BMC Cardiovascular Disorders

SYSTEMATIC REVIEW Open Access

The effects of ursodeoxycholic acid on cardiometabolic risk factors: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Chronic diseases such as obesity, hypertension, and metabolic syndrome are major health concerns worldwide. Ursodeoxycholic acid (UDCA) is a bile acid that is naturally produced in the liver and has been used for the treatment of various liver disorders. In this systematic review and meta-analysis, we investigated how UDCA might affect inflammation, blood pressure, and obesity.

Methods Five major databases were searched from inception to August 2024. The investigated outcomes included body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). A random effect was carried out to estimate pooled weighted mean difference (WMD) with 95% confidence intervals (CI). The registration code is CRD42023428064.

Results Of the 7912 articles in the initial search, 12 were included in the systematic review and meta-analysis. UDCA consumption significantly decreased BMI (WMD: -0.29 kg/m^2, 95% CI: -0.58, -0.01, $P=0.044$), and DBP (WMD: -2.16 mmHg, 95% CI: -3.66, -0.66, $P=0.005$). It also increased SBP (WMD: 5.50 mmHg, 95% CI: 3.65, 7.35, $P<0.001$); however, it was not associated with weight loss (WMD: -0.3 kg, 95% CI: -1.3, 0.71, $P=0.561$). Our systematic review showed that UDCA consumption has no effect on IL-6 and TNF-α.

Conclusion This systematic review and meta-analysis suggest that UDCA supplementation may improve BMI and DBP, whereas it may increase SBP and have no effect on weight or inflammation. Further long-term and well-designed RCTs are needed to further assess and confirm these results.

Keywords Ursodeoxycholic acid, Blood pressure, Body weight, Meta-analysis, Inflammation

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Background

Chronic diseases such as obesity, hypertension, and metabolic syndrome (Mets) are major health concerns worldwide, affecting millions of individuals and contributing to significant morbidity and mortality. These conditions are often associated with increased inflammation, which can contribute to disease progression and complications [1–3]. Ursodeoxycholic acid (UDCA) is a bile acid that is naturally produced in the liver and has been used for the treatment of various liver diseases including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and non-alcoholic fatty liver disease (NAFLD) [4, 5].

Obesity is a complex chronic disease that is associated with multiple comorbidities and decreased life expectancy [6, 7]. The prevalence of obesity has been rapidly increasing worldwide so effective treatment options are urgently needed. Hypertension is a major public health concern and a prominent risk factor for cardiovascular disease (CVD). Despite the availability of numerous antihypertensive medications, many individuals with hypertension remain poorly controlled or experience adverse effects from their medications [8, 9]. Therefore, alternative therapeutic approaches are needed. The drug UDCA is used to treat certain liver disorders, such as primary biliary cholangitis and nonalcoholic steatohepatitis. Inflammation and cholestasis (bile build-up) in the liver are thought to be the main therapeutic effects of UDCA, which can help boost liver health. The exact mechanism of action is not fully understood, and the effectiveness of UDCA in treating these conditions may differ from person to person [10]. Several studies have investigated the effects of UDCA on blood pressure in both animal and human studies. In humans, a randomized controlled trial found that UDCA treatment for 12 weeks significantly reduced systolic blood pressure (SBP) in individuals with Mets [11]. Similarly, another study reported that six months'consumption of UDCA significantly reduced systolic and diastolic blood pressure (DBP) in individuals with NAFLD [12]. Numerous chronic diseases such as CVD, diabetes, and NAFLD are largely caused by an intricate process called inflammation [13–16]. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are examples of pro-inflammatory cytokines that have been shown to be decreased by UDCA treatment [17]. In addition, UDCA has been shown to activate the peroxisome proliferator-activated receptor (PPAR) pathway, which has anti-inflammatory effects [18–20]. It is known that UDCA is primarily used to treat liver diseases, and its effects on other body systems such as the cardiovascular system are not well understood. Understanding the effects of UDCA on cardiometabolic disease could have significant implications. In this meta-analysis, we aimed to assess the impact of UDCA on anthropometric measurements, blood pressure, and inflammation in individuals with chronic diseases such as obesity, Mets, and hypertension for the first time.

Table 1 The population, intervention, comparison, outcome, and study type criteria

Criteria	Description
Population	Adult population (≥ 18 years)
Intervention	Ursodeoxycholic acid
Comparison	Control group (placebo)
Outcome	At least one of the following outcomes of interest: weight, BMI, systolic blood pressure, diastolic blood pressure, interleukin 6, tumor necrosis factor-alpha
Study types	Randomized controlled clinical trials

Methods

The present study was designed following preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline [21]. The protocol was registered in the international prospective register of systematic reviews (PROSPERO) database. (http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42023428064).

Search strategy

The systematic literature searches were conducted until August 31, 2024, on ISI Web of Science, Cochrane library, PubMed, Scopus, and Google scholar databases for the following search strategy including a combination of medical subject headings (MeSH) and non-MeSH keywords: ("ursodeoxycholic acid"[tiab] OR "ursodeoxycholic acid"[Mesh]) AND (intervention[tiab] OR RCT[tiab] OR randomized[tiab] OR random[tiab] OR Randomly[tiab] OR Placebo[tiab] OR Assignment[tiab] OR trial[tiab] OR trials[tiab] OR randomised[tiab] OR "Methods"[Mesh] OR Cross-Over[tiab] OR "Double-Blind"[tiab] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Placebos"[Mesh] OR "Placebo Effect"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh]) (Supplementary Table 1). No language and time filters were applied and EndNote library (version X9, for Windows, Thomson Reuters, Philadelphia, PA, USA) was used to screen studies and remove duplicated ones. The bibliographies of retrieved articles were manually searched to find other eligible papers.

Selection criteria

For the current systematic review and meta-analysis research, as indicated in Table 1, the demographic, intervention, comparison, outcome, and study type criteria [22] were applied. The title and abstract of retrieved studies were scanned by two independent researchers (MRA,

ER) to find relevant and potentially relevant articles. Disagreements were resolved by consensus with AH. Studies with randomized controlled trial (RCT) design (either parallel or cross-over), which evaluated the effects of UDCA on weight, body mass index (BMI), SBP, DBP, IL-6, and TNF-α, reporting means and standard deviations (SDs) (or other convertible effect sizes) of aforementioned outcomes at baseline and the end of the study for both intervention and control groups, performed on adult participants (≥ 18 years) were selected for the full-text review. Studies were excluded if they had any of the following criteria: the recruiting subjects aged less than 18 years, the lack of a control group, having a non-randomized or semi-randomized design, and including combined intervention programs in which the net effect of UDCA could not be assessed. Conference abstracts, books, animal studies, review articles, qualitative studies, and observational papers were also excluded.

