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Review

The Intake, Supplementation and Blood Concentrations of Carotenoids in the Prevention of Cardiovascular Diseases: Insights From an Umbrella Meta-Analysis

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Abstract

Background: Cardiovascular disease (CVD) remains a significant global health burden, while carotenoids are considered to have beneficial protective effects against CVD. Thus this study aimed to synthesize available relevant findings regarding the potential correlation between carotenoid consumption (including α/β-carotene, β-cryptoxanthin, lutein, lycopene, zeaxanthin, and astaxanthin) and CVD risk through an umbrella meta-analysis and systematic reviews. **Methods**: Literature searches were conducted in four online academic databases, including PubMed, Web of Science, Embase, and the Cochrane Library, as well as in the literature reference lists of existing meta-analyses and systematic reviews. The search was completed with a cutoff date of July 2023. **Results**: The association between carotenoids, including blood, carotenoid intake, and carotenoid supplements, and CVD risk was estimated as an odds ratio (OR) of 0.889 (95% confidence interval (95% CI): 0.857–0.922; $p < 0.001$), indicating a notable protective association. Furthermore, our analysis demonstrated that the protective impact of carotenoids on total CVD was the most significant for coronary heart disease (OR = 0.875; 95% CI: 0.822–0.932) and stroke (OR = 0.815; 95% CI: 0.734–0.906). **Conclusions**: By controlling for the confounding effects of heterogeneity, including clinical heterogeneity, methodological heterogeneity, and statistical heterogeneity, and publication bias, including positive result enrichment bias, duplicate publication bias, selective study inclusion bias, and selective bias in data extraction and analysis, etc., this study conducted a methodical assessment of the correlation between carotenoids and clinical outcomes of CVD, demonstrating significant inverse relationships between multiple carotenoids and both CVD incidence and mortality of CVD.

Keywords: carotenoids; cardiovascular disease; stroke; coronary heart disease; umbrella meta-analysis

1. Introduction

Cardiovascular disease (CVD) is defined as disorders of the cardiac and circulatory system caused by multiple factors that evolve gradually throughout life [1], which represent the primary global mortality cause with profound socioeconomic implications [2]. Diet-related risks are now recognized as the primary adjustable risk determinant contributing to the elevation of the global CVD-related burden [3] and plant-based dietary patterns endorsed by major clinical guidelines for CVD prevention [4]. Approximately 12 major carotenoid species, lipophilic bioactive metabolites primarily concentrated in yellow, orange, and red fruits and vegetables, are key contributors to dietary micronutrient consumption [5]. Extensive epidemiological findings indicate that carotenoid-rich fruit and vegetable-dense diets exert protective effects against CVD [6] and several chronic diseases [7].

Risk factors for the development of CVD primarily include oxidative stress [8], chronic inflammation, and metabolic disorders [9], with oxidative stress as a key pathological mechanism underpinning CVD initiation and progression [10–12]. Carotenoid intake mitigates CVD risk through these multifaceted pathways. Notably, carotenoids exhibit robust antioxidant activity, enabling them to scavenge free radicals and attenuate oxidative stress [10–12]. Inflammation represents a major driver of CVD pathogenesis, and carotenoid intake alleviates cardiovascular injury by modulating inflammatory signaling pathways [13]. Furthermore, carotenoid consumption effectively regulates blood pressure, blood lipids, and blood glucose levels, thereby directly targeting CVD risk pathways [14].

Based on their chemical structure, carotenoids can be divided into two classes: xanthophylls, which encompass β-cryptoxanthin, lutein, zeaxanthin, astaxanthin, fucoxanthin, and peridinin, and carotenes, which include α-carotene, β-carotene, and lycopene [15]. Human prospective observational cohort studies demonstrate that greater dietary consumption or supplementation of carotenoids with intense antioxidant properties is related to a decreasing hazard of CVD incidence and mortality [16].

Preclinical investigations demonstrate that carotenoids exhibit antioxidant capacity and immunomodulatory activities [5,17,18], regulating cellular proliferation, gene expression profiles, and immune signaling cascades [19]. However, the evidence regarding benefits of carotenoids to cardiovascular remains inconclusive, primarily due to the structural diversity of these compounds and the heterogeneity in study designs and conflicting findings [20,21]. Therefore, a systematic umbrella review synthesizing epidemiological and mechanistic evidence is warranted to resolve inconsistencies in the evidence base and clarify the protective potential of carotenoids against cardiovascular outcomes.

Despite advancements in evidence synthesis methodologies, the translational utility of meta-analyses and systematic reviews with respect to human health-related outcomes remains constrained through persistent inconsistencies arising from heterogeneous study designs, outcome measurement disparities, and incomplete data reporting. To address these constraints, Ioannidis *et al*. [22] originally conceptualized the umbrella review methodology in 2009 as a framework for synthesizing evidence from multiple systematic reviews. Within nutritional epidemiology, umbrella reviews have been particularly impactful for reconciling conflicting evidence on carotenoid bioavailability and CVD risk, where study designs often diverge in population demographics, intervention durations, and biomarker measurement techniques [23,24]. Up to the present, no umbrella review has conducted a systematic assessment of the strength of evidence and potential sources of bias across meta-analyses that investigate associations between carotenoids and CVD. To achieve a more comprehensive and evaluative understanding of the available evidence, we performed the umbrella review that systematically synthesized all published meta-analyses and systematic reviews. This approach was employed to reappraise and clarify the possible roles of various nutritional interventions in the prevention of CVD.

