

# Methodological Concerns in SR-MA Papers

**نگرانیهای جدی متدولوژیک در**

**مقالات مرور سیستماتیک و متاآنالیز**

**درسهای آموخته از یک مقاله اخیر محققین ایرانی**

**جلسه : شنبه ۹ خرداد ۱۴۰۵  
۸ تا ۱۱ شب**

Presented by:

A Keshtkar MD, MPH, PhD

TUMS – SPH

Researchware Academy

# Research Trends

مجموعه / وینارهای  
«روندهای پژوهشی»



# چرا این وینار : نگرانیهای جدی در مقالات مرور سیستماتیک

دلایل اهمیت این وینار :

- بعد از گذشت بیش از ۳۵ سال از آغاز نهضت انتشار مقالات مرور سیستماتیک و متآنالیز، روز بروز بر سختگیریا و دقت نظرهای ژورنالها، افزوده شده است و این روند در حال تشدید میباشد !
- در طول یکی دو سال اخیر، بیش از ۵۰ مقاله در هر سال بصورت Letter در تشریح این نگرانیها در ژورنالهای مختلف، منتشر شده و پیشبینی میگردد که این روند در حال توسعه باشد.
- در این وینار، به تشریح یک سناریوی واقعی (یک مقاله منتشر شده + یک Letter در مورد نگرانیهای متدولوژیک مقاله موصوف)، خواهیم پرداخت.
- در صورت استقبال عزیزان، از این دست وینارها، بازهم برگزار خواهیم کرد.

# Summary of Topics

- 1 Review of the SR-MA paper
- 2 Indicating the methodological concerns
- 3 Review of the related LETTER
- 4 Conclusion and Recommendation



# Review of **SR-MA** Paper

# مقاله اصلی مرور سیستماتیک و متاآنالیز : عنوان


Clinical Cardiology

WILEY

CLINICAL  
CARDIOLOGY

REVIEW OPEN ACCESS

## The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Leyli Zahra Bahreyni<sup>1</sup> | Mohammad Reza Amini<sup>2</sup>  | Leila Sheikhi<sup>3</sup> | Ehsaneh Taheri<sup>4</sup> | Pardis Rahimi<sup>5</sup> |  
Mahnoush Mehrzad Samarin<sup>6</sup> | Fatemeh Sheikhhossein<sup>7</sup> | Sajjad Etesamnia<sup>7</sup> | Negin Lohrasbi<sup>1</sup> | Azita Hekmatdoost<sup>8</sup>



Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : چکیده

## ABSTRACT

**Background:** The aim of this paper, which includes a meta-analysis, is to elucidate the effects of cranberry consumption on systolic and diastolic blood pressure based on all relevant randomized controlled trials (RCTs).

**Materials and Methods:** A systematic literature search was performed across the ISI Web of Science, PubMed, Embase, the Cochrane Library, and Google Scholar databases, encompassing trials published until December 2024. Weighted mean differences (WMD) were calculated using random or fixed-effects models. Between-study heterogeneity was evaluated using Cochrane's test and the  $I^2$  index. This study's registration number in PROSPERO is CRD420251028424.

**Results:** A total of 1204 publications were reviewed, leading to the inclusion of 12 trials for qualitative synthesis and meta-analysis. The pooled effect size indicated statistically nonsignificant reductions of 1.31 mmHg for systolic blood pressure (SBP) ( $p = 0.19$ ) and 1.31 mmHg for diastolic blood pressure (DBP) ( $p = 0.12$ ). Stratified analysis showed that the reduction in SBP was statistically significant in studies where cranberry was provided in juice form, with a duration of 8 weeks or less, involving participants with a mean age of  $< 50$  years, and predominantly in females. Furthermore, subgroup analysis indicated a significant reduction in DBP in studies that involved both genders, lasted more than 8 weeks, included participants with a normal body mass index, and had a mean age below 50 years.

**Conclusion:** This systematic review and meta-analysis suggest that cranberry consumption was not effective in managing SBP and DBP.

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : مقدمه

## 1 | Introduction

Hypertension is defined as continuously elevated systolic blood pressure (SBP) above 140 and/or diastolic blood pressure (DBP) above 90, and it is one of the risk factors that leads to atherosclerotic cardiovascular diseases (ASCVD) and many other medical conditions [1, 2]. Based on a WHO report, hypertension is responsible for more than 10 million deaths annually [1]. The main etiology of hypertension is unclear but some risk factors that can cause hypertension include gender, genetic factors, family history, low physical activity, and unhealthy diet [1, 3, 4]. Treatment of hypertension includes lifestyle modification in the first line and along with pharmacotherapy; lifestyle modification consists of various parts including diet and complementary medicine [5].

Cranberry or Vaccinium is one of the high-containing polyphenols among fruits and vegetables and is cultivated in the northern part of America, Canada, and some parts of Europe [6, 7]. Based on its size, small or big, the percent of components may differ but it is rich in anthocyanins (ACNs), flavonols, fiber, and different vitamins [6-9]. Its potential effects include increasing plasma antioxidant capacity, reducing cardiovascular disease (CVD) risk factors, 8-isoprostane (lipid peroxidation index), and advanced oxidized protein products (AOPPs), improving visual memory by increasing regional perfusion, prevention and treatment of bladder cancer, and being efficient in readjusting skin lipids and microbiome in women [8, 10-15]. Some studies showed that cranberries

biome in women [8, 10-15]. Some studies showed that cranberries can be effective in lowering DBP [16, 17]. On the other hand, some studies demonstrated no change in blood pressure or central systolic pressure [17, 18].

One systematic meta-analysis, which aimed to review the effect of cranberry and blueberry supplementation on patients with CVD, included data from eight articles on cranberry; no change was seen in SDB or DBP [19].

Due to the controversies in results, small sample sizes in previous studies, and the limited number of studies, we aimed to conduct a systematic review and meta-analysis. By incorporating subgroup analyses, a larger number of included studies, and covering all populations, we can achieve a comprehensive understanding and conclusion regarding the potential effects of cranberries on blood pressure.