Data extraction

The following data were collected from each eligible study using a standardized form by two independent researchers (MRA, ER): general information (the family name of the first author, year of publication, and research location), participants' characteristics (age, sex, BMI, and health status), trial characteristics (design, sample size, intervention duration, and UDCA dose), control group, and means and SDs of weight, BMI, SBP, DBP, IL-6, and TNF-α before and after intervention for both treatment and control groups. If a study did not report the required data, we contacted the corresponding author to acquire them.

Quality assessment of studies

Using the revised Cochrane Risk of Bias Tool (Rob 1) [23], two reviewers independently evaluated papers for bias according to the following methodological domains: (1) random sequence generation, (2) allocation concealment, (3) selective reporting, (4) blinding of participants and personnel, (5) blinding of outcome assessment, (6) incomplete outcome data, and (7) other potential sources of bias (Table 2). Any differences were resolved by discussion with AH. Based on the Cochrane Handbook recommendation, studies were classified into three categories including high quality (all domains had "low risk"), low quality (at least one domain had "high risk"), and moderate quality (at least one domain had "unclear risk").

Statistical analysis

The mean differences in changes with 95% confidence intervals (95% CI) for weight, BMI, SBP, and DBP were calculated to be used as effect size for meta-analyses. A random-effects meta-analysis was carried out to estimate pooled weighted mean difference (WMD) with 95% CI for the effect of UDCA supplementation on anthropometric indices and blood pressure [24]. We conducted only a systematic review on the impact of UDCA supplementation on inflammatory markers since only two studies [25, 26] examined it. In studies that reported standard error of mean (SEM) in place of SDs, the following formula was applied: $SD = SEM \times \sqrt{n}$, where n is the number of individuals in each group. For articles that provided the median and interquartile range, we calculated mean and SD values using formulas suggested by Hozo et al. [27]. When change values were not provided, by the use of $SD_{difference}$ = Square Root $[(SD_{pre-treatment})^2 + (SD_{post-treatment})^2 - (2 \times R \times SD_{pre-treatment} \times SD_{post-treatment})]$, SD for mean changes between baseline and final values were estimated in which the correlation coefficient (R) was considered 0.8 [28]. If studies represented outcomes in graphical form, we used GetData Graph Digitizer version 2.24 [29]

Table 2 Risk of bias for randomized controlled trials, assessed according to the revised cochrane risk-of-bias tool for randomized trials (RoB 1)

Publications	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	other source of bias
1. Leuschner (2010)	L	U	L	L	U	H	L
2. Marks (1996)	L	L	L	L	U	L	L
3. Miller (2003)	L	U	L	L	U	L	L
4. Shiffman (1995)	L	U	L	L	U	L	L
5. Sugerman (1995)	L	U	L	L	U	L	L
6. Lindor (2004)	L	U	L	L	U	L	L
7. Abouzeid (2018)	L	H	L	H	H	H	L
8. Gianturco (2013)	L	L	L	L	U	L	L
9. Méndez-Sánchez (2004)	L	U	L	L	U	H	L
10. Schiedermaier (2000)	L	U	L	L	U	L	L
11. von Haehling (2012)	L	U	L	L	U	L	L
12. Balmer (20019)	L	U	L	L	U	L	L

L, Low risk of bias; H, High risk of bias; U, Unclear risk of bias

to extract them. Cochran's Q test and I^2 statistic were applied to check the possibility of heterogeneity and its amount, respectively [30]. If I-squared values were more than 50% or Cochran's Q test p values were less than 0.05, the between-studies heterogeneity was considered significant [31]. To explore the source of heterogeneity among the analyzed RCTs, we performed subgroup analyses based on the duration of intervention (≤6 months/ >6 months) and mean age of participants (≤40 years/ > 40 years). The potential publication bias was detected using a visual check of Funnel plots and Egger's regression test [32]. To determine the sensitivity of pooled effect sizes to one individual study, we excluded trials one-by-one from the meta-analysis and recalculated the pooled effect size. Body weight and BMI were reported in kg and kg/m^2, and SBP and DBP were reported in mmHg. Units reported for IL-6 and TNF-α were pg/mL. All analyses were performed using STATA, version 14 (Stata Corp, College Station, Texas, USA). P-values less than 0.05 were considered statistically significant.

Results

Literature search

The primary search identified 7910 studies, in addition to two new papers found by manual searching. Removing duplicated papers resulted in 6183 papers that were scanned titles and abstracts. Then, 4787 studies were excluded due to the lack of relevant or original data, 225 being animal studies, and 1150 review articles. From 21 articles included in the full-text review stage, six studies were irrelevant, two prescribed control group medicine [33, 34] and one was conducted on subjects less than 18 years old [35]. The remaining 12 papers were included in the qualitative and quantitative synthesis except for two studies on IL-6 and TNF-α, which were only included in the systematic review. The PRISMA flow diagram of the study selection process is shown in Fig. 1.

Study characteristics

Table 3 summarizes the characteristics of selected papers. A large number of studies were a parallel double-blinded trial in design [25, 36–44], and the other studies were cross-over double-blinded trials [26, 45] with a range of publication years between 1995 and 2019. The present study included a total of 1796 people aged over 18 years with an intervention period of 4–96 weeks. The dosage of prescribed UDCA ranged between 300 and 1200 mg/day except for three studies [25, 38, 39] in which the UDCA was prescribed in the range from 12 to 28 mg/kg/day. The median prescribed dose of UDCA was (interquartile range 500–1200 mg/day). The majority of studies were performed on both genders [25, 36–40, 42–45], and two studies were conducted on only females [41] or males [26]. The mean BMI of participants in ten studies [25, 26, 36, 37, 39–44] that provided it, was in the range of obesity. Except for three studies [40, 43, 45] conducted on healthy individuals, others were carried out on unhealthy subjects. In the majority of selected studies, UDCA was prescribed as a part of a regular diet; however, one RCT examined the effect of UDCA in the context of a very low-calorie diet [40] and one along with a health management program [43]. All co-interventions (very low-calorie diet and health management program) were also considered in the control groups. In terms of study quality (Table 2), nine [25, 26, 37, 39, 40, 42–45] out of 12 trials were categorized as moderate quality whereas others were low quality studies [36, 38, 41].