2. Methods

This umbrella review adheres to PRISMA reporting guidelines and was prospectively registered with PROSPERO under identifier CRD42023426292, ensuring transparency and reproducibility in evidence synthesis.

2.1 Literature Search Strategy

This umbrella review systematically evaluated the assessment of evidentiary data from existing systematic reviews and meta-analyses to assess correlations between carotenoid and CVD outcomes, adhering to rigorous methodological standards for evidence synthesis. Two investigators independently and systematically performed a literature search in the PubMed, Web of Science, Embase, and Cochrane Library databases. This review covered the period was set from the inception of each database to July 2023, with the restriction that only English-language articles were included. The search included the following Medical Subject Headings (MeSH) terms: "(carotenoids OR α-carotene OR alpha carotene OR β-carotene OR beta carotene OR ζ-carotene OR zeta Carotene OR β-cryptoxanthin OR lutein OR lycopene OR zeaxanthin OR phytoene OR phytofluene OR violaxanthin OR neoxanthin OR astaxanthin) AND (cardiovascular diseases OR CVD OR stroke OR coronary heart disease OR myocardial infarction OR ischemic heart disease) AND (systematic review OR meta-analysis)". Reference lists of total previously confirmed studies were screened through manual checking to search and obtain additional relevant research literature.

2.2 Study Eligibility and Enrollment/Exclusion Standards

In this study, systematic reviews or meta-analyses that estimate the correlation between carotenoid and CVD risk were deemed eligible for inclusion: (1) encompassed cohort studies, cross-sectional studies, and case-control studies, as well as randomized controlled trials (RCTs); (2) assessed α/β-carotene, β-cryptoxanthin, lutein, lycopene, zeaxanthin, or astaxanthin; (3) documented the incidence or mortality of cardiovascular outcomes, including CVD, stroke, coronary heart disease, myocardial infarction, and ischemic heart disease; (4) provided effect sizes (odds ratio (OR)/relative risk (RR)/Hazard Ratio (HR) with 95% CI), heterogeneity indices (I^2/Cochran's Q); (5) adhered to PRISMA guidelines, included risk of bias assessments, and were prospectively registered; and (6) were English-language full-text articles published by July 2023.

Criteria for exclusion were defined as follows: (1) meta-analyses focusing on non-observational research or non-randomized controlled trials; (2) studies lacking original data for analyzing pooled risk estimates and 95% confidence intervals (95% CI); (3) systematic reviews that did not incorporate a meta-analytic component; (4) non-research articles (e.g., letters, editorials, and conference abstracts); (5) duplicated publications.

The PRISMA-compliant systematic screening workflow, shown in Fig. 1, details database searches for carotenoid-CVD meta-analyses.

2.3 Data Extraction and Quality Assessment

Extraction of Data was independently carried out by reviewers using a standardized protocol, capturing study characteristics, cardiovascular endpoints, carotenoid types, study designs, summary effect metrics, meta-analytic parameters, and risk of bias assessment tools.

Methodological evaluation of quality of eligible meta-analyses was systematically estimated using the A MeaSurement Tool to Assess the methodological Quality of systematic reviews (AMSTAR-2) [25], which evaluates 16 domains across 7 critical and 9 non-critical items. Each meta-

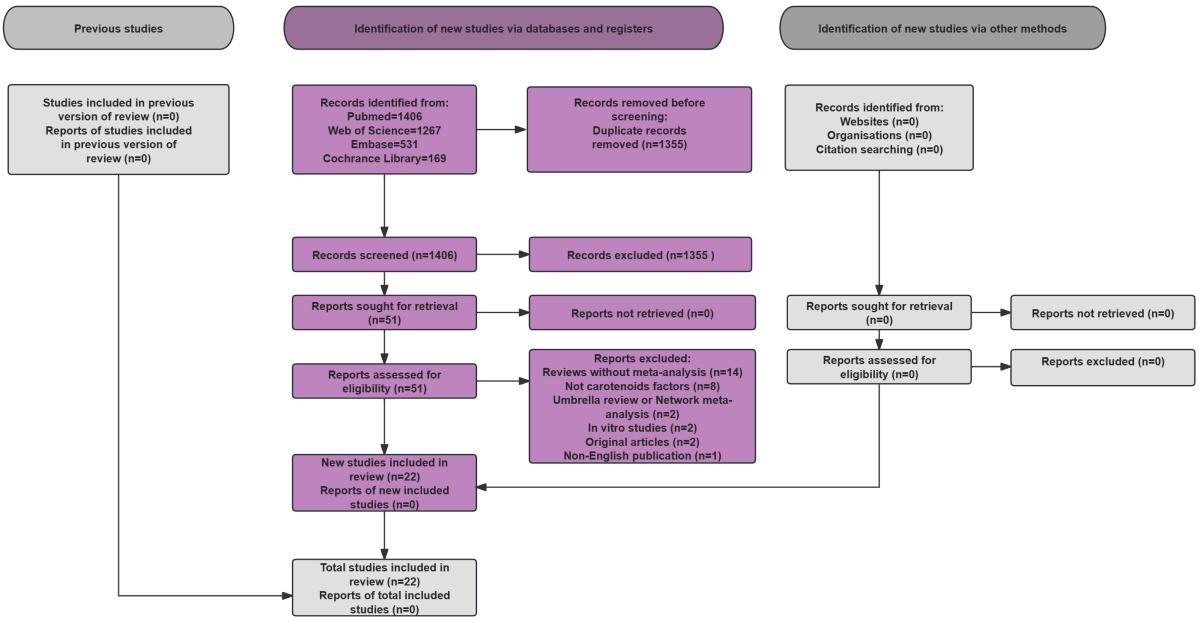

Fig. 1. Flow chart of the literature search.

analysis was categorized into High, Moderate, Low, or Critically Low quality based on item-level assessments.

