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# Role of lycopene from tomato on cardiovascular risk: an umbrella review of systematic reviews and meta-analyses of intervention studies

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This umbrella review assessed evidence from systematic reviews (SRs) and meta-analyses (MAs) on the effects of tomato-derived lycopene on cardiovascular risk factors. A comprehensive search was conducted on April 8, 2025, across PubMed, Scopus, and ScienceOn. Eligible studies were SR/MAs of intervention studies involving adult participants consuming tomatoes and/or naturally occurring lycopene and reported cardiovascular outcomes. SR/MA quality and evidence certainty were assessed using A Measurement Tool to Assess Systematic Reviews 2 and Grading of Recommendations Assessment, Development and Evaluation (GRADE). Data synthesis results were expressed as standardized mean differences with 95% confidence intervals. A total of nine SRs were included, seven of which involved MAs. Five moderate-to-high-quality MAs were included in the quantitative synthesis after quality assessment. These demonstrated significant improvements in blood pressure, but lipid profile results were inconsistent. GRADE assessments confirmed high certainty for blood pressure but very low certainty for high-density lipoprotein cholesterol due to heterogeneity. Tomato-derived lycopene consumption lowers blood pressure and modestly improves cardiovascular risk. Daily intake of 5–30 mg lycopene, equivalent to one or two raw tomatoes, appears beneficial.

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## Introduction

Tomatoes are widely consumed and contain a broad spectrum of nutrients and phytochemicals, including vitamin C, potassium, folate, and carotenoids. Among these, carotenoids constitute a particularly important functional class among tomato phytochemicals. The tomato carotenoid profile includes the colorless precursors, phytoene and phytofluene, which contribute to overall carotenoid exposure and have demonstrated antioxidant and photoprotective effects.[1] Within this spectrum, lycopene stands out as the predominant and most extensively studied carotenoid; lycopene—a lipophilic carotenoid predominantly found in red and orange fruits and vegetables, such as tomatoes, watermelons, and papayas—is renowned for its potent antioxidant properties.[2]

Research has demonstrated that lycopene exhibits antioxidant, anti-inflammatory, and anticancer properties. These properties suggest that lycopene can contribute to the prevention of chronic diseases, including cancer, cardiovascular disease (CVD), and metabolic syndrome. Mechanistically, lycopene's cardiovascular benefits may be mediated through multiple pathways, including the prevention of low-density lipoprotein (LDL) oxidation, inhibition of NF-κB-mediated inflammatory responses, and modulation of lipid metabolism *via* nuclear hormone receptor signaling.[3] Numerous systematic reviews (SRs) and meta-analyses (MAs) have investigated the potential benefits and safety of lycopene, with particular emphasis on its role in cardiovascular health.[4–6] Among its various health benefits, lycopene's role in modulating cardiovascular risk factors, such as blood pressure, lipid profiles, blood glucose levels, and endothelial function, has been the focus of numerous clinical trials. However, these SR/MAs have often yielded inconsistent results likely due to variations in their quality and lycopene formulation and dosage, as well as other methodological differences.

To address these inconsistencies, a comprehensive umbrella review evaluating the health benefits of tomato and lycopene consumption was conducted in 2021.[7] This review provides an extensive examination of the effects of tomato and lycopene consumption, including safety and mortality considerations. However, despite the substantial body of research investigating the association between tomatoes, lycopene, and CVD, only three SR/MAs on this topic were included in the previous review. Therefore, this umbrella review of SR/MAs aimed to systematically evaluate and synthesize evidence from existing SRs and MAs examining the relationship between dietary lycopene intake from tomatoes and cardiovascular risk factors, including blood pressure and lipid profiles.

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# Experimental

We followed the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency in this umbrella review.[8] The protocol was established in advance and registered in PROSPERO (registration no. CRD420251022941).

### Search strategy

A comprehensive literature search was performed on April 8, 2025, using three electronic databases: PubMed, Scopus, and ScienceON. The search strategy combined terms related to the target subject—tomato*, lycopene, and "Solanum lycopersicum"—with terms commonly used in systematic reviews and meta-analyses, including "systematic review*", "meta-analy*", "metaanaly*", and "meta analy*". In all three databases, search terms were applied to appropriate indexing fields (*e.g.*, Title/Abstract in PubMed, TITLE-ABS-KEY in Scopus, and Title/Abstract/Keyword in ScienceON). The complete search syntax for each database is provided in SI Table S1.

### Inclusion criteria

Eligible SR/MAs of intervention studies were considered if they met the following inclusion criteria:

- Population (P): adult participants (≥18 years).
- Intervention (I): oral consumption of tomatoes and/or naturally occurring lycopene from food sources.
- Comparator (C): placebo, no treatment, or other control interventions.
- Outcomes (O): primary outcomes related to cardiovascular risk factors, specifically systolic blood pressure (SBP) and diastolic blood pressure (DBP) and lipid profile parameters, including triglycerides (TGs), total cholesterol (TC), LDL cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).
- Publication written in English.