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : متد (۱)

## 2.1 | Search Strategy

The present systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [20]. The registration number for this study in PROSPERO is CRD420251028424. Electronic databases, including PubMed, Web of Science, and Scopus, were searched to include trials published up to December 2024. We used the following keywords in our non-MeSH terms: (Cranberry OR “*Vaccinium macrocarpon*” OR “*Vaccinium microcarpum*” OR “*Vaccinium oxycoccos*”) in combination with (“Blood Pressure” OR “Pressure, Blood” OR “Diastolic Pressure” OR “Pressure, Diastolic” OR “Pulse Pressure” OR “Systolic Pressure” OR Hypertension). The reference lists of retrieved and related review studies were hand-searched to find more relevant studies.

## ✓ مشکلات راهبرد جستجو :

- تناقض در بانکهای اطلاعاتی مندرج در چکیده و متن کامل
- سینتاکس سه جزیی
- عدم ورود Gray literature

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

## مقاله اصلی مرور سیستماتیک و متاآنالیز : متد (۲)

### 2.2 | Study Inclusion and Exclusion Criteria

Original articles were selected if they had the following PICOS criteria [21]: (1) **Participants: aged  $\geq 18$  years**, (2) **Intervention: Cranberry supplement or cranberry juice or cranberry extracts**, (3) **Comparison (placebo)**, (4) **Outcomes: having data on SBP/DBP in the baseline and the end of the intervention**, and (5) **Study design: randomized controlled trials (RCTs) with either parallel or cross-over design**.

Publications were excluded if they had one of the following criteria (1) research on pregnant women, children, animals, (2) non-controlled or non-randomized clinical trials, (3) studies without a placebo group, (4) combined cranberry with other dietary supplements or interventions, (4) duplicated studies, (5) studies with not sufficient data for analysis, and (6) review, meta-analysis, conference papers, and protocol.

✓ مشکلات معیارهای ورود و خروج :

▪ چرا پیامدها بصورت اولیه و ثانویه تعریف

نشده است؟!؟ (مشکل رایج برخی از

مبتدیان)

▪ عدم اشاره به Blinding در معیار

مطالعات واجد شرایط ...

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : متد (۳)

## 2.3 | Data Extraction

Two independent reviewers (L.Z.B. and M.R.A.) screened the titles and abstracts and then the full text of relevant studies by considering the above inclusion and exclusion criteria. Finally, the references of the selected studies were reviewed. Any disagreement between the reviewers were discussed and solved by the third reviewer (A.H.). We used Excel 2019 and the standard form to extract the main information from the eligible articles.

## ✓ مشکلات استخراج دیتا :

- عدم درج توضیح در مورد داده های مهم
- مورد استخراج در مقالات
- عدم اشاره به دیتای مورد نیاز برای محاسبه
- یا برآورد شاخص اندازه اثر ...

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

## مقاله اصلی مرور سیستماتیک و متاآنالیز : متد (۴)

### 2.4 | Quality Assessment of Meta-Analysis

Two reviewers (L.Z.B. and M.R.A.) independently assessed the risk of bias for each RCT using the Cochrane Risk of Bias Tool for RCTs [22]. This tool contains seven domains including (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other bias. For each item, the risk of bias was categorized as low risk, high risk, or unclear. Discuss with the third researcher (A.H.) was our selection to resolve any inconsistencies between the two reviewers.

### ✓ مشکلات ارزیابی کیفیت مطالعات :

- مشخص نبودن نحوه جمع‌بندی ارزیابی در هر مطالعه اولیه واجد شرایط
- دقت فرماید که بیشتر ژورنال‌های High IF به ابزار Cochrane RoB-2 تاکید دارند !

# مقاله اصلی مرور سیستماتیک و متاآنالیز : متد (۵)

## 2.5 | Statistical Analyses

Data was analyzed using Stata software, version 14.0 (Stata Corp, College Station, TX). We used weighted mean differences (WMD) and 95% confidence intervals (CI) of SBP and DBP to estimate the treatment effects [23]. The following equation was used to calculate changes in standard deviation (SD):  $SD \text{ change} = \text{square root} (SD^2_{\text{baseline}} + SD^2_{\text{endpoint}} - [2R \times SD_{\text{baseline}} \times SD_{\text{endpoint}}])$  [24], correlation coefficient  $R = 0.8$  [25]. When data were presented as standard error (SE), SD was estimated using this formula:  $SD = SEM * \text{sqrt}(n)$ ;  $n$  is the number of subjects. Inter-study heterogeneity was evaluated using Cochran's  $Q$  and  $I^2$  statistics.  $I^2 < 30\%$ ,  $I^2 = 30\% - 75\%$ , and  $I^2 > 75\%$  were categorized as low, moderate, and high heterogeneity, respectively [26]. As the results showed moderate heterogeneity for SBP and high heterogeneity for DPB, we applied a random-effect model in the meta-analysis. To assess the source of bias, we conducted subgroup analysis for the type of intervention, duration of treatment, BMI, age, and gender. The risk of publication biases was evaluated using both the visual funnel plot and Egger's test [27]. Both the visual funnel plot and Egger's test were conducted to indicate the presence of the risk of publication bias. The significance level was considered as  $p < 0.05$  [28].

## ✓ مشکلات روشهای آماری (متاآنالیز) :

- ابهام در انتخاب «اندازه اثر» و محاسبه آنها در مطالعات اولیه
- عدم توجه به فاکتور زمان در سنجش پیامدها در مطالعات اولیه
- ابهام بین متغیرهای زیرگروه و دلایل سوگرایی (عدم درک صحیح هتروژنیته متدولوژیک و سوگرایی)
- عدم توجه به تحلیل حساسیت ... !
- نحوه برخورد با تریالهای متقاطع یا cross-over
- عدم استفاده از راهکار GRADE (ارزیابی قطعیت شواهد)

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۱)

## 3 | Results

### 3.1 | Search Results

Figure 1 shows the flowchart of the article selection process in this meta-analysis. A total of 1884 articles were identified from our database searches ( $n = 1882$ ) and the reference list of relevant articles ( $n = 2$ ). After removing duplicates, 1204 articles were screened by title and abstracts, and 1189 articles were excluded including no relevant articles with no required data ( $n = 995$ ), animal studies ( $n = 122$ ), and review articles ( $n = 112$ ). We assessed the full text of 15 eligible articles, and finally, 12 articles were included in this analysis [16–18, 29–37].