2.4 Data Analysis

Effect sizes (OR/RR/HR with 95% CI) from qualified meta-analyses were systematically evaluated to quantify carotenoid-CVD associations, with subgroup analyses stratified by carotenoid type and CVD outcome. The presence and magnitude of heterogeneity were determined through using Cochran's Q test and the I^2 statistic [26], with random-effects models applied when $I^2 > 50\%$ or $p < 0.10$ indicating significant variability. Fixed-effects models were used for homogeneous datasets. Assessment of funnel plot asymmetry and Egger's regression analysis were employed to determine publication bias [27], while sensitivity analyses were implemented to confirm the robustness of the study conclusions. Heterogeneity and publication bias were appraised via Cochran's Q test and Egger's regression test, and the statistical significance level was set at $p < 0.05$ to address small-study effects. For all other statistical tests, a significance cutoff of $p < 0.05$ was adopted. Meanwhile, subgroup assessments were performed on the basis of carotenoid types, including α-carotene, β-carotene, ζ-carotene, and lycopene. For this study, all statistical examinations and analyses were conducted using Comprehensive Meta Analysis (version 3.3, Biostat, Inc., Englewood Cliffs, NJ, USA).

3. Results

3.1 Study Identification

Following systematic database searches (PubMed, Web of Science, Cochrane Library, Embase), 3373 records were identified, yielding 22 eligible articles containing 64 meta-analyses evaluating carotenoid-CVD associations (Table 1, Ref. [23,28–48]). Published between 1998 and 2023, these studies were systematically categorized into four CVD risk categories based on carotenoid type and outcome specificity. Eligible meta-analyses were categorized into four CVD outcome categories: total CVD, coronary heart disease, stroke and myocardial infarction and ischemic heart disease [28–49]. Given the limited number of available meta-analyses, myocardial infarction and ischemic heart disease were combined into a single category.

3.2 Quality Evaluation of Meta-Analyses Incorporated in the Study

Methodological quality assessment using the AMSTAR 2 tool revealed that included meta-analyses (n = 64) comprised 10 high-quality, 6 moderate-quality, and 24 low and 24 critically low-quality meta-analyses (**Supplementary Table 1**). And the association linking carotenoids and CVD risk was OR = 0.889; 95% CI: 0.857–0.922; $p < 0.001$ (**Supplementary Fig. 1**).

Using the leave-one-out deletion method, we found the study that Asplund *et al.* [46] exerted a relatively large influence. After its removal, the risk was OR = 0.899; 95% CI: 0.868–0.931; $p < 0.001$. Similarly, Law *et al.* [48] had a substantial impact; following its exclusion, the risk was OR = 0.896; 95% CI: 0.865–0.929; $p < 0.001$. Additionally, An *et al.* [31] showed a notable influence, and its deletion resulted that the risk was OR = 0.884; 95% CI: 0.852–0.918; $p < 0.001$. After removing these studies with significant influence, we analyzed the remaining literature, and no significant changes were observed in the final results. By excluding 24 critically low-quality meta-analyses,

Table 1. Summary of the meta-analyses of carotenoids and CVD risk.