SR/MAs involving animals or interventions using only purified or synthetic lycopene supplements (*e.g.*, capsules, tablets, or other non-food formulations) were excluded. No restrictions were applied regarding study design, lycopene dosage, lycopene type, or duration.

### Study screening and data extraction

Retrieved SR/MAs were first deduplicated and then reviewed by two independent reviewers (Y-EN and H-HJ), who assessed titles and abstracts according to the inclusion and exclusion criteria. Rayyan (https://www.rayyan.ai) was used as a screening tool to ensure blinding. The SR/MAs with uncertain eligibility were advanced to the full-text review stage to minimize the risk of inadvertent exclusion. Disagreements were resolved through discussion, and reasons for excluding papers were documented. This process is summarized in the PRISMA flowchart (Fig. 1).

Standardized data extraction from the included SR/MAs was performed by one author (Y-EN) using a preformatted spreadsheet. A second reviewer (H-HJ) verified the extracted data to minimize reviewer error and bias. The extracted information included author, publication year, title, review type, population characteristics (age, sex, and sample size), intervention details (type, dose, and duration), outcomes, and significance. Primary study funding sources could not be extracted as most SR/MAs did not reported.

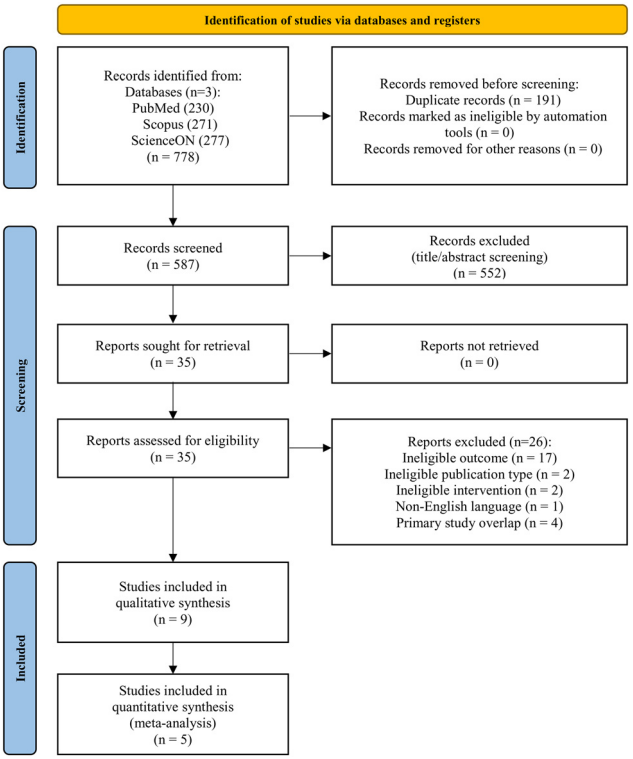


**Fig. 1** PRISMA flow diagram of study selection. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

### Quality assessment

The methodological quality of the SRs was evaluated using a modified version of the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) tool based on the extracted data.[9] The tool categorizes study quality into four levels—high, moderate, low, and very low—based on 16 domains. Y-EN conducted the initial evaluation, and discrepancies were resolved through consensus.

### Overlap assessment

Furthermore, the corrected covered area (CCA) was calculated to quantify the overlap of primary studies across the selected SRs.[10] In addition to the overall overlap value, we assessed the degree of overlap between all research article pairs to identify which specific pairs exhibited significant overlap. A CCA of less than 5% was designated as slight overlap, 5% to 10% as moderate overlap, 10% to 15% as high overlap, and 15% or more as very high overlap.

### Data synthesis and statistical analysis

An MA of the extant literature was conducted using the R programming language (version 4.2.0; Austria). The *meta*, metafor, and dplyr packages were used to aggregate and