Qualitative synthesis

Six studies did not report any significant effects on body weight [38–40, 42–44]. Although seven arms [36, 39–41, 43] indicated that UDCA intervention had no significant effect on BMI, one study [37] found a negative effect on BMI. From three trials investigated the impact of UDCA supplementation on SBP, two studies [26, 45] did not find any substantial effects while one study [37] indicated a positive effect. Except for one study [37] reporting a non-significant effect on DBP, the other two studies [26, 45] showed a significant reduction in DBP.

Meta-analyses

Since the data for inflammatory markers were not enough to be quantitatively synthesized, we analyzed data concerning anthropometric measurements and blood pressure.

UDCA and anthropometric measurements

A meta-analysis including six articles (1510 participants) indicated that UDCA supplementation did not have any significant effect on body weight (WMD: -0.3 kg, 95% CI: -1.3, 0.71, $P=0.561$), there was no evidence of heterogeneity among studies ($I^2=0\%$, $P=0.891$) (Fig. 2). When trials were stratified based on the intervention period (≤6 months/ >6 months) and the age of participants (≤40 years/ > 40 years), the impact of UDCA on weight remained non-significant (Table 4). The pooled estimate (six articles, including 1190 participants) showed a significant reduction in BMI following UDCA consumption (WMD: -0.29 kg/m^2, 95% CI: -0.58, -0.01, $P=0.044$), there was no evidence of heterogeneity among studies ($I^2=0\%$, $P=0.802$) (Fig. 3), which remained significant when the mean age of participants was over 40 years (Table 4).

UDCA and blood pressure

Three studies (129 participants) revealed that SBP increased in the intervention group compared to the control group following UDCA supplementation (WMD: 5.50 mmHg, 95% CI: 3.65, 7.35, $P<0.001$), there was

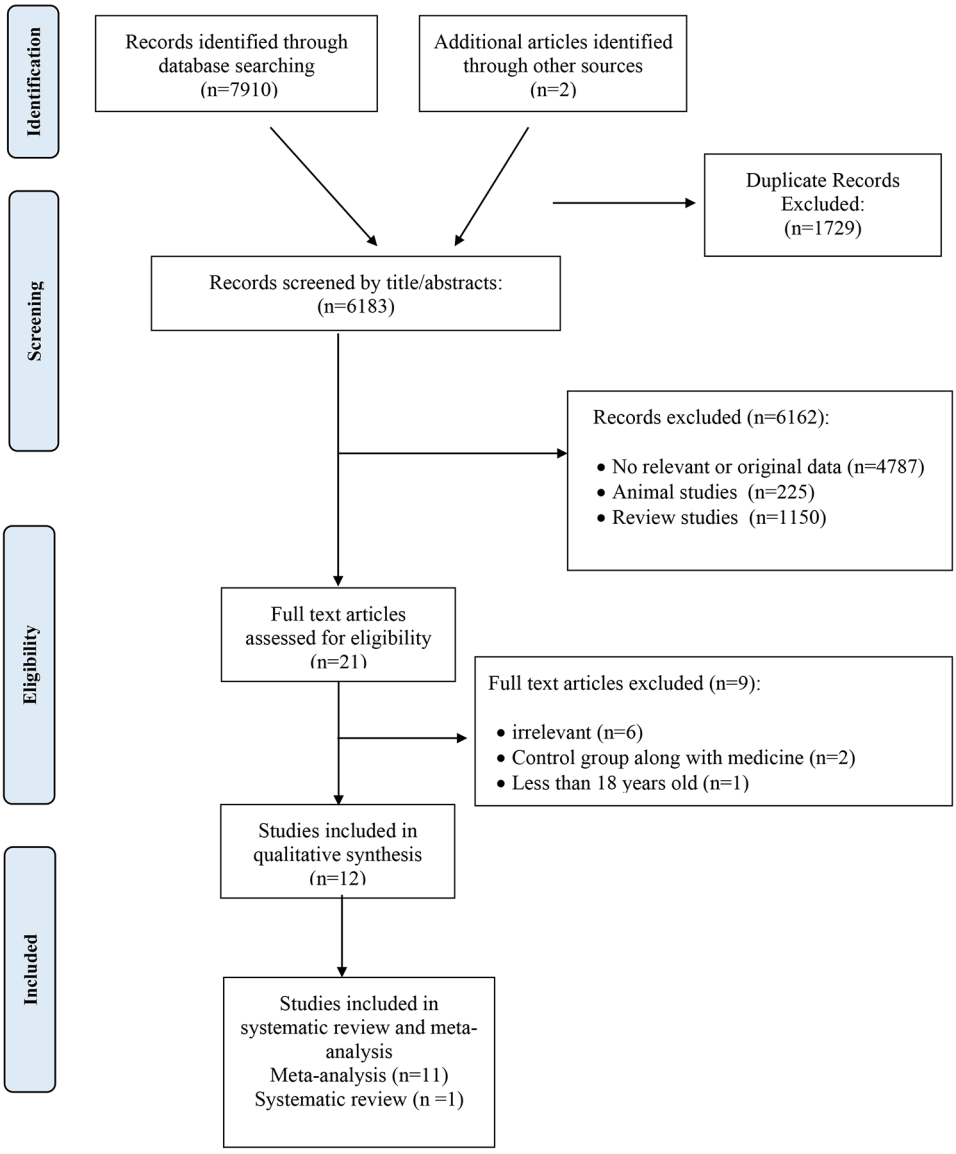

Fig. 1 Flow chart of the number of studies identified and selected into the meta-analysis

no evidence of heterogeneity among studies ($I^2 = 0\%$, $P = 0.574$) (Fig. 4); however, a significant decline was observed in DBP in comparison to the control group (WMD: -2.16 mmHg, 95% CI: -3.66, -0.66, $P = 0.005$), there was no evidence of heterogeneity among studies ($I^2 = 0\%$, $P = 0.530$) (Fig. 5).