Author & year	Type of CVD	N	Type of studies	Type of carotenoids	Type of metrics	Summary effect size (95% CI)	Model	I^2	Egger's *p* value	Statistically significant
Li *et al*. 2021 a [23]	coronary heart disease	10	cohort	lutein intake	RR	0.88 (0.80–0.98)	random	0.242	NR	Yes
Li *et al*. 2021 b [23]	stroke	3	cohort	lutein intake	RR	0.82 (0.72–0.93)	random	0	NR	Yes
Farashi *et al*. 2023 [28]	stroke	6	CC, cohort, RCT	β-carotene intake/blood/supplement	OR	0.66 (0.47–0.92)	random	0.69	0.3	Yes
Corbi *et al*. 2022 [29]	CVD mortality	12	RCT	β-carotene supplement	RR	1.04 (0.98–1.11)	random	0	NR	No
O'Connor *et al*. 2022 a [30]	CVD mortality	5	RCT	β-carotene supplement	OR	1.10 (1.02–1.19)	random	0	NR	Yes
O'Connor *et al*. 2022 b [30]	CVD incidence	2	RCT	β-carotene supplement	OR	1.01 (0.92–1.10)	random	0	NR	No
An *et al*. 2022 a [31]	CVD mortality	12	RCT	β-carotene supplement	RR	1.12 (1.06–1.18)	random	0.4	0.38	Yes
An *et al*. 2022 b [31]	stroke mortality	6	RCT	β-carotene supplement	RR	1.09 (1.01–1.17)	random	0.73	0.065	Yes
An *et al*. 2022 c [31]	Myocardial Infarction	7	RCT	β-carotene supplement	RR	0.99 (0.93–1.05)	random	0.02	0.428	No
Yang *et al*. 2022 a [32]	CVD incidence	15	RCT	β-carotene supplement	RR	1.04 (1.00–1.08)	random	0	0.051	Yes
Yang *et al*. 2022 b [32]	CVD mortality	12	RCT	β-carotene supplement	RR	1.12 (1.04–1.19)	random	0.24	0.5	Yes
Cheng *et al*. 2019 a [33]	stroke	4	CC, cohort	lycopene Intake	HR	0.79 (0.64–0.97)	random	0.44	NR	Yes
Cheng *et al*. 2019 b [33]	stroke	4	CC, cohort	lycopene blood	HR	0.61 (0.40–0.92)	random	0.157	NR	Yes
Cheng *et al*. 2019 c [33]	CVD incidence	3	CC, cohort	lycopene Intake	HR	0.88 (0.78–0.99)	random	0	NR	Yes
Cheng *et al*. 2019 d [33]	CVD incidence	4	CC, cohort	lycopene blood	HR	0.78 (0.63–0.98)	random	0	NR	Yes
Jayedi *et al*. 2019 a [34]	CVD mortality	4	CC, cohort, RCT	β-carotene intake	RR	0.89 (0.73–1.05)	random	0.35	NR	No
Jayedi *et al*. 2019 b [34]	CVD mortality	6	CC, cohort, RCT	β-carotene blood	RR	0.68 (0.52–0.83)	random	0.5	NR	Yes
Aune *et al*. 2018 a [35]	coronary heart disease	4	cohort	total carotenoids intake	RR	0.82 (0.69–0.99)	random	NR	NR	Yes
Aune *et al*. 2018 b [35]	coronary heart disease	3	cohort	total carotenoids blood	RR	0.68 (0.50–0.93)	random	NR	NR	Yes
Aune *et al*. 2018 c [35]	coronary heart disease	4	cohort	β-carotene intake	RR	0.73 (0.63–0.85)	random	NR	NR	Yes
Aune *et al*. 2018 d [35]	coronary heart disease	4	cohort	β-carotene blood	RR	0.69 (0.53–0.90)	random	NR	NR	Yes
Aune *et al*. 2018 e [35]	coronary heart disease	4	cohort	α-carotene blood	RR	0.88 (0.71–1.10)	random	NR	NR	No
Aune *et al*. 2018 f [35]	coronary heart disease	2	cohort	β-cryptoxanthin blood	RR	1.01 (0.43–2.37)	random	NR	NR	No
Aune *et al*. 2018 g [35]	coronary heart disease	2	cohort	lycopene blood	RR	0.88 (0.71–1.10)	random	NR	NR	No
Aune *et al*. 2018 h [35]	stroke	3	cohort	lycopene Intake	RR	0.80 (0.63–1.01)	random	NR	NR	No
Aune *et al*. 2018 I [35]	cardiovascular disease	2	cohort	total carotenoids intake	RR	0.87 (0.74–1.01)	random	NR	NR	No
Aune *et al*. 2018 j [35]	cardiovascular disease	2	cohort	total carotenoids blood	RR	0.81 (0.64–1.03)	random	NR	NR	No
Aune *et al*. 2018 k [35]	stroke	7	cohort	β-carotene intake	RR	0.84 (0.75–0.94)	random	NR	NR	Yes
Aune *et al*. 2018 l [35]	cardiovascular disease	4	cohort	β-carotene intake	RR	0.98 (0.84–1.15)	random	NR	NR	No
Aune *et al*. 2018 m [35]	stroke	3	cohort	β-carotene blood	RR	0.85 (0.71–1.01)	random	NR	NR	No
Aune *et al*. 2018 n [35]	cardiovascular disease	6	cohort	β-carotene blood	RR	0.73 (0.57–0.92)	random	NR	NR	Yes
Aune *et al*. 2018 o [35]	stroke	3	cohort	α-carotene blood	RR	0.74 (0.48–1.14)	random	NR	NR	No
Aune *et al*. 2018 p [35]	cardiovascular disease	3	cohort	α-carotene blood	RR	0.91 (0.64–1.29)	random	NR	NR	No
Aune *et al*. 2018 q [35]	cardiovascular disease	3	cohort	β-cryptoxanthin blood	RR	0.83 (0.67–1.03)	random	NR	NR	No
Aune *et al*. 2018 r [35]	cardiovascular disease	2	cohort	lycopene Intake	RR	0.94 (0.79–1.12)	random	NR	NR	No

Table 1. Continued.