analyze the findings. To ensure robustness and reliability, only SRs with a methodological quality rating of moderate or higher according to the AMSTAR 2 criteria were included in the analysis. For SR/MAs reporting weighted mean differences, effect sizes were converted to standardized mean differences (SMDs; Hedges' g) using the pooled standard deviation. Specifically, when SRs reported weighted mean differences (WMDs), these were converted to SMDs by dividing the mean difference between the intervention and control groups by the pooled standard deviation, calculated as ($SD_{Pooled} = \sqrt{SD_1{}^2 + SD_2{}^2/2}$). Random-effects models were fitted for each outcome factor using the restricted maximum likelihood method, with pooled effect sizes expressed as Hedges' g and 95% confidence intervals (CIs). To facilitate clinical interpretation, SMDs for blood pressure and lipid outcomes were translated into absolute units (mmHg for blood pressure; mg $dL^{-1}$ for lipids) by multiplying the SMD by a pooled standard deviation derived from the included studies. The extent of statistical heterogeneity was measured using the $I^2$ statistic. Forest plots were generated to visually present the pooled estimates, with square sizes proportional to precision (inverse of variance) and annotated with study counts, case numbers, and $I^2$ values. To identify potential sources of heterogeneity, we conducted leave-one-out sensitivity analyses for outcomes with substantial heterogeneity ($I^2 > 50\%$), systematically excluding each SR and re-estimating the pooled effect size and heterogeneity statistics. However, publication bias assessment and further sensitivity analyses (*e.g.*, subgroup analyses, meta-regression) were not performed due to the limited number of included studies ($n < 10$). All visualizations were created in ggplot2, and results were reported as SMDs with 95% CIs.

### Grading of the evidence

The certainty of evidence for each marker was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, developed by the independent GRADE Working Group and widely adopted by organizations, such as the Cochrane Collaboration, World Health Organization, and National Institute for Health and Care Excellence.[11,12] The evaluation process was conducted using GRADEpro GDT software (McMaster University and Evidence Prime, 2025), available at https://www.gradepro.org. Based on predefined methodological criteria, the quality of evidence was categorized into four levels: high, moderate, low, or very low.

## Results

### Study selection and characteristics of included reviews

The PRISMA flowchart shown in Fig. 1 outlines the study selection process. Overall, 587 papers were screened after removing duplicates from the 778 papers initially identified through April 2025. During title and abstract screening, 552 SR/MAs were excluded. Subsequently, 26 SR/MAs were removed after full-text review, leaving nine SR/MAs for final inclusion. The reasons for exclusion were as follows: ineligible outcomes, 17; ineligible publication types, two; ineligible interventions, two; publication language other than English, one; and completely duplicated primary studies, four.

The characteristics of the nine included SRs are presented in Table 1. Of these, seven conducted MAs, while two were SRs without MAs. The study participants ranged in age from 18 to 80 years, and all SR/MAs analyzed both men and women without exception. The included SR/MAs synthesized diverse populations ranging from healthy adults to patients with various cardiovascular risk factors, including hypertension, type 2 diabetes (T2D), dyslipidemia, obesity, metabolic syndrome, and established CVD (detailed population characteristics are provided in SI Table S2). The interventions encompassed various forms of lycopene, including raw tomatoes, tomato juice, tomato sauce, and tomato extracts. There was considerable variability in the lycopene dosage, ranging from 1.44 mg $day^{-1}$ to 250 mg $day^{-1}$, and the intervention duration ranged from 6 days to 24 weeks.

**Effects on blood pressure and lipid profiles.** Several included SR/MAs reported associations between lycopene intake and various physiological parameters, including blood pressure and lipid profiles. Joung *et al.* (2023) conducted an SR of 13 studies with lycopene doses of 1.44–50 mg $day^{-1}$ consumed for one day to 12 weeks.[5] Their analysis found significant reductions in SBP, DBP, TC, and LDL-C, along with significant increases in HDL-C. Senkus *et al.* (2019) performed an SR of 11 studies examining the effects of tomato juice (280–750 mL $day^{-1}$) without a specified lycopene dose for 2 months.[13] They reported significant reductions in both SBP and DBP. For lipid profiles, significant reductions were observed in LDL-C and TC, but effects on HDL-C and TG were inconclusive. Tierney *et al.* (2020) performed an SR and MA of 43 studies with lycopene doses ranging from 1.44 to 75 mg $day^{-1}$ and exposure durations from 6 days to 6 months.[14] Overall, no statistically significant differences were observed in SBP, DBP, TC, LDL-C, or HDL-C. Subgroup analyses stratified by baseline health status (healthy *vs.* hyperlipidemic participants for lipid outcomes; healthy *vs.* hypertensive participants for blood pressure outcomes) also showed no significant effects. Wan *et al.* (2024) also conducted an SR and MA of 130 studies examining various antioxidant lipids, including 10 studies for lycopene with doses of 5–30 mg $day^{-1}$ combined with 1–2.5 mg $day^{-1}$ melatonin for 6 weeks to 1 year.[15] In the total population, they reported significant reductions in SBP and improvements in DBP, LDL, HDL, TC, and TG, though effects were not statistically significant. Subgroup analyses by cardiometabolic health status revealed differential effects across risk groups. Significant improvements in HDL-C and TG were observed in healthy participants, participants with pre-diabetes or T2D, and those with overweight or obesity. Hypertensive participants showed significant TC reduction, while dyslipidemic participants demonstrated improvements in DBP, HDL-C, and TG. Participants with metabolic syndrome showed significant DBP reduction. Zamani *et al.* (2023) conducted an SR and MA