UDCA and inflammation

Based on the results of two studies [25, 26], no significant changes were noted for IL-6 and TNF-α. IL-6 and TNF-α were not taken into account for the current meta-analysis due to the dearth of accessible data.

Publication bias and sensitivity analysis

The results of Egger's test indicated no evidence of publication bias for the weight ($P = 0.468$), BMI ($P = 0.193$), SBP ($P = 0.712$), and DBP ($P = 0.906$), which was in accordance with the visual inspection of funnel plots. To determine the dependency of pooled effect sizes on any single RCT, we eliminated each study at a time and recalculated the overall estimates. Sensitivity analysis for weight, BMI, SBP, and DBP showed that the overall effect sizes were not influenced by the exclusion of included studies.

Discussion

We performed a systematic review and meta-analysis to investigate the effects of UDCA supplementation on anthropometric measurements, blood pressure, and inflammation in adults. In this meta-analysis, we investigated the effects of UDCA on weight, BMI, SBP, DBP, TNF-α, and IL-6. To our knowledge, this is the first systematic review and meta-analysis to evaluate the effects

Table 3 Demographic characteristics of the included studies

First Author (year)	Location	Study Design	Health status	Sex	Sample size	Duration (week)	Mean age (year)	Baseline BMI (kg/m^2)	Intervention group	Comparator group	Outcome
1. Leuschner (2010)	Germany and Greece	Multicenter, RCT, double-blind, parallel	NASH	Both	186	72	43.23	Not reported	23–28 mg/kg/day UDCA	Placebo	Weight
2. Marks (1996)	USA	RCT, double-blind, parallel	Healthy	Both	32	6	40.4	35.9	A very low calorie diet (VLCD) (520 kcal/day) + 1200 mg/day UDCA	A very low calorie diet (VLCD) (520 kcal/day) + Placebo	Weight/BMI
3. Miller (a) (2003)	Austria	RCT, double-blind, parallel	Patients with vertical banded gastroplasty (VBG)	Both	58	96	35.2	44	500 mg/day UDCA	Placebo	Weight
4. Miller (b) (2003)	Austria	RCT, double-blind, parallel	Patients with adjustable gastric banding (AGB)	Both	66	96	35.2	44	500 mg/day UDCA	Placebo	Weight
5. Shiffman (a) (1995)	USA	Multicenter, RCT, double-blind, parallel	Healthy	Both	252	16	40.25	44.3	Patients were initially enrolled in a 16-week, 520-kcal/d, Health Management Resources liquid protein diet program + 300 mg/day UDCA	Patients were initially enrolled in a 16-week, 520-kcal/d, Health Management Resources liquid protein diet program + Placebo	Weight/BMI
6. Shiffman (b) (1995)	USA	Multicenter, RCT, double-blind, parallel	Healthy	Both	268	16	40.25	44.4	Patients were initially enrolled in a 16-week, 520-kcal/d, Health Management Resources liquid protein diet program + 600 mg/day UDCA	Patients were initially enrolled in a 16-week, 520-kcal/d, Health Management Resources liquid protein diet program + Placebo	Weight/BMI
7. Shiffman (c) (1995)	USA	Multicenter, RCT, double-blind, parallel	Healthy	Both	267	16	39.6	44.3	Patients were initially enrolled in a 16-week, 520-kcal/d, Health Management Resources liquid protein diet program + 1200 mg/day UDCA	Patients were initially enrolled in a 16-week, 520-kcal/d, Health Management Resources liquid protein diet program + Placebo	Weight/BMI
8. Sugerman (a) (1995)	USA	Multicenter, RCT, double-blind, parallel	gastric-bypass (GBP)	Both	71	24	36.9	50.3	300 mg/day UDCA	Placebo	Weight
9. Sugerman (b) (1995)	USA	Multicenter, RCT, double-blind, parallel	gastric-bypass (GBP)	Both	80	24	37.6	49.6	600 mg/day UDCA	Placebo	Weight
10. Sugerman (c) (1995)	USA	Multicenter, RCT, double-blind, parallel	gastric-bypass (GBP)	Both	82	24	36.7	49.8	1200 mg/day UDCA	Placebo	Weight
11. Lindor (2004)	United States and Canada	Multicenter, RCT, double-blind, parallel	NASH	Both	166	96	47.2	32	13–15 mg/kg/day UDCA	Placebo	Weight/BMI

Table 3 (continued)

First Author (year)	Location	Study Design	Health status	Sex	Sample size	Duration (week)	Mean age (year)	Baseline BMI (kg/m^2)	Intervention group	Comparator group	Outcome
12. Abouzeid (2018)	Egypt and Saudi Arabia	Two-center, RCT, double-blind, parallel	Patients with Post laparoscopic sleeve gastrectomy (LSG)	Both	89	48	38.3	47	500 mg/day UDCA	Placebo	BMI
13. Gianturco (2013)	Italy	RCT, double-blind, parallel	NAFLD	Both	93	48	61.5	29.5	300 mg/day UDCA	Placebo	BMI/SBP/DBP
14. Méndez-Sánchez (2004)	Mexico	RCT, double-blind, parallel	NAFLD	Female	23	6	38.75	33.75	1200 mg/day UDCA	Placebo	BMI
15. Schiedermaier (2000)	Germany,	RCT, double-blind, cross-over	Healthy	Both	20	4	28.5	Not reported	750 mg/day UDCA	Placebo	SBP/DBP
16. von Haehling (2012)	United Kingdom	RCT, double-blind, cross-over	Chronic heart failure (CHF)	Male	16	4	65.75	29.1	1000 mg/day UDCA	Placebo	SBP/DBP/IL-6/TNF-α
17. Balmer (20019)	Switzerland	RCT, double-blind, parallel	NASH	Both	27	96	46.5	30.5	12–15 mg/kg/day UDCA	Placebo	IL-6/TNF-α

of UDCA on anthropometric measurements, blood pressure, and inflammation in adults. Twelve studies were included in the systematic review and 11 of them were included in the meta-analysis with 17 arms and 1796 participants. These studies suggest that UDCA supplementation has significant beneficial effects on BMI and DBP. According to subgroup analysis, BMI has decreased significantly at the age of ≥ 40 years. No substantially significant correlations were identified for body weight, TNF-α, or IL-6. Additionally, it was found that UDCA consumption caused a significant increment in SBP.