Author & year	Type of CVD	N	Type of studies	Type of carotenoids	Type of metrics	Summary effect size (95% CI)	Model	I^2	Egger's *p* value	Statistically significant
Aune *et al*. 2018 s [35]	stroke	2	cohort	lycopene blood	RR	0.59 (0.36–0.96)	random	NR	NR	Yes
Aune *et al*. 2018 t [35]	cardiovascular disease	4	cohort	lycopene blood	RR	0.88 (0.70–1.10)	random	NR	NR	No
Schwingshackl *et al*. 2017 a [36]	CVD mortality	8	RCT	β-carotene supplement	RR	1.06 (0.93–1.21)	random	0	NR	No
Schwingshackl *et al*. 2017 b [36]	CVD incidence	5	RCT	β-carotene supplement	RR	1.14 (0.87–1.48)	random	0	NR	No
Song *et al*. 2017 a [37]	CVD incidence	7	CC, cohort	lycopene Intake	RR	0.87 (0.79–0.96)	random	0.063	0.236	Yes
Song *et al*. 2017 b [37]	CVD incidence	7	CC, cohort	lycopene blood	RR	0.74 (0.62–0.87)	random	0.45	0.753	Yes
Leermakers *et al*. 2016 a [38]	coronary heart disease	10	CC, cohort	lutein intake	RR	0.89 (0.83–0.97)	fixed	0.242	0.221	Yes
Leermakers *et al*. 2016 b [38]	stroke	5	CC, cohort	lutein intake	RR	0.82 (0.72–0.93)	fixed	0	0.47	Yes
Li *et al*. 2014 [39]	stroke	7	CC, cohort	total lycopene	RR	0.81 (0.68–0.96)	random	0.255	0.277	Yes
Fortmann *et al*. 2013 [40]	CVD incidence	2	RCT	β-carotene supplement	RR	1.01 (0.93–1.09)	random	NR	NR	No
Myung *et al*. 2013 [41]	CVD	17	RCT	β-carotene supplement	RR	1.04 (0.96–1.12)	random	0.55	NR	No
Mente *et al*. 2009 a [42]	coronary heart disease	10	cohort	β-carotene intake	RR	0.73 (0.65–0.82)	random	NR	NR	Yes
Mente *et al*. 2009 b [42]	coronary heart disease	14	RCT	β-carotene supplement	RR	1.01 (0.92–1.09)	random	NR	NR	No
Ye *et al*. 2008 [43]	coronary heart disease	3	cohort	β-carotene intake	RR	0.78 (0.53–1.04)	random	NR	NR	No
Knekt *et al*. 2004 a [44]	coronary heart disease incidence	9	cohort	α-carotene intake	RR	0.90 (0.77–1.04)	NR	NR	NR	No
Knekt *et al*. 2004 b [44]	coronary heart disease incidence	9	cohort	β-carotene intake	RR	0.92 (0.79–1.06)	NR	NR	NR	No
Knekt *et al*. 2004 c [44]	coronary heart disease incidence	9	cohort	lycopene Intake	RR	0.99 (0.85–1.14)	NR	NR	NR	No
Knekt *et al*. 2004 d [44]	coronary heart disease incidence	9	cohort	β-Cryptoxanthin intake	RR	0.94 (0.79–1.12)	NR	NR	NR	No
Knekt *et al*. 2004 e [44]	coronary heart disease incidence	9	cohort	lutein intake	RR	0.89 (0.75–1.04)	NR	NR	NR	No
Vivekananthan *et al*. 2003 [45]	CVD mortality	6	RCT	β-carotene supplement	OR	1.10 (1.03–1.17)	random	NR	NR	Yes
Asplund *et al*. 2002 a [46]	CVD	8	cohort	β-carotene intake	OR	0.88 (0.77–1.01)	fixed	NR	NR	No
Asplund *et al*. 2002 b [46]	CVD	4	cohort	β-carotene blood	OR	0.46 (0.37–0.58)	fixed	NR	NR	Yes
Asplund *et al*. 2002 c [46]	CVD	6	RCT	β-carotene supplement	OR	1.02 (0.96–1.08)	fixed	NR	NR	No
Marchioli *et al*. 1999 a [47]	CVD	7	cohort	β-carotene intake	OR	0.66 (0.57–0.78)	random	NR	NR	Yes
Marchioli *et al*. 1999 b [47]	CVD	3	CC	β-carotene intake	OR	0.61 (0.40–0.93)	random	NR	NR	Yes
Marchioli *et al*. 1999 c [47]	coronary heart disease	5	RCT	β-carotene	OR	1.02 (0.98–1.07)	random	NR	NR	No
Law *et al*. 1998 a [48]	ischaemic heart disease	4	CC, cohort	carotenoids intake	RR	0.85 (0.77–0.93)	NR	NR	NR	Yes
Law *et al*. 1998 b [48]	ischaemic heart disease	3	CC, cohort	carotenoids blood	RR	0.57 (0.47–0.69)	NR	NR	NR	Yes
Law *et al*. 1998 c [48]	ischaemic heart disease	5	RCT	β-carotene supplement	RR	1.07 (0.98–1.16)	NR	NR	NR	No

CVD, cardiovascular disease; N, number of meta-analyses; RCT, randomized controlled trial; CC, case control; CI, confidence interval; OR, odds ratio; RR, relative risk; NR, not reported; a-t, different letters present Meta-analyses selected from an article.

the association linking carotenoids and CVD risk was OR = 0.878; 95% CI: 0.838–0.920; $p < 0.001$. By excluding 24 low and 24 critically low-quality meta-analyses, the association linking carotenoids and CVD risk was OR = 0.944; 95% CI: 0.891–1.000; $p = 0.051$. By excluding low and critically low-quality meta-analyses, while characterized by low methodological quality, such studies exerted no influence on the overall results, demonstrating the reliability of the research findings.

3.3 Total CVD Outcomes

Across all qualified meta-analyses investigating the association between dietary carotenoid intake, carotenoid supplementation, or blood concentrations and CVD outcomes, and a total number of 64 effect meta-analyses were identified. These included studies focused on total CVD (n = 30) as well as three other specific subtypes of CVD (n = 34), with the latter collectively accounting for the remaining 34 effect meta-analyses in the dataset. A notable inverse correlation was identified between carotenoid and CVD risk (OR = 0.889; 95% CI: 0.857–0.922; $p < 0.001$) (**Supplementary Fig. 1**) with substantial heterogeneity (I^2= 0.847, $p < 0.001$) employing the random effects model. Subgroup analysis demonstrated protective effects of total carotenoids (OR = 0.852; 95% CI: 0.748–0.970), α-carotene (OR = 0.910; 95% CI: 0.640–1.290), β-carotene (OR = 0.959; 95% CI: 0.906–1.015), β-cryptoxanthin (OR = 0.830; 95% CI: 0.670–1.030), and lycopene (OR = 0.857; 95% CI: 0.807–0.909) against total CVD (Table 2). Evaluation of publication bias employed a funnel plot and Egger's regression test, and the results demonstrated a significant small-study effect ($p < 0.001$). Nevertheless, trim-and-fill analysis incorporating 21 imputed research studies revealed no significant bias confounding the overall effect estimate (OR = 0.998; 95% CI: 0.985–1.010) (Table 2).