 

**Table 1** Study characteristics and confidence rating of included studies

| Authors (year) | Review type (included studies, *n*) | Population (age, sex, *n*) | Intervention (lycopene dose, duration) | Results (outcomes, significance) | Confidence rating (AMSTAR2) |
|---|---|---|---|---|---|
| Inoue *et al.* (2021)[20] | SR (18) MA (12) | ≥18, M/F (1635) | 6–75 mg $d^{-1}$ (1 week–6 months) | • HDL-c ↑ (S)<br>• TG (NS) | High |
| Joung *et al.* (2023)[5] | SR (13) | 18–74, M/F (385) | 1.44–50 mg $d^{-1}$ (1 d–12 weeks) | • SBP, DBP ↓ (S)<br>• TC, LDL-c ↓ (S)<br>• HDL-c ↑ (S) | Low |
| Rattanavipanon *et al.* (2021)[17] | SR + MA (11) | ≥18, M/F (548) | 5–30 mg $d^{-1}$ (1.3–24 weeks) | • SBP ↓ (S)<br>• DBP (NS) | Moderate |
| Rezaei Kelishadi *et al.* (2022)[18] | SR + MA (10) | ≥18, M/F (688) | 5–30 mg $d^{-1}$ (4–12 weeks) | • SBP ↓ (S)<br>• DBP (NS) | Moderate |
| Senkus *et al.* (2019)[13] | SR (11)<br>Cross-sectional (8)[a];<br>Interventional trials (3) | 20–80, M/F (29 957) | Tomato juice: 280–750 mL $d^{-1}$ (2 months) | • SBP, DBP ↓ (S)<br>• TG, HDL-c (mixed)<br>• TC, LDL-c ↓ (S) | Low |
| Tierney *et al.* (2020)[14] | SR + MA (43) | ≥18, M/F (2306) | 1.44–75 mg $d^{-1}$ (360 min–6 months) | SBP, DBP, TC, LDL-C, HDL-C, TG (NS) | Low |
| Wan *et al.* (2024)[15] | SR + MA (130) | 18–75, M/F (666) | Lycopene: 5–30 mg $d^{-1}$<br>Melatonin: 1–2.5 mg $d^{-1}$ 6 weeks–1 years) | • SBP ↓ (S)<br>• DBP, LDL, HDL, TC, TG (NS) | Moderate |
| Wang *et al.* (2020)[19] | SR + MA (9) | 18–74, M/F (758) | Lycopene: 10–60 mg $d^{-1}$<br>Tomato: 250–300 g $d^{-1}$, 7.0 g $kg^{-1}$ (BW)<br>Tomato juice: 200 g $d^{-1}$<br>Tomato sauce: 3.5 g $kg^{-1}$ (BW)<br>(3–12 weeks) | • SBP, DBP (NS) | Low |
| Zamani *et al.* (2023)[16] | SR + MA (34) | ≥18, M/F (1980) | Lycopene: 5.7–250 mg $d^{-1}$<br>Tomato: 100–300 g $d^{-1}$<br>Tomato juice: 100 g $d^{-1}$, 330 ml $d^{-1}$<br>Tomato extract: 70–150 mg $d^{-1}$<br>LycoRed: 2000 μg $d^{-1}$ (1–24 weeks) | • SBP, DBP, TG, TC, LDL-C, HDL-C (NS) | Moderate |

[a] Only interventional trials from this SR were included in our data extraction and analysis. Abbreviations: SR, systematic review; MA, meta-analysis; M, male; F, female; S, significant; NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; BW, body weight.

of 34 studies examining the effects of lycopene (5.7–250 mg $day^{-1}$; 2000 μg $day^{-1}$ lycoRed) and tomato consumption (100 g–330 mL $day^{-1}$ tomato juice; 70–150 mg $day^{-1}$ tomato extract) for 1–24 weeks.[16] They found no significant effect on SBP, DBP, TG, TC, LDL-C, and HDL-C.