The mechanism of UDCA consumption on BMI and blood pressure is unclear, but UDCA may decrease weight by activating bile acid receptors, and increasing thyroid-stimulating hormone (TSH) and glucagon-like peptide-1 (GLP-1) levels [46–49]. In terms of UDCA consumption's influence on blood pressure, there is a controversy. Chronic administration of UDCA decreases portal pressure through inducible NO synthase (iNOS) and thromboxane A2 (TXA2). However, UDCA may cause SBP to rise due to fluid retention [50].

UDCA, or ursodiol, a secondary bile acid in humans, dissolves cholesterol gallstones [51], which is actually an isomer of deoxycholic acid, with well-established therapeutic and cytoprotective properties [52–54]. UDCA supplementation has various therapeutic properties for various and numerous diseases such as antihyperlipidemic, antifibrotic, antiproliferative liver protection, and weight reduction effects in numerous in vivo and in vitro studies [26, 41, 42, 55–58]. According to the study's findings, UDCA had a significant decrease in BMI compared with baseline. The present study's results align with some RCTs that have been done so far [40, 41]. In a double-blind, placebo-controlled trial, a significant decrease in BMI was reported with UDCA supplementation compared to the placebo group. This study examined women with a BMI of > 30 and NAFLD. This study showed that daily supplementation with 1200 mg of UDCA for 6 weeks caused a significant reduction in BMI in the group treated with UDCA [41]. In our study, subgroup analysis showed that the BMI decreased in patients younger than 40 years old. Thus, it seems that UDCA is more effective in younger people in the reduction of BMI. Marks et al. showed that the consumption of 1200 mg ursodiol for 12 weeks was well tolerated by 47 obese patients, with an average age of 40.5 years. At the end of this clinical trial, ursodiol supplementation decreased the mean BMI of the intervention group significantly [40]. In Winston et al. study, a significant decrease in body weight was observed. In this in vivo study, three doses of ursodiol (50, 150, or 450 mg/kg/day) were given for 3 weeks. They reported significant weight reduction in animals treated with the 50 and 450 mg/kg/day doses of ursodiol [59]. Unlike BMI, no significant effect on weight was observed

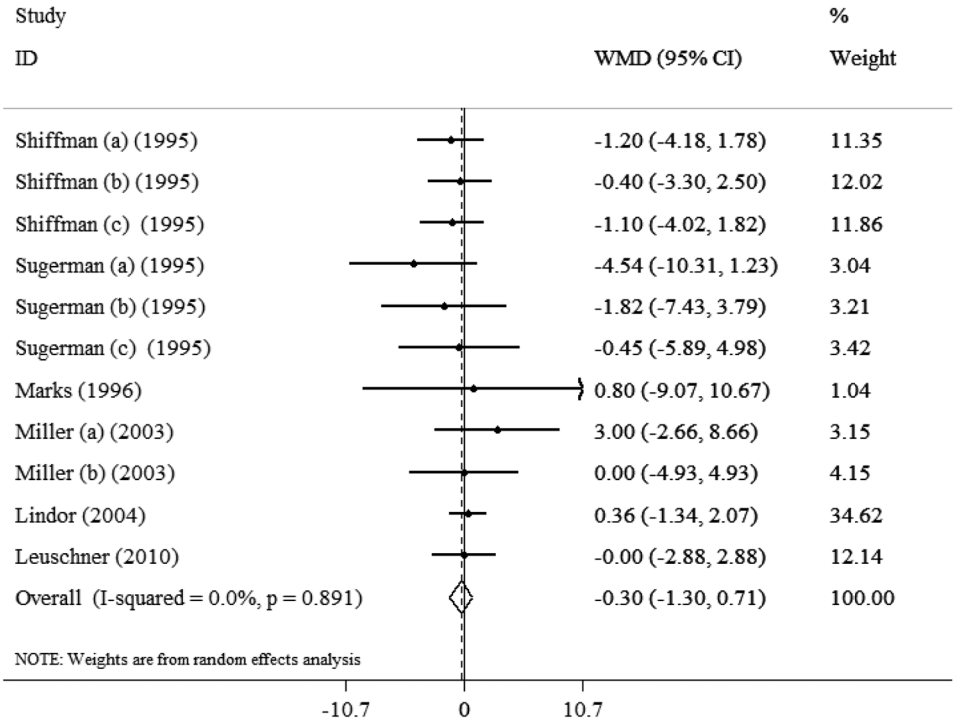

Fig. 2 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ursodeoxycholic acid on weight

Table 4 Subgroup analysis of included randomized controlled trials in meta-analysis of the effect of ursodeoxycholic acid on weight and BMI

Group	No. of effect size	WMD (95% CI)	*P* value	I^2 (%)	*P*-heterogeneity	*P* for between subgroup heterogeneity
Weight						
Pooled effect size	11	-0.30 (-1.30, 0.71)	0.561	0.0	0.891	-
Duration (month)						0.135
≤ 6	7	-1.13 (-2.61, 0.35)	0.136	0.0	0.933	
> 6	4	0.41 (-0.96, 1.77)	0.559	0.0	0.822	
Mean age						0.486
≤ 40	6	-0.86 (-2.73, 1.01)	0.369	0.0	0.604	
> 40	5	-0.07 (-1.26, 1.12)	0.907	0.0	0.927	
BMI						
Pooled effect size	8	-0.29 (-0.58, -0.01)	0.044	0.0	0.802	-
Duration (month)						0.986
≤ 6	5	-0.29 (-0.77, 0.19)	0.238	0.0	0.967	
> 6	3	-0.29 (-0.65, 0.06)	0.103	38.4	0.197	
Mean age						0.742
≤ 40	3	-0.18 (-0.90, 0.54)	0.625	0.0	0.678	
> 40	5	-0.31 (-0.62, -0.00)	0.048	0.0	0.572	

Abbreviations: **BMI**, Body mass index; **WMD**, Weight mean difference

in the current study. This discrepancy in findings may be explained by the different studies included for weight and BMI. Among the included studies, some reported data only for weight and some only for BMI. Therefore, the analysed studies were not the same for weight and BMI and consequently, we observed a significant effect for BMI, but the result was not significant for weight. The different nature of weight and BMI may also partially explain this discrepancy. Weight is a direct measurement of mass, while BMI is a calculated value that takes into account height and weight. BMI is calculated using the formula: BMI = weight (kg)/(height $(m)^2$. Therefore, two participants with the same weight but different heights will have different BMIs. This means that variations in weight can lead to different BMI values.