✓ مشکلات یافته‌ها (فرایندهای سه گانه) :

▪ تردید در تعداد مطالعات واجد شرایط در گام

«فرایند انتخاب» ... !

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

## مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۲)

First author (year)	Location	Study design	Health status	Sex	Sample size	Duration (week)	Mean age (year)	Baseline BMI (kg/m <sup>2</sup> )	Intervention group	Comparator group	Outcome
1. Basu (2011)	USA	RCT, parallel	Metabolic syndrome	Female	31	8	52	40	480 mL Low-calorie cranberry juice	Placebo	SBP/DBP
2. Dohadwala (2011)	USA	RCT, crossover	Coronary artery disease	Both	44	4	62	29.5	480 mL cranberry juice, double-strength (54% juice)	Placebo	SBP/DBP
3. Eftekhari (2016)	Iran	RCT, parallel	Metabolic syndrome	Female	48	8	42	29.3	400 mg cranberry supplement	Placebo	SBP/DBP
4. Flammer (2012)	USA	RCT, parallel	Peripheral endothelial dysfunction and cardiovascular risk factors	Both	69	16	49.5	27.4	460 mL cranberry juice cocktail	Placebo	SBP/DBP
5. Flanagan (2022)	United Kingdom	RCT, parallel	Healthy	Both	60	12	65.5	25	9 g freeze-dried cranberry powder or 100 g of fresh cranberries	Placebo	SBP/DBP
6. Hsia (2020)	USA	RCT, parallel	Elevated fasting glucose or impaired glucose tolerance	Both	35	8	47.5	36.9	450 mL cranberry juice	Placebo	SBP/DBP
7. Lee (2008)	Taiwan	RCT, parallel	Type 2 diabetes	Both	30	12	65.5	26	500 mg cranberry extract	Placebo	SBP/DBP
8. Masnadi Shirazi (2021)	Iran	RCT, parallel	NAFLD	Both	94	24	43.1	28.4	144 mg Vaccinium macrocarpon (equal to 13 g dried cranberry fruit)	Placebo	SBP/DBP
9. Novotny (2015)	USA	RCT, parallel	Healthy	Both	56	8	50	28	480 mL low-calorie cranberry juice	Placebo	SBP/DBP
10. Richter (2021)	USA	RCT, crossover	Elevated Blood Pressure	Both	40	8	47	28.7	500 mL cranberry juice	Placebo	SBP/DBP
11. Ruel (2013)	Canada	RCT, parallel	Healthy	Male	35	4	45	28.3	500 mL low-calorie cranberry juice cocktail	Placebo	SBP/DBP
12. Valentova (2007)	Czech Republic	RCT, parallel	Healthy	Female	65	8	21.6	21	400 and 1200 mL dried cranberry juice	Placebo	SBP/DBP

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; NAFLD, non-alcoholic fatty liver disease; RCT, randomized controlled trial; SBP, systolic blood pressure.

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۳)

## 3.3 | Quality of the Studies and Risk of Bias

We used the Cochrane risk-of-bias tool for assessing each trial included in this systematic review. All 12 trials were at low risk of five domains, including random sequence generation, selective reporting, blinding participants, outcome assessment, and other sources of bias (Table 2). None of the included studies presented an overall high risk of bias in at least one domain. Four trials [17, 18, 31, 33] reported sufficient information for a domain of “selective outcome reporting” and two trials [31, 37] regarding blinding outcome assessment.

✓ مشکلات گزارش ارزیابی کیفیت یا RoB :

▪ گزارش وضعیت ایتها با جدول ۱ (گزارش RoB)،

تناقض دارد.

▪ بسیار بعید است که در یک ایتم، تمام مطالعات

دارای شرایط Low RoB باشند !

▪ واژه Overall RoB درست استفاده نشده است !

...