**Effects on blood pressure.** Rattanavipanont *et al.* (2021) conducted an SR and a network MA of 11 studies examining the effects of 5–30 mg $day^{-1}$ of lycopene for 10 days to 24 weeks.[17] They found significant SBP reduction, with DBP showing a decreasing trend that was not statistically significant. Rezaei Kelishadi *et al.* (2022) performed an SR and MA of 10 randomized controlled trials (RCTs) examining the effects of 5–30 mg $day^{-1}$ of lycopene for 4–12 weeks.[18] They reported significant SBP reduction with non-significant DBP reduction in overall analysis. Subgroup analyses were conducted based on baseline blood pressure levels, lycopene dosage, intervention duration, and health status. Significant SBP reductions were observed in participants with baseline SBP ≥130 mmHg, lycopene dosage ≥15 mg $day^{-1}$, intervention duration ≥8 weeks, and hypertensive participants. For DBP, significant reductions were observed in participants with baseline DBP ≥80 mmHg and hypertensive participants. Wang *et al.* (2020) also conducted an SR and MA examining the effects of lycopene intake of 10–60 mg $day^{-1}$ and tomato products (250–300 g $day^{-1}$, 7.0 g per kg body weight tomato; 200 g $day^{-1}$ tomato juice; 3 g per kg body weight tomato sauce) for 3–12 weeks.[19] They found no significant effects on either SBP or DBP.

**Effects on lipid profiles.** Inoue *et al.* (2021) performed an SR with an MA of 18 studies examining the effects of 6–75 mg $day^{-1}$ of lycopene for 1 week to 6 months.[20] They reported significant increases in HDL-C levels, with TG showing a decreasing trend that was not statistically significant.

### Methodological quality assessment

The final column of Table 1 summarizes the quality assessment of the included MAs based on the AMSTAR 2 tool. Among the SRs included, only one study received a high quality rating,[20] while four were assessed as moderate quality[15–18] and four as low quality.[5,13,14,19] The most common methodological limitation across included SR/MAs was the failure to report funding sources of included primary studies (Item 10), which was not addressed in six of the nine SR/MAs. This omission is critical as funding sources can introduce potential conflicts of interest and publication bias. Among the

AMSTAR 2 critical domains, the most frequent deficiency was inadequate consideration of RoB when interpreting results (Item 13), which was observed in four SR/MAs.[5,13,19] These SR/MAs did not explicitly discuss how the quality or RoB of the included studies might have affected their findings, potentially leading to overconfident conclusions despite heterogeneity in study quality. Additional methodological concerns included insufficient assessment or discussion of publication bias (Item 15), particularly in SR/MAs rated as low quality, and lack of duplicate data extraction (Item 6) in some SR/MAs, which increases the risk of data extraction errors. A domain-specific evaluation of each included SR/MA, based on the 16 items of the AMSTAR 2 checklist, is presented in SI Fig. S1 and detailed item descriptions are provided in SI Fig. S1 legend.

### Quantitative evaluation of overlap between systematic reviews

The overlap evaluation among the selected SR/MAs yielded an overall CCA of 9.10%, which increased slightly to 9.65% after adjusting for papers that could not be structurally included. When recalculated for the five SRs with moderate-to-high AMSTAR 2 quality ratings that were included in the MA, the CCA increased to 13.02%. As shown in Fig. 2, the CCA was evaluated for all individual study pairs in addition to the overall CCA. The analysis revealed that 25%, 19%, 25%, and 31% of the systematic review pairs exhibited slight overlap, moderate overlap, high overlap, and very high overlap, respectively.

### Effect of lycopene intake on blood pressure and lipid profiles

A total of six cardiometabolic factors were evaluated across the included MAs that received a moderate or higher methodological quality rating. The effect sizes, CIs, heterogeneity estimates, and credibility classes are presented in Fig. 3.

Among the outcomes assessed, SBP showed a small but statistically significant reduction (SMD = −0.15, 95% CI: −0.23 to −0.07) with no observed heterogeneity ($I^2$ = 0%). On translating this SMD into absolute units, lycopene intake was associated with an approximate reduction of 2.41 mmHg in SBP (95% CI: −3.74 to −1.09 mmHg). Similarly, DBP also exhibited a significant reduction (SMD = −0.13, 95% CI: −0.22 to −0.03, $I^2$ = 0%), corresponding to an absolute reduction of approximately 1.33 mmHg (95% CI: −2.33 to −0.33 mmHg).

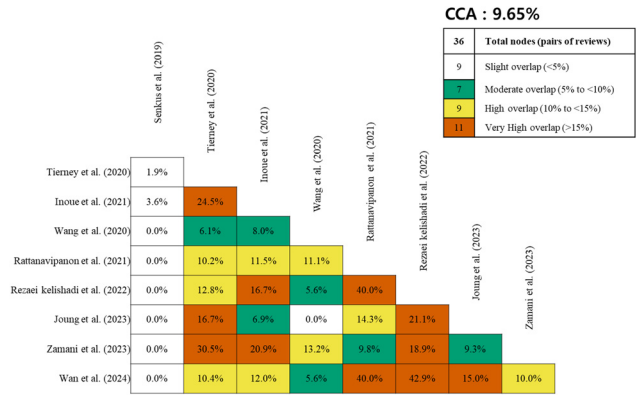


Fig. 2 Detailed assessment of corrected covered area. An overall CCA is presented in the upper right corner of the figure, while CCA values for each SR pair are shown individually within the figure. White boxes indicate low overlap (CCA < 5%), green boxes indicate moderate overlap (CCA > 5% and <10%), yellow boxes indicate high overlap (CCA > 10% and <15%), and red boxes indicate very high overlap (CCA ≥ 15%). CCA, corrected covered area; SR, systematic review.