3.4 Coronary Heart Disease Outcomes

A systematic literature search yielded 18 meta-analyses investigating carotenoids and coronary heart disease. This umbrella meta-analysis revealed a statistically notable protective role of carotenoids against coronary heart disease (OR = 0.875; 95% CI: 0.822–0.932; $p < 0.001$, Fig. 2) with notable heterogeneity identified ($I^2 = 0.743$, $p < 0.001$). Subgroup analysis demonstrated notable associations for total carotenoids (OR = 0.781; 95% CI: 0.664–0.917) (Table 2), β-carotene (OR = 0.849; 95% CI: 0.743–0.970), β-cryptoxanthin (OR = 0.943; 95% CI: 0.795–1.119), lutein (OR = 0.887; 95% CI: 0.841–0.935), lycopene (OR = 0.954; 95% CI: 0.845–1.078), and α-carotene (OR = 0.894; 95% CI: 0.789–1.011). Begg's regression test for the funnel plot indicated no publication bias ($p = 0.426$). Trim-and-fill analysis involving eight imputed research studies revealed no statistically significant correlation between carotenoid consumption and coronary heart disease risk (OR = 0.969; 95% CI: 0.946–0.993) (Fig. 2).

3.5 Stroke Outcomes

Of the 64 meta-analyses reviewed, 12 demonstrated a statistically significant finding regarding the lowering of stroke risk with carotenoids. Fig. 3 presented a significant negative correlation between carotenoid intake/blood levels and stroke risk (OR = 0.815; 95% CI: 0.734–0.906; $p < 0.001$) through employing a random-effects model, which was applied due to moderate heterogeneity ($I^2 = 0.762$, $p < 0.001$). Subgroup analyses conducted in this study revealed statistically significant protective effects of total carotenoids (OR = 0.811; 95% CI: 0.674–0.975), α-carotene (OR = 0.740; 95% CI: 0.480–1.140), β-carotene (OR = 0.877; 95% CI: 0.722–1.064), lutein (OR = 0.820; 95% CI: 0.749–0.898), and lycopene (OR = 0.774; 95% CI: 0.695–0.862) on the risk of stroke (Table 2). And Begg's correlation test demonstrated that there is no conclusive evidence of notable publication bias ($p = 0.411$), meanwhile the stability of the overall effect estimate was confirmed via trim-and-fill analysis with 5 imputed research studies (OR = 0.921; 95% CI: 0.883–0.961) (Fig. 3).

3.6 Myocardial Infarction and Ischemic Heart Disease Outcomes

The methodologically rigorous systematic review was performed on the limited available meta-analyses evaluating carotenoid consumption and myocardial infarction/ischemic heart disease, with the objective of deriving pooled effect estimates. This umbrella review identified four meta-analyses reporting non-significant associations between carotenoids and two key cardiovascular conditions: myocardial infarction and ischemic heart disease (OR = 0.866; 95% CI: 0.727–1.031; $p = 0.105$, Fig. 4), characterized by substantial heterogeneity ($I^2 = 0.928$, $p < 0.001$). Subgroup analysis demonstrated a non-significant protective impact of total carotenoids (OR = 0.702; 95% CI: 0.475–1.039) in terms of the hazard of myocardial infarction/ischemic heart disease (Table 2). Nevertheless, two studies reported a non-significant positive correlation between β-carotene consumption and myocardial infarction/ischemic heart disease (OR = 1.023; 95% CI: 0.949–1.103). Begg's regression test for funnel plot indicated no indication of publication bias within this umbrella meta-analysis ($p = 0.308$). And one imputed study included in the trim-and-fill analysis indicated that carotenoids exerted a protective impact against myocardial infarction and ischemic heart disease (OR = 0.978; 95% CI: 0.939–1.020) (Fig. 4).

3.7 Subgroup Analyses Exploring the Impact of Carotenoid Sources on Various CVD Subtypes

Additional subgroup analyses were implemented to investigate source-specific effects of carotenoids on CVD outcomes. No significant effect modifications were observed by dietary intake (OR = 0.859; 95% CI: 0.820–0.900) and serum concentrations (OR = 0.738; 95% CI:

Table 2. Subgroup analysis of types of carotenoids on various CVD.

Type of CVD	Type of carotenoids	Number of meta-analyses	OR (95% CI)	I^2 (p value)
CVD	total carotenoids	2	0.852 (0.748–0.970)	0 (0.622)
	β-cryptoxanthin	1	0.830 (0.670–1.030)	NA (NA)
	β-carotene	20	0.959 (0.906–1.015)	0.863 (<0.001)
	lycopene	6	0.857 (0.807–0.909)	0 (0.417)
	α-carotene	1	0.910 (0.640–1.290)	NA (NA)
Coronary heart disease	total carotenoids	2	0.781 (0.664–0.917)	0.004 (0.307)
	β-carotene	7	0.849 (0.743–0.970)	0.884 (<0.001)
	β-cryptoxanthin	2	0.943 (0.795–1.119)	0 (0.872)
	lutein	3	0.887 (0.841–0.935)	0 (0.982)
	lycopene	2	0.954 (0.845–1.078)	0 (0.381)
	α-carotene	2	0.894 (0.789–1.011)	0 (0.868)
Stroke	β-carotene	4	0.877 (0.722–1.064)	0.870 (<0.001)
	lycopene	5	0.774 (0.695–0.862)	0 (0.596)
	lutein	2	0.820 (0.749–0.898)	0 (0.950)
	α-carotene	1	0.740 (0.480–1.140)	NA (NA)
Myocardial infarction/ischaemic heart disease	total carotenoids	2	0.702 (0.475–1.039)	0.925 (<0.001)
	β-carotene	2	1.023 (0.949–1.103)	0.535 (0.143)

CI, confidence interval; OR, odds ratio; NA, not available.