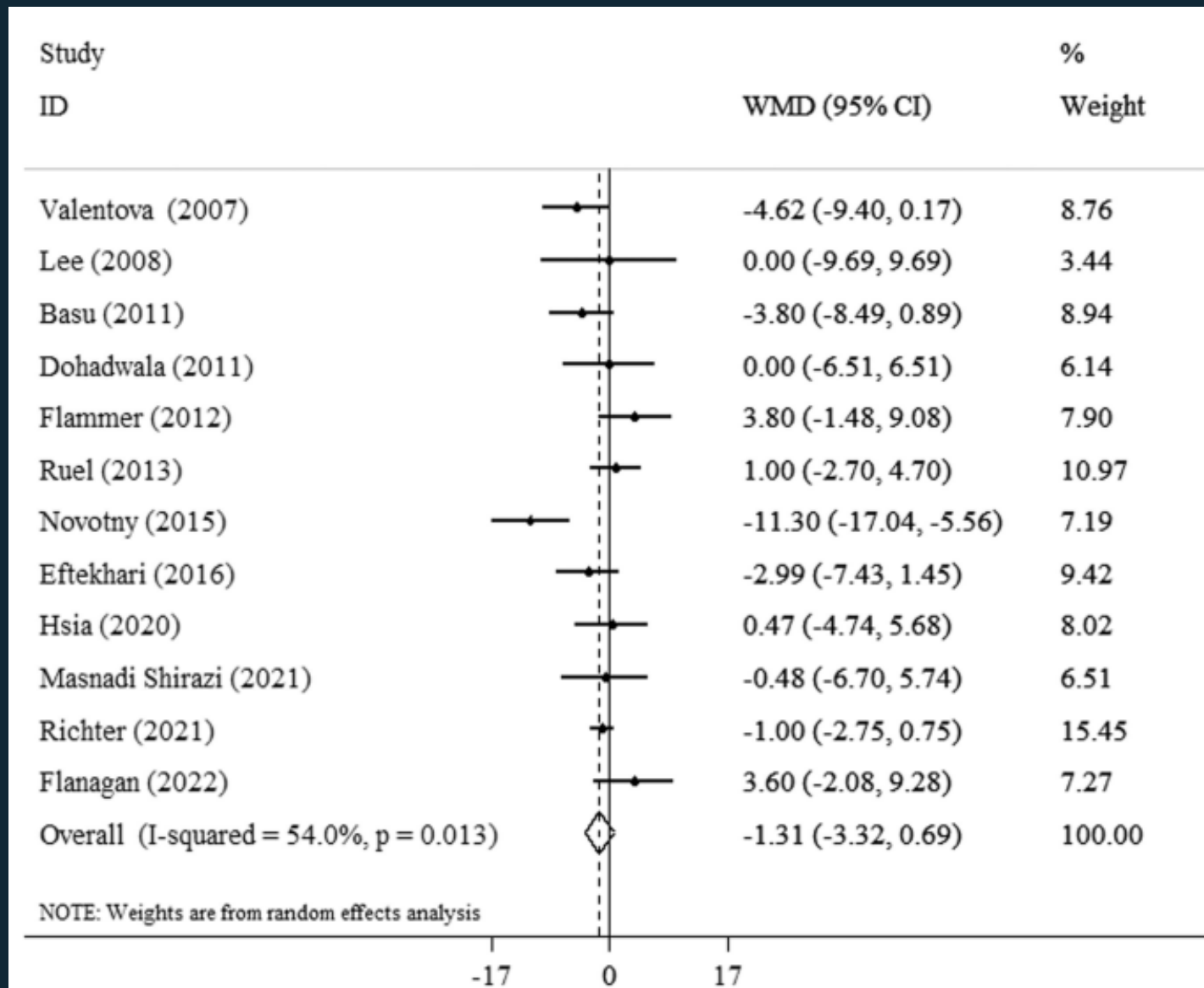
TABLE 1 | Risk of bias for randomized controlled trials, assessed according to the revised Cochrane risk-of-bias tool for randomized trials.

Publications	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Other source of bias
1. Basu (2011)	L	U	L	L	L	L	L
2. Dohadwala (2011)	L	U	L	L	U	L	L
3. Eftekhari (2016)	L	L	L	L	U	L	L
4. Flammer (2012)	L	U	L	L	U	L	L
5. Flanagan (2022)	L	U	L	L	U	L	L
6. Hsia (2020)	L	L	L	L	U	L	L
7. Lee (2008)	L	U	L	L	U	L	L
8. Masnadi Shirazi (2021)	L	L	L	L	L	L	L
9. Novotny (2015)	L	U	L	L	U	L	L
10. Richter (2021)	L	L	L	L	U	L	L
11. Ruel (2013)	L	U	L	L	U	L	L
12. Valentova (2007)	L	U	L	L	U	L	L

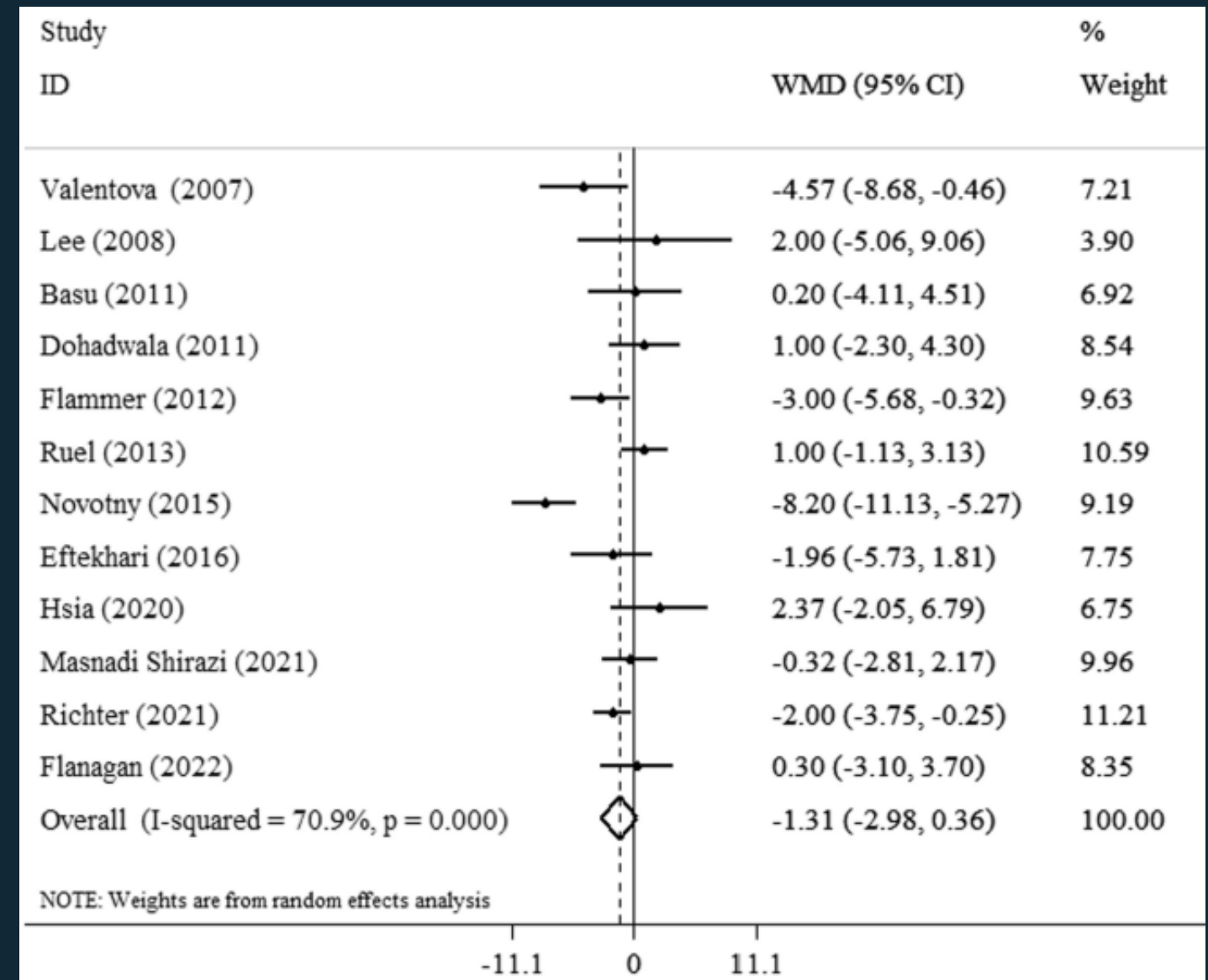
Abbreviations: H, high risk of bias; L, low risk of bias; U, unknown.