The mechanism of weight loss caused by ursodiol administration is probably due to the effect of bile acids on G protein-coupled bile acid receptor 1 (GPBAR1)

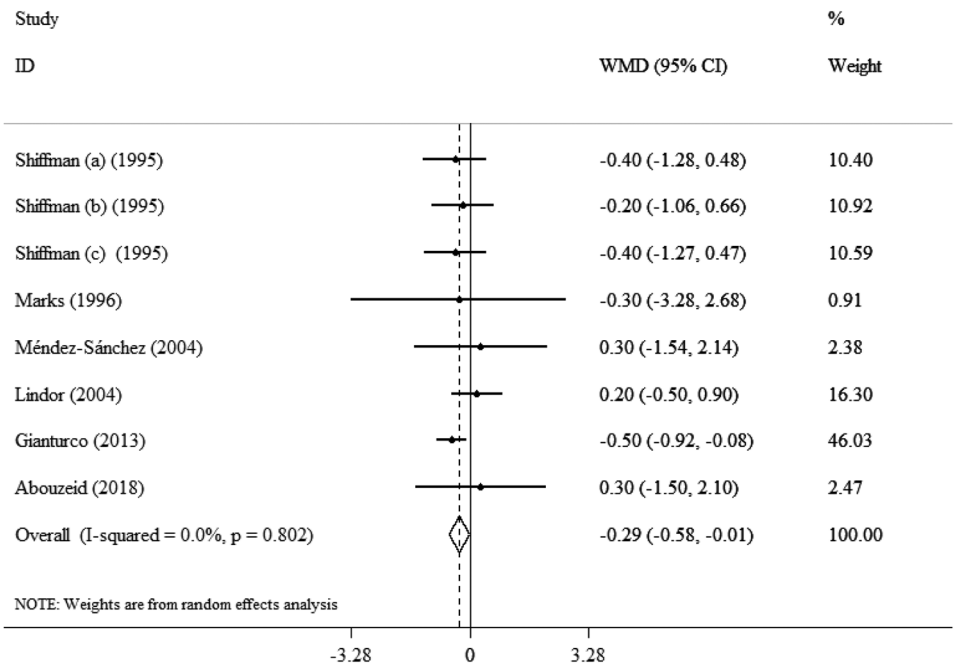

Fig. 3 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ursodeoxycholic acid on BMI

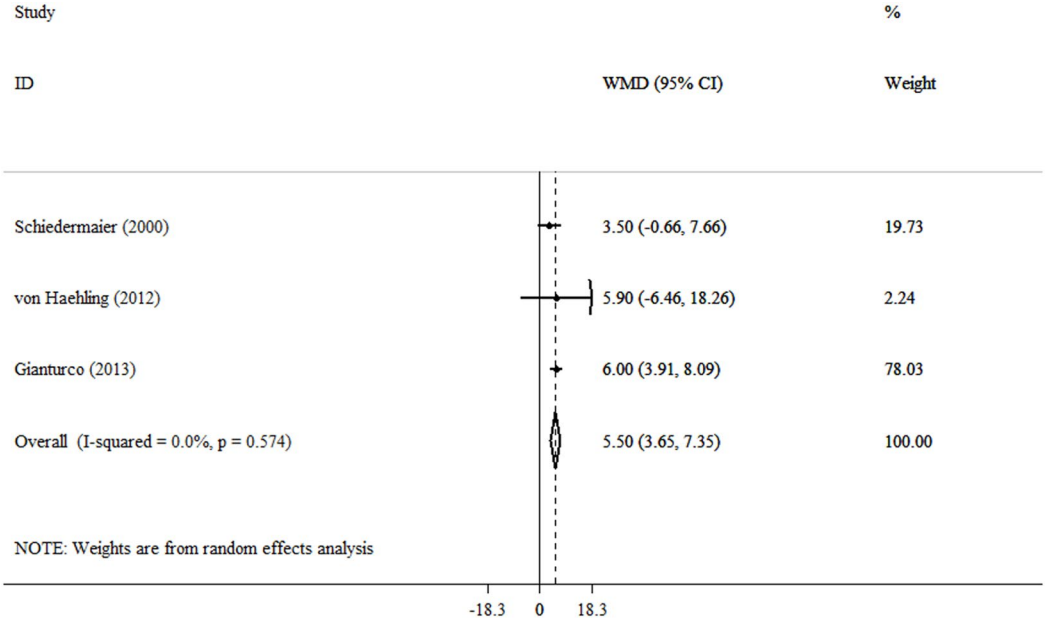

Fig. 4 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ursodeoxycholic acid on SBP

and Takeda G protein-coupled receptor 5 (TGR5), bile acid-activated receptors, and stimulating the increase in conversion of thyroxine into thyroid hormone [48, 49]. This increase in the levels of the thyroid hormone 4 (T4) causes an increase in the level of energy consumption in people [46]. TGR5 plays a role in regulating functions such as thermogenesis and resting energy expenditure (REE) [47, 60]. It is activated in adipose tissue and skeletal muscle mass and increases the conversion of thyroid hormones from inactive form to active form by the iodothyronine deiodinase enzyme, which increases REE [46]. Another effective mechanism for body weight changes is related to another bile acid receptor, the farnesoid X receptor (FXR), which causes a change in the metabolic response of people by regulating the metabolism of glucose, insulin, and lipids [47, 60, 61]. Bile acids can increase the secretion of fibroblast growth factor 19 (FGF19), which activates the FXR, inhibits lipogenesis,