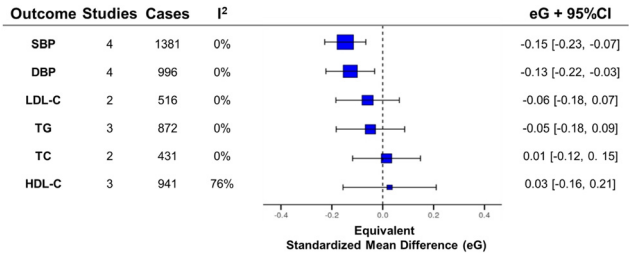


Fig. 3 Forest plot of meta-analytic standardized mean differences for cardio-metabolic outcomes. Each square represents the pooled standardized mean difference for the corresponding cardiometabolic factor, with horizontal lines indicating 95% confidence intervals. Square size is proportional to the inverse variance of the estimate (*i.e.*, precision). SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density.

By contrast, lipid profile-related outcomes showed non-significant associations. For HDL-C, a non-significant increase was observed (SMD = 0.03, 95% CI: −0.16 to 0.21), translating to approximately 0.30 mg $dL^{-1}$ (95% CI: −1.71 to 2.31 mg $dL^{-1}$), accompanied by high between-study heterogeneity ($I^2$ = 76%). TC (SMD = 0.01, 95% CI: −0.12 to 0.15; MD = 0.24 mg $dL^{-1}$, 95% CI: −1.91 to 2.39 mg $dL^{-1}$), TG (SMD = −0.05, 95% CI: −0.18 to 0.09; MD = −0.70 mg $dL^{-1}$, 95% CI: −2.63 to 1.24 mg $dL^{-1}$), and LDL-C (SMD = −0.06, 95% CI: −0.18 to 0.07; MD = −0.06 mg $dL^{-1}$, 95% CI: −0.19 to 0.07 mg $dL^{-1}$) all yielded effect estimates with confidence intervals that included the null, indicating no significant evidence of an effect.

The leave-one-out sensitivity analysis of HDL-C with >50% heterogeneity revealed that this heterogeneity was driven entirely by the study by Inoue *et al.* (2021)[20]; when this study was excluded, heterogeneity disappeared ($I^2$ = 0%), and the pooled estimate shifted to −0.04 mg $dL^{-1}$ (95% CI: −0.13 to 0.06) (SI Fig. S2).

### GRADE summary for biomarker outcomes

The certainty of evidence for each outcome was assessed using the GRADE approach and is summarized in Table 2. Among the six outcomes evaluated, SBP and DBP exhibited the highest certainty of evidence, which was rated as high and supported by four SR/MAs with no serious concerns identified across all domains.

In the case of lipid outcomes, the certainty of evidence for TG and TC was rated as moderate, with downgrades due to serious imprecision. Similarly, the certainty of evidence for LDL-C was rated as moderate, supported by two SR/MAs without any critical limitations. By contrast, the certainty of evidence for HDL-C was rated as very low primarily due to very serious inconsistency and serious imprecision, despite other-

Table 2 GRADE assessment

| Certainty assessment | | | | | | | | No. of patients | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Outcomes | No. of studies | Study design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intervention | Placebo | Certainty |
| SBP | 4 | RCT | Not serious | Not serious | Not serious | Not serious | None | 1381 | 1054 | ⊕⊕⊕⊕ High |
| DBP | 4 | RCT | Not serious | Not serious | Not serious | Not serious | None | 996 | 736 | ⊕⊕⊕⊕ High |
| TG | 3 | RCT | Not serious | Not serious | Not serious | Serious[a] | None | 872 | 788 | ⊕⊕⊕○ Moderate |
| TC | 2 | RCT | Not serious | Not serious | Not serious | Serious[a] | None | 431 | 434 | ⊕⊕⊕○ Moderate |
| LDL-C | 2 | RCT | Not serious | Not serious | Not serious | Serious[a] | None | 516 | 476 | ⊕⊕⊕○ Moderate |
| HDL-C | 3 | RCT | Not serious | Very serious[b] | Not serious | Serious[c] | None | 941 | 790 | ⊕○○○ Very low |

[a] CI crosses no effect, with moderate width. [b] $I^2$ = 60–100%. [c] CI crosses no effect and is wide.

wise robust methodology and low risk of bias across the included studies. For each biomarker, the contributing SR/MAs included ≤10 studies; consequently, formal assessments under "other considerations" (*e.g.*, small-study effects/publication bias) were not feasible and were not incorporated into the GRADE ratings.