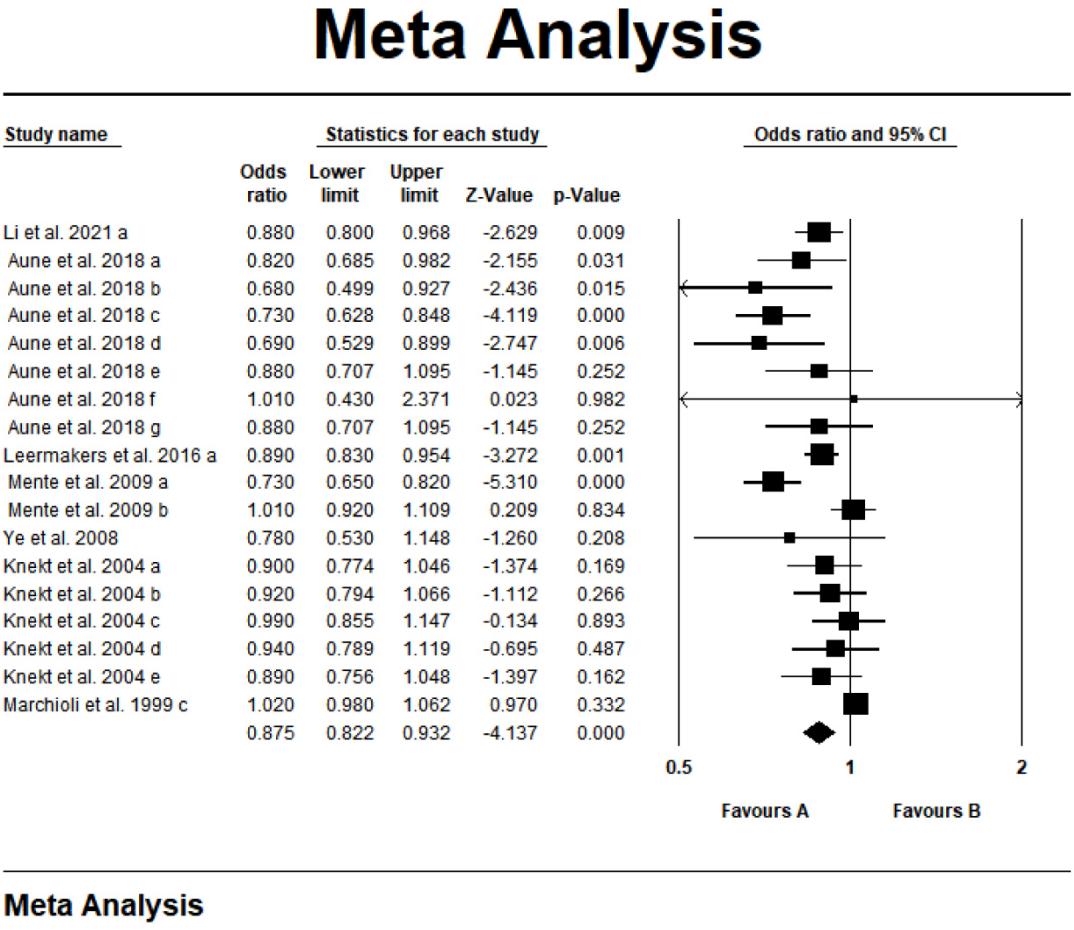

Fig. 2. Forest plot of the effect of carotenoids on coronary heart disease. a-g, different letters represent different Meta-analyses selected from an article.