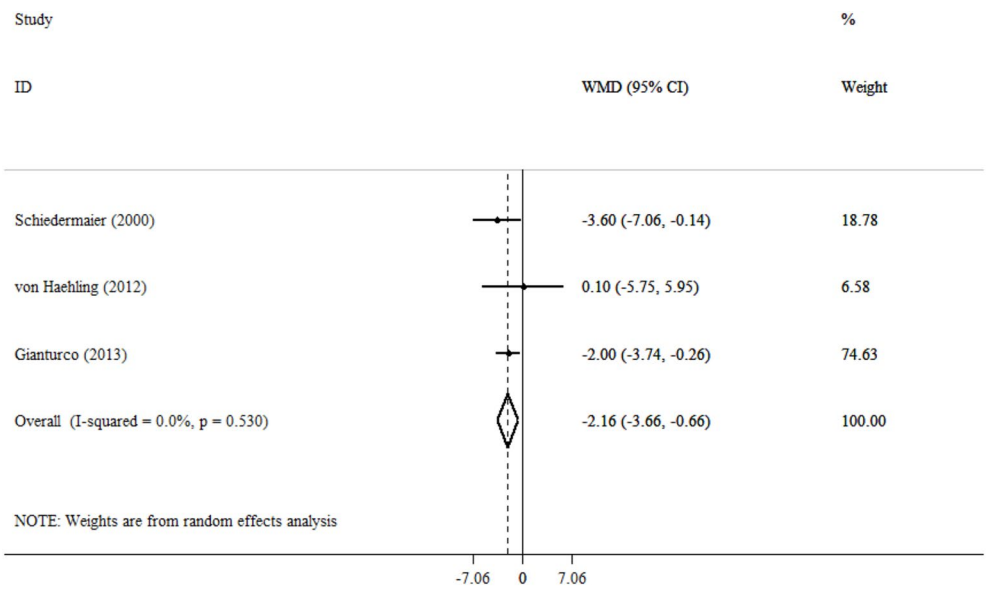

Fig. 5 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ursodeoxycholic acid on DBP

and increases the oxidation of fats in the liver (the FXR-FGF pathway) [62, 63]. FXR controls the expression of different genes, which reduce the hepatic synthesis of different fats [46]. Moreover, TSH, GLP-1 secretion, and FGF are targets of bile acid receptors, including TGR5 and FXR [48, 61, 63]. Another mechanism that may play a role in body weight changes is probably the microbiome population of the gastrointestinal (GI) tract [59]. The ursodiol supplementation can change the microbiota community structure and GI ecosystem [59]. Several previous studies have shown that some types of bacteria are associated with adiposity, overweight, and obesity [64, 65]. For example, Parabacteroides distasonis can increase the secretion of secondary bile acids and control weight gain by controlling intestinal gluconeogenesis and the FXR-FGF15 pathway [62]. Indeed, Obesity causes detrimental changes in white adipose tissue, which can result in metabolic dysfunction [66, 67]. As well as weight and birth weight are associated with cardiometabolic risk in childhood and adolescence [68].

In this meta-analysis, UDCA increased the SBP, which was mainly affected by the Gianturco et al. study [37] because the weight% of this study was high. It also reduced DBP, which is the reason for the high weight% of the Gianturco study [37]. In the trial of Gianturco and colleagues, a significant decrease in DBP and a significant increase in SBP were reported with UDCA supplementation. This study demonstrated that UDCA supplementation reduced DBP in adults. Based on the obtained results, it can be stated that UDCA can be suitable for decreasing DBP in patients with metabolic syndrome; however, it increases SBP in patients with metabolic syndrome. In our meta-analysis, the finding that UDCA decreases DBP but increases SBP may be influenced by multiple factors. Publication bias could skew the results if studies showing significant effects are more likely to be published, while neutral or conflicting data might be underreported. Also, confounding factors such as the use of other medications or the presence of comorbidities (e.g., cardiovascular or liver disease) could influence blood pressure differently. Moreover, fluid retention caused by UDCA could raise SBP through increased blood volume. Additionally, changes in metabolic or inflammatory pathways may also contribute to these contrasting effects.

Yang et al. showed the decreasing effect of chronic administration of UDCA on portal pressure, transforming growth factor-β_1 (TGF-β_1), iNOS, and TXA_2 in rats with biliary cirrhosis [50]. The mechanism of action of UDCA could be due to its antioxidant property, which causes the reduction of portal pressure by increasing the antioxidant defense [50]. Also, in another in vitro study, the administration of 70 mg/kg/day of UDCA in C57Bl6 wild-type mice caused a decrease in blood pressure after 24 weeks due to the reduction of the angiotensin II level [69]. Similar to our results, Schiegermaier et al. showed that the consumption of 750 mg/d of UDCA for 4 weeks was well tolerated by 20 healthy volunteers and caused a mild decrease in DBP due to the impact on vascular smooth muscles [45].

In contrast to our results, Berzigotti et al. showed that the consumption of the NCX-1000 derivative of UDCA for 16 days in animal models of cirrhosis caused a significant reduction of SBP due to a vasodilatory effect on intrahepatic circulation. There was no significant effect on DBP [70]. Bile acids have vasodilation properties. Bile

acids have receptors in vascular muscle cells, including the X receptor and TGR5, which play an important role in lowering systemic and portal blood pressure [71]. Also, in another trial, the administration of UDCA for 6 months prevented hypertension in wild-type mice maintained on a high-fat and high-fructose diet [72].