## Discussion

This umbrella review aimed to comprehensively evaluate the evidence from previous SR/MAs examining the effects of tomato-derived lycopene intake on cardiovascular risk factors, particularly blood pressure and lipid profiles. Most of the included SR/MAs were MAs that encompassed diverse forms of tomato intake (*e.g.*, raw tomatoes, tomato juice, and tomato extracts) and a broad range of doses. While research on lycopene intake has demonstrated potential benefits for improving blood pressure and lipid profiles, the findings remain inconsistent.

In this MA, we confirmed that lycopene intake from tomatoes significantly improves blood pressure indices. Although these reductions are modest (approximately 2–3 mmHg for SBP), they have meaningful clinical implications. MAs of large-scale trials have demonstrated that every 5 mmHg reduction in SBP is associated with an approximately 10% lower risk of major cardiovascular events.[21] This consistency may be attributable to the inclusion of only SRs with methodological quality ratings of moderate or higher, which likely enhanced the internal validity of the pooled estimates. However, there was an overlap in primary studies among the included SR/MAs, which necessitated careful interpretation. While the overall overlap across all nine SR/MAs was moderate, the overlap among the five SR/MAs included in the MA was higher, as high-quality SR/MAs tend to identify and cite the same primary RCTs through comprehensive search strategies.[22] While mapping tools can quantify the extent of duplication, there is no widely endorsed, standardized framework for fully accounting for this overlap in quantitative synthesis at the review level. In recognition of this, we explicitly reported pairwise overlap and CCA, and interpreted the pooled estimates with appropriate caution. Taken together, although primary study overlap remains a limitation, the blood-pressure-lowering effect was statistically significant and, given the high certainty rating under the GRADE framework, is likely to be clinically applicable.

In contrast to the consistent findings observed for blood pressure indices, the results for lipid profiles were more variable and less conclusive. Although HDL-C levels exhibited statistically significant improvements in individual SRs, this effect was not confirmed in the MA. High heterogeneity across the included SR/MAs ($I^2$ = 76%) and a wide CI crossing the line of no effect resulted in a non-significant pooled effect. Consequently, the GRADE assessment lowered the certainty of evidence for HDL-C to very low, indicating concerns regarding inconsistency and imprecision. To identify the source of this heterogeneity, we conducted a leave-one-out sensitivity analysis, which revealed that this heterogeneity originated entirely from the study by Inoue *et al.* (2021).[20] Comparison of study characteristics identified two key differences. First, the study by Inoue *et al.* was the only SR/MA to explicitly include populations with low baseline HDL-C, alongside patients with hyperlipidemia and metabolic syndrome. Lycopene's antioxidant and anti-inflammatory properties may preferentially enhance reverse cholesterol transport and HDL functionality in individuals with baseline HDL-C deficiency or oxidative stress, while showing minimal effects in normolipidemic populations due to ceiling effects.[23] Second, the study by Inoue *et al.* (2021)[20] included interventions as short as 1 week, potentially capturing acute metabolic responses—such as rapid changes in HDL antioxidant capacity—that differ from steady-state effects in longer-term trials.[24] These findings suggest that lycopene modestly increases HDL-C specifically in populations with metabolic dysregulation or low baseline HDL-C, rather than in the general population. However, these observations remain hypothesis generating, as there are only three corresponding SRs, and will need to be confirmed through future MAs as more studies become available. For other lipid parameters, including TG and LDL-C, slight reductions in levels were observed; however, these changes did not reach statistical significance. The GRADE assessment reflected the limited strength of this evidence. The ratings assigned to TG, TC, and LDL-C were all classified as having moderate certainty, with downgrades occurring primarily due

to imprecision. Despite the overlap in the primary studies included in the analyses by Inoue *et al.* (2021),[20] Zamani *et al.* (2023),[16] and Wan *et al.* (2024),[15] the findings regarding lipid profile markers were not consistent across these SR/MAs. The observed dissimilarity may be attributable to disparities in the synthesis of the evidence, including variations in intervention types or outcome definitions. For instance, Wan *et al.* (2024) examined the combination of lycopene with other bioactive compounds, such as melatonin, which may obscure the specific effects of lycopene.[15] These discrepancies, which were observed despite the presence of substantial duplication in the underlying studies, underscore the complexity of interpreting pooled results when review methodologies and inclusion criteria vary. These conclusions suggest that lycopene intake from tomatoes does not lead to consistent or clinically meaningful improvements in lipid profiles. Subgroup analyses across the included SR/MAs revealed that the beneficial effects of lycopene on both blood pressure and lipid profiles were more pronounced in populations with elevated baseline CVD risk factors.[14,15,18] In particular, hypertensive participants demonstrated greater reductions in SBP and DBP, while participants with dyslipidemia, metabolic syndrome, obesity, or T2D exhibited more favorable changes in HDL-C, TG, and TC compared to healthy participants. This baseline-dependent effect may explain the heterogeneity observed findings. However, only one SR/MA reported lycopene dosage and intervention duration effect on blood pressure, suggesting that further research will be needed as primary studies are updated.