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۴)



**SBP**



**DBP**

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

## مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۵)

Group	No of trials	WMD (95% CI)	p value	I <sup>2</sup> (%)	p-heterogeneity	p for between-subgroup heterogeneity
<i>SBP</i>						
Type of intervention						0.58
Powder	4	-0.45 (-3.35, 2.46)	0.76	6.80	0.35	
Juice	8	-1.33 (-2.60, -0.05)	0.04	65.7	0.005	
Duration (week)						0.01
≤ 8	4	-1.75 (-3.01, -0.45)	0.006	58.8	0.01	
> 8	8	2.28 (-0.83, 5.39)	0.15	0.0	0.68	
Age						0.65
≤ 50	8	-1.30 (-2.57, -0.03)	0.04	64.6	0.006	
> 50	4	-0.56 (-3.56, 2.45)	0.71	23.8	0.26	
Mean BMI						0.30
< 25	1	-4.62 (-9.40, 0.17)	0.06	—	—	
25–29.9	9	-0.84 (-2.13, 0.44)	0.20	60.2	0.01	
≥ 30	2	-1.89 (-5.37, 1.59)	0.29	29.9	0.23	
Sex						0.07
Both	8	-0.80 (-2.19, 0.59)	0.26	62.1	0.01	
Female	3	-3.76 (-6.43, -1.09)	0.006	0.0	0.88	
Male	1	1.00 (-2.70, 4.70)	0.60	—	—	

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

## مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۶)

Group	No of trials	WMD (95% CI)	p value	I <sup>2</sup> (%)	p-heterogeneity	p for between-subgroup heterogeneity
<i>DBP</i>						
Type of intervention						< 0.001
Powder	4	-0.37 (-2.08, 1.35)	0.68	0.0	0.73	
Juice	8	-1.75 (-2.72, -0.78)	< 0.001	79.8	< 0.001	
Duration (week)						0.53
≤ 8	8	-1.59 (-2.59, -0.85)	0.21	79.2	< 0.001	
> 8	4	-0.99 (-2.56, 0.57)	0.002	18.7	0.29	
Age						0.02
≤ 50	8	-1.87 (-2.81, -0.94)	< 0.001	87.4	< 0.001	
> 50	4	0.67 (-1.32, 2.66)	0.51	0.0	0.96	
Mean BMI						0.07
< 25	1	-4.57 (-8.68, -0.46)	0.03	—	—	
25–29.9	9	-1.49 (-2.39, -0.59)	0.001	75.1	< 0.001	
≥ 30	2	1.26 (-1.83, 4.34)	0.42	0.0	0.49	
Sex						0.05
Both	8	-1.81 (-2.82, -0.81)	< 0.001	76.1	< 0.001	
Female	3	-2.17 (-4.50, 0.17)	0.07	19.6	0.28	
Male	1	1.00 (-1.13, 3.13)	0.35	—	—	

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

## مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۷)

### ✓ مشکلات تحلیل زیرگروهها :

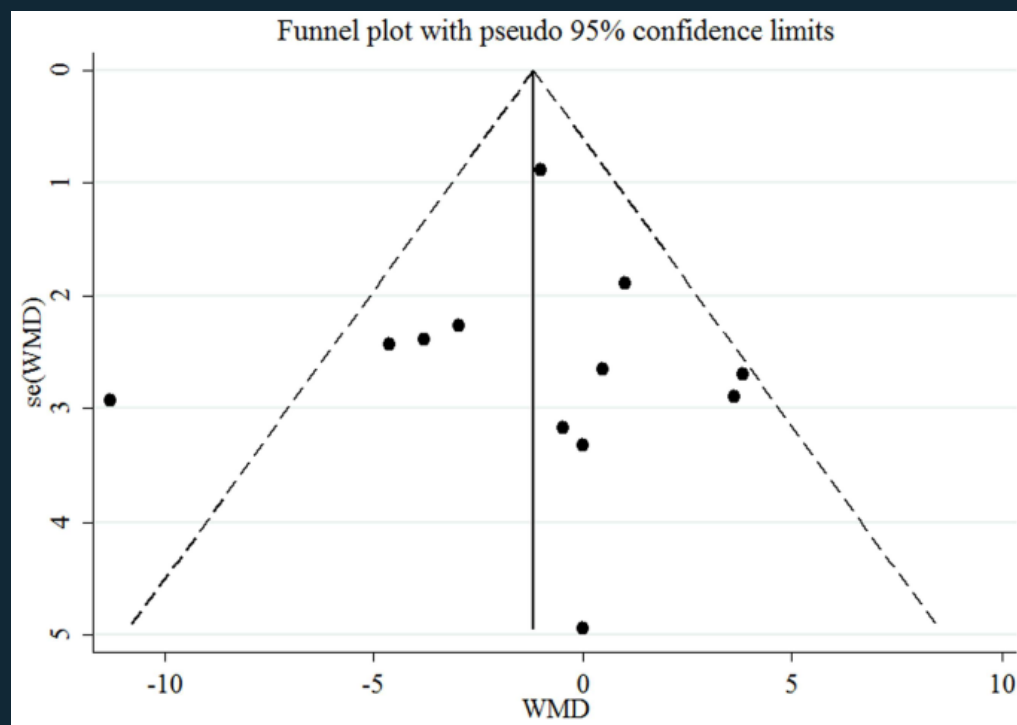
- برخی از گزارشات تحلیل زیرگروهها در متن با جدول زیرگروهها، همخوانی ندارد.
- زیرگروه مهم آزمودنیهای **Healthy vs any disorder** مورد توجه قرار نگرفته است.
- بجای تحلیل زیرگروهها در طبقات میانگین BMI آزمودنیها (در سه گروه)، انجام متارگرسیون منطقیتر بنظر میرسد که انجام نشده است.
- برای دوزهای مختلف مداخله (Cranberry) نیز تحلیل زیرگروه یا متارگرسیون انجام نشده است !