The present systematic review and meta-analysis indicated that there were no significant effects on TNF-α and IL-6 concentrations in adults by consuming the UDCA. There were no consistent results about the UDCA effects on inflammatory biomarkers. Inflammation is a central factor in the development of hypertension and is closely linked to variations in blood pressure [73]. Evidence showed that inflammation triggers early microvascular dysfunction in atherosclerotic lesions [74]. We did not observe any significant effect on inflammatory biomarkers. Similar to this meta-analysis, Balmer et al. did not report the overall favorable effect of UDCA on TNF-α and IL-6 [25]. In an RCT by Balmer et al. on 14 patients treated with 12–15 mg/kg/day UDCA, 14 patients treated with 12–15 mg/kg/day UDCA plus 400 IU vitamin E, and 13 patients received a placebo, there was no significant association between UDCA intake and inflammatory markers including TNF-a, monocyte chemoattractant protein-1 (MCP-1), IL-6, and IL-8 [25]. Oh et al. showed a trend for decreasing TNF-α and IL-6 after UDCA supplementation in mice with UDCA supplementation for 25 weeks [75]. However, the reduction of TNF-α mRNA levels was not significant in female mouse hepatocytes [75]. In this study, there was no change in phosphorylated nuclear factor kappa-light chain enhancer of activated B cells (NF-κB) and IκBα levels in mice, but there was a decrease in hepatic phospho-JNK [75]. Moreover, UDCA can reduce inflammation through three possible mechanisms including NF-κB/TNF-α, Bax/Bcl-xl/Caspase-3, and eNOS/iNOS signaling pathways [76]. However, there are no consistent results in different studies about the effects of UDCA supplementation on different inflammatory biomarkers. We did not observe any improvement effect on inflammation. This effect is likely because prior studies involved more intense inflammatory conditions like cancer, whereas our patients, who were healthy or had metabolic syndrome, had a low chronic level of inflammation. Additionally, these inconsistent results may be due to differences in study design, methodologies, the dose and duration of the intervention, characteristics of the sample populations, or the presence of confounding factors. Future studies with larger sample sizes conducted over a longer duration will be essential to validate these findings. Also, research could explore the potential underlying mechanisms, particularly the role of bile acid receptors, the autonomic nervous system, and fluid balance. Additionally, subgroup analyses can help understand how factors like pre-existing conditions and medications affect outcomes, while RCTs specifically focused on cardiometabolic risk factors as a primary outcome are needed for more definitive conclusions.

This study has some limitations. Different laboratory kits have been used to measure desired outcomes. Most of the included studies in this systematic review and meta-analysis were conducted in Europe. So, these results might not fully translate to other individuals living in different areas and regions. In our study, there was no evidence of statistical heterogeneity among studies. However, there were differences between studies in terms of methodology and clinical factors. Therefore, to address these issues, we used subgroup analysis in addition to the random effects model. There was no evidence of heterogeneity between subgroups in subgroup analyses stratified by study characteristics including duration of intervention and age. However, a non-significant P value for the Q statistic and an I^2 estimate of 0% should not be interpreted as the absence of heterogeneity. Therefore, the results of the subgroup analysis should be interpreted with caution. Also, the other limitations of the study are potential biases in the included studies, heterogeneity among study populations, and short follow-up periods. Another limitation of this study is the absence of data on "hard outcomes." Also, the use of a meta-analysis to evaluate "tertiary" outcomes in CVD represents a substantial limitation. Lastly, the influence of UDCA on BMI and hypertension should be evaluated alongside other confounding factors such as the effects of additional medications and the presence of other underlying health conditions. Due to all these limitations, more long-term, well-designed, and rigorous RCTs are needed to confirm the role of UDCA as a human therapeutic strategy.

This study has some advantages. This is a comprehensive systematic review and meta-analysis that includes all RCTs. We did not set any limitations in terms of dates or language. We used a standardized methodology in this study, which is an important strength. Due to the existing heterogeneity, we performed subgroup analysis to find the exact impact of UDCA with the reduction in heterogeneity.

Conclusion

In adults, UDCA supplementation may improve BMI and DBP; however, it might increase SBP with no effect on weight or inflammation, according to this comprehensive review and meta-analysis. These findings could significantly influence future research directions and support the creation of comprehensive guidelines for UCDA use in managing CVD, especially in areas where there are substantial evidence gaps or where the existing data is inconclusive. UDCA may help manage cardiometabolic risk factors in patients with metabolic syndrome and liver diseases. Additionally, its positive effects on BMI can

benefit overall metabolic health. As such, UDCA could be integrated into a comprehensive treatment strategy alongside lifestyle modifications and other pharmacological interventions. Further research is needed to optimize its use in clinical practice.

Abbreviations

Mets	Metabolic syndrome
UDCA	Ursodeoxycholic acid
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
NAFLD	Non-alcoholic fatty liver disease
BMI	Body mass index; WC, waist circumference
PBF	Body fat percentage
CVD	Cardiovascular disease
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
IL-6	Interleukin-6
PPAR	Peroxisome proliferator-activated receptor
RCT	Randomized controlled trial
SDs	Standard deviations
WMD	Weighted mean difference
SEM	Standard error of mean
GPBAR1	G protein-coupled bile acid receptor 1
TGR5	Takeda G protein-coupled receptor 5
T4	Thyroid hormone 4
REE	Resting energy expenditure
FXR	Farnesoid X receptor
FGF19	Fibroblast growth factor 19
GI	Gastrointestinal
TGF-β1	Transforming growth factor-β1
iNOS	Inducible NO synthase
TXA2	Thromboxane A2
MCP-1	Monocyte chemoattractant protein-1
NF-κB	Nuclear factor kappa-light chain enhancer of activated B cells

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04549-3.

Supplementary Material 1

Acknowledgements

DeclarationsEthics approval and consent to participateEthical approval was not applicable for this systematic review and meta-analysis.Consent for publicationNot applicable.Availability of data and materials Datasets are available through the corresponding author upon reasonable request. Competing interestsThe authors declare no competing interests.Clinical trial number Not applicable.FundingThis study is related to the project NO. 1401/59212 From Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran.We also appreciate the "Student Research Committee" and "Research & Technology Chancellor" in Shahid Beheshti University of Medical Sciences for their financial support of this study.Authors' contributionsConceptualization: Amini MR; Data curation: Amini MR; Formal analysis: Amini MR; Methodology: Rashidbeygi E; Project administration: Hekmatdoost A; Supervision: Hekmatdoost A; Writing - original draft: Rashidbeygi E, Rasaei N, Salavatizadeh M, Mohammadizadeh M; Writing - review & editing: Rashidbeygi E and Amini MR. Acknowledgements Not applicable.

Author contributions

Conceptualization: Amini MR; Data curation: Amini MR; Formal analysis: Amini MR; Methodology: Rashidbeygi E; Project administration: Hekmatdoost A; Supervision: Hekmatdoost A; Writing - original draft: Rashidbeygi E, Rasaei N, Salavatizadeh M, Mohammadizadeh M; Writing - review & editing: Rashidbeygi E and Amini MR.

Funding

This study is related to the project NO. 1401/59212 From Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate the "Student Research Committee" and "Research & Technology Chancellor" in Shahid Beheshti University of Medical Sciences for their financial support of this study.

Data availability

Availability of data and materials Datasets are available through the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was not applicable for this systematic review and meta-analysis.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 10 June 2024 / Accepted: 5 February 2025
Published online: 21 February 2025

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