The cardiovascular protective effects of tomato-derived lycopene are mediated through multiple biological mechanisms beyond its antioxidant capacity.[6,25] Lycopene scavenges reactive oxygen and nitrogen species, enhances endothelial nitric oxide production, and inhibits angiotensin-converting enzyme activity, collectively improving vascular function and reducing oxidative-stress-induced endothelial dysfunction. While lycopene has been the primary focus of tomato-related cardiovascular research, it is important to recognize that tomatoes contain a complex matrix of bioactive constituents that may contribute synergistically to cardiovascular health benefits. Other carotenoids, particularly the colorless precursors—phytoene and phytofluene—are present in substantial quantities in tomatoes and are readily absorbed in humans, with emerging evidence suggesting their own antioxidant and cardiovascular protective properties.[26] Additionally, tomatoes provide dietary fiber, polyphenols (including quercetin, naringenin, and rutin), and phenolic acids that favorably influence redox balance, modulate inflammatory pathways, and support endothelial function.[27,28] The relatively consistent and significant effects of tomato lycopene intake on blood pressure compared to on lipid profile parameters can be attributed to fundamental differences in the underlying regulatory mechanisms and time requirements for measurable changes. Blood pressure is regulated by rapid physiological feedback systems involving endothelial nitric oxide bioavailability and vascular tone,[29] which can respond relatively quickly to antioxidant and vasodilatory interventions. By contrast, changes in circulating lipid concentrations are mediated by more complex and slower hepatic metabolic pathways.[30–32] Experimental evidence indicates that lycopene's effects on lipid metabolism are dose- and time-dependent, with reductions in plasma LDL-C requiring adequate dosages and extended intervention periods to modulate hepatic cholesterol synthesis and LDL receptor activity.[33] This differential responsiveness aligns with our findings that blood pressure reductions were consistently observed across various intervention types, whereas lipid profile improvements exhibited considerable heterogeneity. This heterogeneity may reflect variations in study quality, participant characteristics, and intervention formulations rather than clear dose–response or temporal patterns. Nevertheless, blood pressure benefits were observed across a range of lycopene doses (5–30 mg $day^{-1}$), suggesting a threshold effect for vascular improvements.

This umbrella review has several strengths. First, it provides a comprehensive synthesis of existing SRs and MAs on tomato-derived lycopene and cardiovascular risk factors. Second, the integration of GRADE assessments enabled transparent evaluation of evidence certainty, while explicit reporting of primary study overlap allowed for more nuanced interpretation of pooled estimates. However, several limitations warrant consideration. The relatively small number of included SR/MAs precluded formal assessment of publication bias and limited our ability to conduct meta-regression analyses for exploring dose–response relationships or intervention-specific effects. Additionally, substantial overlap among primary studies across SR/MAs may have inflated the precision of pooled estimates. Finally, the included SR/MAs encompassed both healthy individuals and patients with various cardiovascular and metabolic conditions, limiting generalizability to specific population subgroups.

## Conclusions

In conclusion, this umbrella review suggests that despite some variability, tomato and lycopene intake likely contributes to improvements in key cardiovascular risk factors, especially blood pressure indices. Based on the included SR/MAs, our findings suggest that a daily intake of 5–30 mg of lycopene can contribute to an improvement in CVD risk factors. This amount corresponds to consuming at least one to two raw tomatoes daily, which is based on the average lycopene content of approximately 3.0 mg per 100 g.

## Author contributions

Conceptualization: Yea-eun Nam, Hwan-Hee Jang; data curation: Yea-eun Nam, In-Guk Hwang, Hwan-Hee Jang; formal analysis and investigation: Yea-eun Nam, Hwan-Hee Jang; methodology: Yea-eun Nam, Hwan-Hee Jang; writing – original draft: Yea-eun Nam; writing – review & editing: Hwan-Hee Jang; supervision: Hwan-Hee Jang.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

This study did not generate or collect new primary data. We re-standardized and re-computed effect sizes and summary estimates reported in published systematic reviews/meta-analyses to perform the meta-analyses. The resulting derivative datasets are available in the results and supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5fo04213e.

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