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۸)

The funnel plots for assessing the publication bias for the effects of cranberry on SBP is shown in Figure 3. The results of the Egger test revealed no publication bias for SBD ( $p = 0.86$ ).

Figure 5. The results of the Egger test revealed no publication bias for DBP ( $p = 0.75$ ).

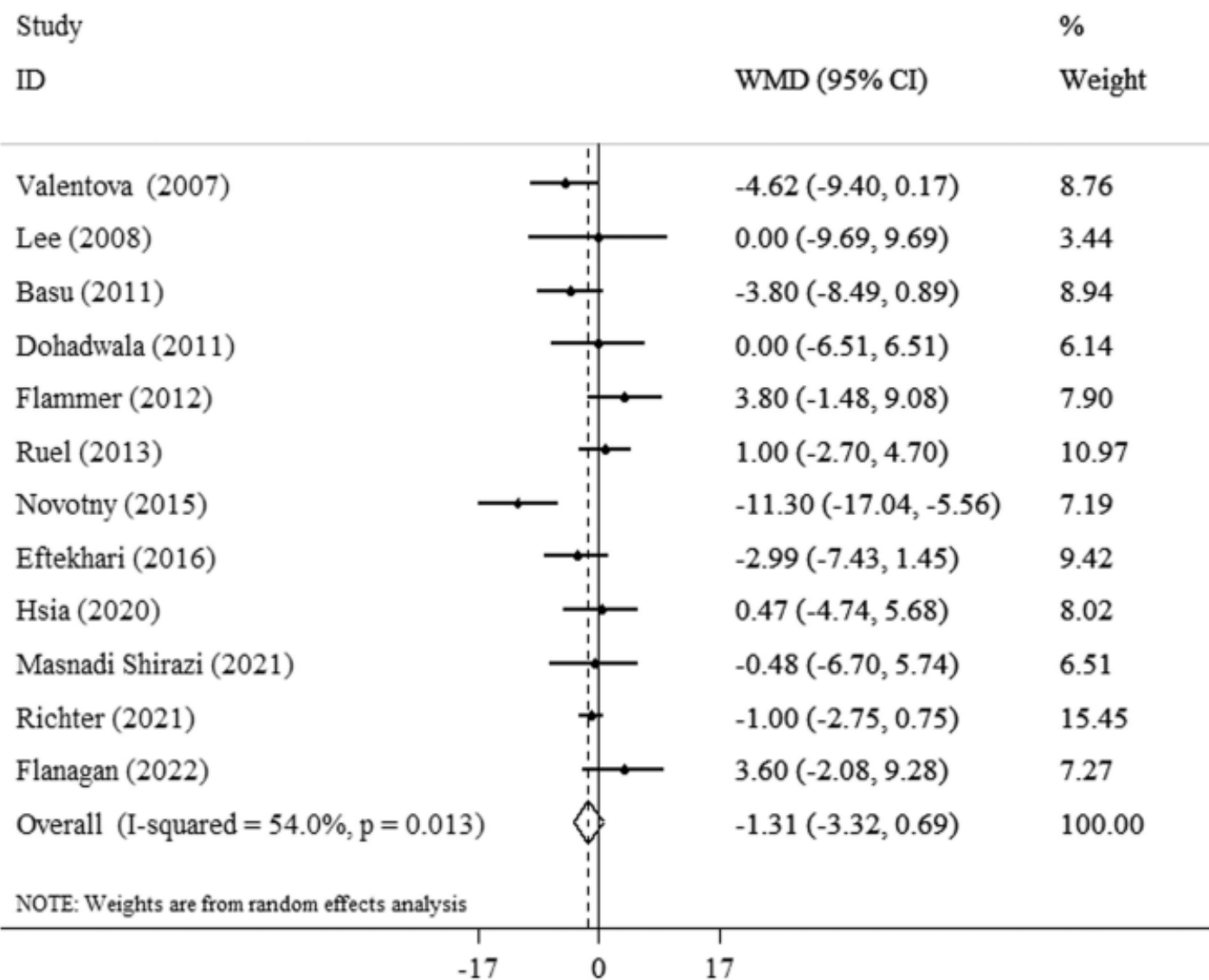


## مشکلات ارزیابی Publication Bias ✓

- تفسیر غلط آزمون Egger
- عدم ارزیابی Small Study Effect (اثر قویتر در مطالعات با حجم نمونه کمتر)؛ متاسفانه در forest plot ها نیز حجم نمونه مشخص نشده است.
- روش Trim & Fill استفاده نشده است ...

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : نتایج (۹)



SBP

## مشکلات ارزیابی Sensitivity Analysis :

- به هیچ وجه به این مقوله توجهی نشده است !
- در نمودارهای Forest Plot، بوضوح اثر غالب یک مطالعه خاص قابل مشاهده است !
- به تاثیر کیفیت مطالعات (RoB) بر نتایج، اثر حجم نمونه، اثر توازن Baseline characteristics و ...، توجهی نشده است.

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.

# مقاله اصلی مرور سیستماتیک و متاآنالیز : بحث

## 4 | Discussion

The current systematic review and meta-analysis assessed the impact of different forms of cranberry consumption (juice and supplements) on systolic and diastolic blood pressure. The findings indicated that cranberry consumption did not lead to a significant reduction in SBP. However, subgroup analyses revealed significant effects in studies using cranberry juice, those with interventions lasting 8 weeks or less, in participants aged 50 or younger, and in females.

