76 (1.22 to 2.54)	.003
7 ≤	10	1.25 (1.08 to 1.45)	.003
Age Group			
< 30	5	1.37 (1.20 to 1.55)	< .001
30 ≤	10	1.35 (1.20 to 1.52)	< .001
Adjustment of Confounding Variables			
Yes (Multivariable analysis)	8	1.23 (1.04 to 1.45)	.018
No (Univariable analysis)	7	1.58 (1.22 to 2.05)	< .001

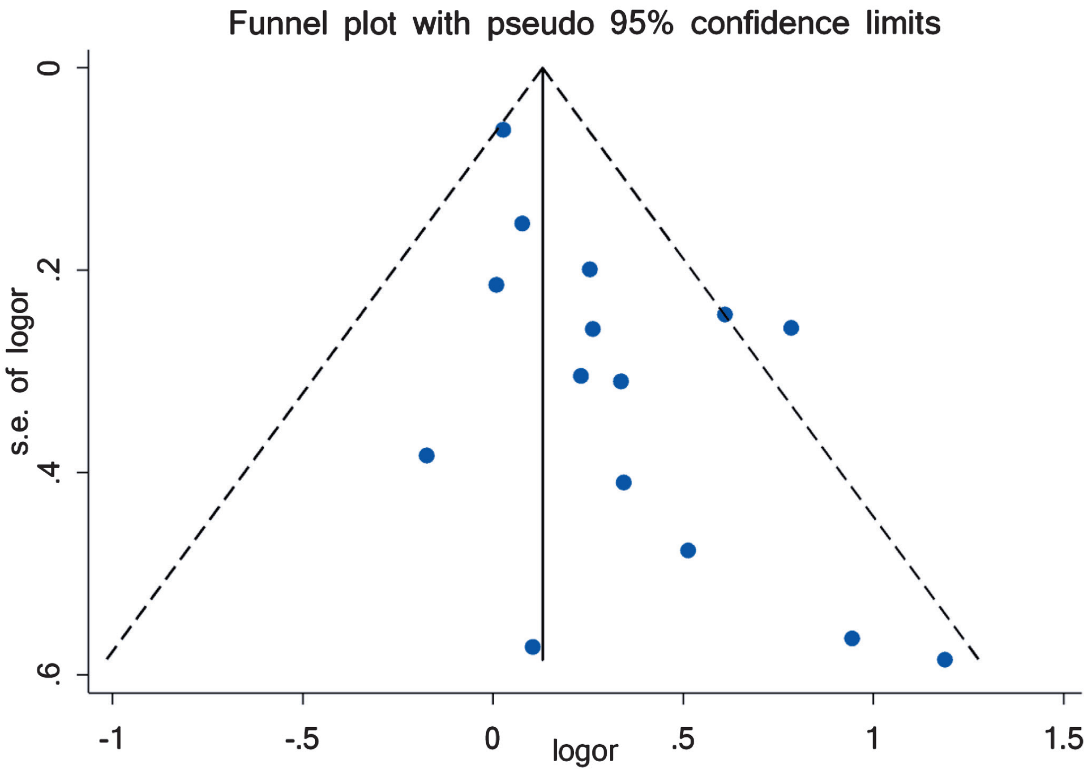

Figure 4. Funnel Plot of the Association Between Obesity and the Risk of Developing Kidney Stones

DISCUSSION

Obesity is an important risk factor that increases risk of several diseases. It is also linked to an increased probability of kidney stone development. Additionally, it alters numerous biochemical compositions in the body. For example, calcium oxalate and uric acid stones are the most frequent types of stones seen in obese individuals. Obesity is also linked to low urine pH, which is the main factor contributing to an increase in uric acid stones. In addition, inflammation, and oxidative stress, may increase the probability of kidney stones in obese patients.[19,58-60]

The results of this systematic review and meta-analysis study demonstrate that when non-obese and obese individuals were compared, the OR of kidney stones was 1.36 (95% CI: 1.19 to 1.54, $P < .001$). Therefore, as BMI increases and the individual become more obese, their risk factor for kidney stones multiplies. A previous systematic review and meta-analysis study in 2018 reported RR was 1.21 (95% CI: 1.12 to 1.30, I2 = 76%, n = 8) per 5-unit increment in BMI; 1.06 (95% CI: 1.04 to 1.08, I2 = 67%, n = 3) per 5 kg increase in weight; 1.12 (95% CI: 1.06 to 1.18, I2 = 86%, n = 3) per 5 kg of weight gain, and 1.16 (95% CI: 1.12 to 1.19, I2 = 0%, n = 5) per 10 cm increase in waist circumference.[61] Rahman *et al.* reported the impact of metabolic syndrome (frequently observed in those with obesity) on the incidence of nephrolithiasis; and, they found that those with obesity had an OR of (95% CI: 1.099 to 2.109) related to kidney stones. Obesity is linked to multiple co-morbidities, including an increased risk of developing nephrolithiasis.[62] A meta-analysis performed by Wong *et al.* found a positive link between obesity and kidney stones [63]. Therefore, this review is consistent with previous results in the literature. Most review studies approve that obesity should be considered as a possible factor for developing kidney stones. Due to the increasing number of individuals with obesity, all physicians should outline the risk to their patients who are overweight or obese to minimize the complications of these diseases.[12,20,21]

This study supports the consensus that obesity is a risk factor for kidney stones as observed in the review of previous systematic studies and meta-analyses. However, there is a lack of investigation into potential confounding factors, a limitation in current literature and in this study. In addition, several studies have been conducted with small sample sizes. A lack of consideration to include adiposity criteria or measurements such as waist circumference, hip circumference, and weight-related measures are also limitations of the present study.

Based on our results, the analysis confirmed that obesity increases the risk of kidney stone development. However, more studies are needed due to a lack of data specifically focused on obesity. To fill the knowledge gap, future studies need to control the confounding factors to gather more accurate information. Obesity prevention strategies need to become a priority in health policies. Healthcare activities should be implemented to prevent the effects of obesity in communities. In this regard, understanding the physiological concerns associated with adiposity and weight gain is essential. However, a better understanding of the environmental factors associated with an individual will also help minimize risk of kidney stones. Therefore, studies should be undertaken in communities where the incidence of obesity is high, and thereby, the risk of developing kidney stones is eminent.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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