Regarding DBP, no significant changes were observed in the intervention group compared to the control group. However, subgroup analyses by form of cranberry consumption and treatment duration indicated that cranberry juice and interventions lasting more than 8 weeks significantly reduced DBP. Furthermore, DBP reductions were notably significant in participants aged 50 or younger and in studies that included both genders. A previous meta-analysis examining the effects of berries on blood pressure found no significant impact on SBP and DBP in patients with cardiometabolic diseases [38]. Another review investigating the impact of cranberries on metabolic profiles found no significant effect of cranberries on blood pressure [39]. A recently published review indicated that cranberry consumption may lower SBP but does not have a significant effect on DBP [40]. While previous reviews on the effects of

## مشکلات بخش Discussion :




- در مقالات متاآنالیز نباید رویکرد «معنی داری آماری» صرف غالب باشد !
- توجه به «معنی داری بالینی» که یکی از محورهای اصلی قضاوت و تفسیر در ارزیابی GRADE است، دقیقاً به همین خاطر است !
- در متاآنالیزهای مداخله‌ای، بدون ارزیابی GRADE قضاوت در مورد اثربخشی / عدم اثربخشی مداخله، غیرمنطقی است .

Bahreyni, L. Z., Amini, M. R., Sheikhi, L., Taheri, E., Rahimi, P., Samarin, M. M., ... & Hekmatdoost, A. (2026). The Effect of Cranberry Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Cardiology*, 49(4), e70254.



# Review on **the** **Related Letter**

## Methodological Concerns Regarding the Meta-Analysis of Cranberry Consumption and Blood Pressure

Shaher Yar<sup>1</sup>  | Muhammad Touseef<sup>1</sup>  | Ishvah Shashwat Nag<sup>2</sup> 

<sup>1</sup>The University of Lahore University College of Medicine and Dentistry, Lahore, Pakistan | <sup>2</sup>State Non-Profit Enterprise Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

**Correspondence:** Ishvah Shashwat Nag ([ishvahneg@gmail.com](mailto:ishvahneg@gmail.com))

**Received:** 23 April 2026 | **Revised:** 23 April 2026 | **Accepted:** 28 April 2026

Yar, S., Touseef, M., & Nag, I. S. (2026). Methodological Concerns Regarding the Meta-Analysis of Cranberry Consumption and Blood Pressure. *Clinical Cardiology*, 49(5), e70339.

## مشکلات مقاله مورد اشاره در Letter : (۱)

### ✓ مشکل اول :

- تناقض در خروجی P value یکی از تحلیلهای زیرگروه با CI 95% اندازه اثر مربوطه که میتواند از جابجایی این موارد بین دو زیرگروه یا بین معنی داری اندازه اثر با معنی داری متروژنیستی اتفاق افتاده باشد

First, we noticed what appears to be a typographical inconsistency in Table 3 that the authors may wish to clarify. For DBP stratified by duration, the  $\leq 8$  week row lists a weighted mean difference of  $-1.59$  mmHg (95% CI  $-2.59$  to  $-0.85$ ) with  $p = 0.21$ , and the  $> 8$  week row lists  $-0.99$  mmHg (95% CI  $-2.56$  to  $0.57$ ) with  $p = 0.002$ . A confidence interval that excludes zero should not yield a non-significant  $p$ , and vice versa, so we wondered whether the two  $p$  values may have been transposed. A brief clarification or erratum would help readers identify which duration stratum reached statistical significance.

Yar, S., Touseef, M., & Nag, I. S. (2026). Methodological Concerns Regarding the Meta-Analysis of Cranberry Consumption and Blood Pressure. *Clinical Cardiology*, 49(5), e70339.

## مشکلات مقاله مورد اشاره در Letter (۲)

### ✓ مشکل دوم :

- با توجه به تعداد محدود مطالعات اولیه و تعداد نسبتاً زیاد متغیرهای زیرگروه، تفسیر نتایج مربوطه باید بصورت Hypothesis-generated باشد و نه بصورت Confirmatory
- متاسفانه Priori subgroup variable ها هم مشخص نیستند.

Second, the overall subgroup pattern may benefit from cautious interpretation. Significant SBP reductions appear in the shorter-duration stratum while significant DBP reductions appear in the longer, and reductions seen in female-only trials are not mirrored in the mixed-sex trials that contain most of the female participants. With 12 trials distributed across five effect modifiers, and in the absence of formal interaction testing or multiplicity adjustment, we would gently suggest that these findings be treated as hypothesis-generating [2] rather than confirmatory.

Yar, S., Touseef, M., & Nag, I. S. (2026). Methodological Concerns Regarding the Meta-Analysis of Cranberry Consumption and Blood Pressure. *Clinical Cardiology*, 49(5), e70339.

## مشکلات مقاله مورد اشاره در Letter (۳)

### ✓ مشکل سوم :

- هر چند در تحلیل زیرگروهها به دو شکل رایج مداخله (پودر و آب میوه) توجه شده است، اما مقدار یا دوز مداخله مورد توجه قرار نگرفته، بخصوص اینکه در مطالعات پیشین، آستانه دوز تاثیر بالینی نیز مشخص شده است.
- چنانچه دوزها مشخص نباشد، باید در محدودیتها ذکر شود و در غیراینصورت متارگرسیون، حداقل انتظار است.

Third, the cranberry interventions themselves vary considerably across the included studies, ranging from juices of differing strengths (400–500 mL) to freeze-dried powder (9 g) and capsules (144–500 mg). Proanthocyanidin (PAC) and anthocyanin content differs widely across these formats, with prior work suggesting a clinically relevant PAC threshold around 72 mg/day [3]. A dose–response meta-regression by mg PAC/day might offer more mechanistic insight than the “juice versus powder” contrast, and we offer this as a suggestion for future syntheses.

Yar, S., Touseef, M., & Nag, I. S. (2026). Methodological Concerns Regarding the Meta-Analysis of Cranberry Consumption and Blood Pressure. *Clinical Cardiology*, 49(5), e70339.

## مشکلات مقاله مورد اشاره در Letter (۴)

### ✓ مشکل چهارم :

- عدم توجه به وضعیت baseline آزمودنیها از نظر فاکتورهای normotensive بودن یا داشتن (یا نداشتن) کوموربیدیت‌های متابولیک ...
- شاید دلیل آن عدم استفاده از متخصصین قلب و عروق یا فشار خون در بین اعضای تیم تحقیق باشد.

Fourth, only 1 of the 12 included trials, Richter et al. [4] enrolled participants with elevated BP at entry; the remainder recruited normotensive populations or those with other comorbidities. An additional subgroup analysis by baseline BP category could strengthen the interpretation of pooled effects in the populations most likely to benefit clinically.

Yar, S., Touseef, M., & Nag, I. S. (2026). Methodological Concerns Regarding the Meta-Analysis of Cranberry Consumption and Blood Pressure. *Clinical Cardiology*, 49(5), e70339.

## مشکلات مقاله مورد اشاره در Letter : (۵)

### ✓ مشکل پنجم :

- پایین بودن قابلیت اعتماد (و اعتبار) سنجش BP در سطح کلینیکها در تریالهای با مداخلات تغذیه و اشاره به گایدلاین ۲۰۲۵ انجمنهای قلب و عروق امریکا که سنجش BP monitoring (۲۴ ساعته یا ۷ روزه) را جایگزین مناسب برای سنجش فشار خون میداند که این موضوع باید توسط تریالیستها، در نظر گرفته شود.



Finally, the reliance of included trials on office BP, while understandable given the historical literature, may limit sensitivity to small dietary effects. The 2025 ACC/AHA hypertension guideline [5] now recommends ambulatory or 7-day home BP monitoring for both diagnosis and response assessment, and we hope future trials in this area will adopt these more sensitive endpoints.

Yar, S., Touseef, M., & Nag, I. S. (2026). Methodological Concerns Regarding the Meta-Analysis of Cranberry Consumption and Blood Pressure. *Clinical Cardiology*, 49(5), e70339.

REVIEW

OPEN ACCESS

# The Effect of Cranberry Consumption on C-Reactive Protein and Interleukin-6: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Mohammad Reza Amini<sup>1</sup>  | Mahsa Elahikhah<sup>2</sup> | Sajjad Etesamnia<sup>3</sup> | Motahareh Yadegari<sup>4</sup> |  
Mohammadreza Moradi Baniasadi<sup>5</sup> | Negin Lohrasbi<sup>6</sup> | Gholamreza Askari<sup>1</sup> 

<sup>1</sup>Nutrition and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran | <sup>2</sup>Department of Nutrition Sciences, School of Paramedical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran | <sup>3</sup>Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran | <sup>4</sup>Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran | <sup>5</sup>Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran | <sup>6</sup>Student Research Committee, Department of Clinical Nutrition & Dietetics, National Nutrition & Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## جمع بندی و پیشنهادات : (۱)

✓ **فاز طراحی** : توجه عمیق و دقیق به فاز طراحی یک مطالعه مرور سیستماتیک و متآنالیز :

- تشکیل تیم پژوهش بصورت متنوع (از نظر رشته و تخصص و از نظر دانش و مهارت)
- تا جایکه امکان دارد مرتکب **slicing** نشوید، اگر هم ضروری است (بدلیل حجم بالای داده‌های پیامدی و ...)، در پروتکول اشاره گردد.
- فاز جستجوی مقدماتی و بخصوص ارزیابی محتوای چند مطالعه اولیه را جدی بگیرید.
- ثبت یا به اشتراک گذاری پروتکول را جدی بگیرید.

## جمع بندی و پیشنهادات : (۲)

✓ فاز اجراء:

- سعی کنید دقیقاً بر مبنای پروتکول مطالعه، مراحل را اجراء کنید، هر جایکه ناگزیر به تغییر (یا اصلاحیه‌ای) در پروتکول میشوید، آنها را مو به مو یادداشت نموده و برای هر یک از این موارد اصلاحی، توجیه در نظر بگیرید تا در متن مقاله و ارزیابی داوری سختگیرانه، دچار مشکل نشوید.
- یکی از مهمترین وظایف محقق اصلی این است که وظایف تقسیم شده بین محققین را چک نموده و در این موارد با انتظارات هر مرحله آشنایی داشته باشد. در برخی موارد شاید **Double-checking** بهترین راه حل باشد (مفهوم عملی **Rigorous**)

## جمع بندی و پیشنهادات : (۳)

### ✓ فاز تحلیل آماری :

- هر چند فاز تحلیل آماری نیز مطابق با پروتکول پیش میرود، اما توجه به شاخص / شاخصهای اندازه اثر، متغیرهای زیرگروه پیشین، تعریف مهمترین متغیرهای زیرگروه براساس اهمیت موضوع، وجود دیتای مربوطه در مقالات و انتخاب متغیر / متغیرهای مناسب برای متارگسیون، از مهمترین فعالیتهای این مرحله است.
- ضمناً دقت نمایید که هر گونه نقص در دیتای متغیرهای زیرگروه (براساس اهمیت) را بعداً در مقاله به بخش محدودیتها (در زیرمجموعه Discussion) منتقل نمایید!
- به تعریف رویکردهای تحلیل حساسیت و اجرای آنها، توجه گردد.

## جمع بندی و پیشنهادات : (۴)

✓ فاز ارزیابی قطعیت شواهد:

- در مرور سیستماتیک و متآنالیزهای مداخله‌ای، حتماً ارزیابی قطعیت شواهد با ابزار **GRADE** را در دستور کار پروژه خود قرار دهید.
- متأسفانه هنوز هم کم نیستند محققینی که کارکرد این ابزار را مشابه ارزیابی **RoB** دانسته و به همین خاطر از اجرای آن چشم پوشی میکنند، در حالیکه این ابزار میخواهد به ما در خصوص اینکه چقدر یک نتیجه بدست آمده (حتی اگر عدم اثربخشی مداخله باشد ...)، قطعیت دارد، اطلاعات بدهد.
- برای تحلیلهای زیرگروه مهم نیز میتوان از ابزار قطعیت شواهد **ICEMAN** استفاده نمود.

پایان مجموعه دهم ...

برنامه های آینده را دنبال نمایید!