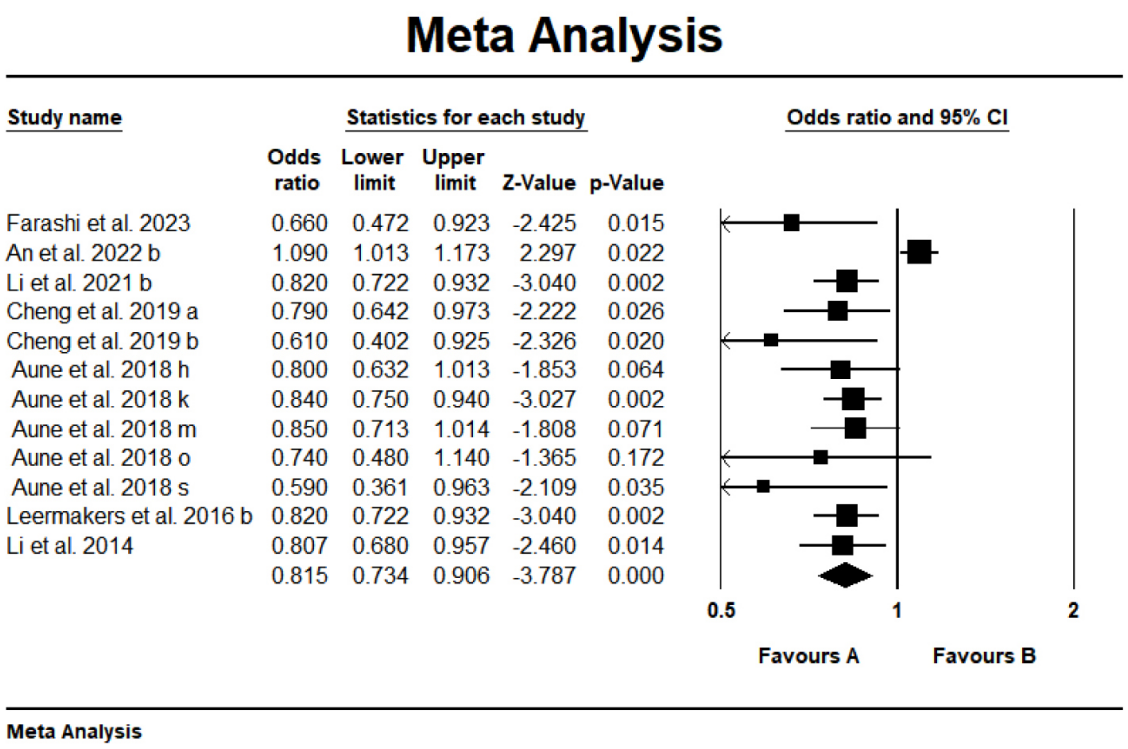

Fig. 3. Forest plot of the effect of carotenoids on stroke. a-s, different letters represent different Meta-analyses selected from an article.

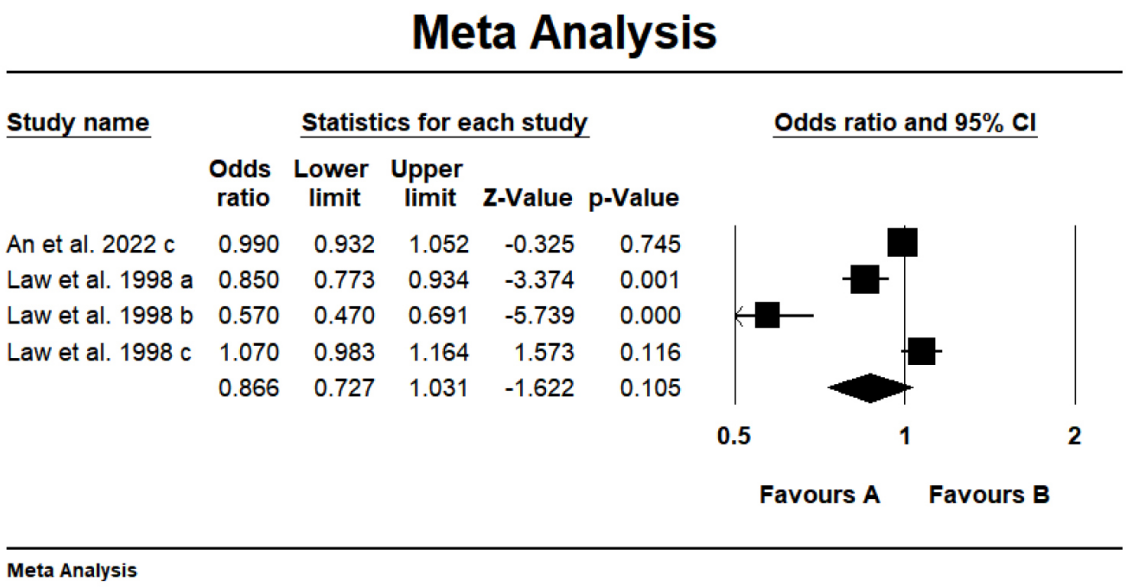

Fig. 4. Forest plot of the effect of carotenoids on myocardial infarction/ischemic heart disease. a-c, different letters represent different Meta-analyses selected from an article.

0.676–0.806) of carotenoids. However, supplementation was correlated with significantly increased risks for total CVD (OR = 1.061; 95% CI: 1.037–1.086), coronary heart disease (OR = 1.018; 95% CI: 0.982–1.057), stroke (OR = 1.090; 95% CI: 1.010–1.117), and myocardial infarction/ischemic heart disease (OR = 1.023; 95% CI: 0.949–1.103) (Table 3).

4. Discussion

This umbrella meta-analysis aimed to synthesize current evidence and deliver a comprehensive review of carotenoid effects on CVD risk, building on previous systematic reviews and meta-analyses. Total 64 eligible meta-analyses from 22 primary studies were incorporated to evaluate the impact of carotenoids on CVD. Total carotenoids demonstrated significant inverse associations with inci-

Table 3. Subgroup analysis of source of carotenoids on various CVD.

Type of CVD	Source of carotenoids	Number of meta-analyses	OR (95% CI)	I^2 (p value)
CVD	Blood	9	0.741 (0.650–0.845)	0.653 (0.003)
	Carotenoids intake	9	0.855 (0.789–0.926)	0.583 (0.014)
	Carotenoids supplement	12	1.061 (1.037–1.086)	0.234 (0.213)
Coronary heart disease	Blood	5	0.806 (0.714–0.910)	0 (0.408)
	Carotenoids intake	11	0.862 (0.813–0.914)	0.492 (0.032)
	Carotenoids supplement	2	1.018 (0.982–1.057)	0 (0.849)
Stroke	Blood	4	0.757 (0.634–0.903)	0.156 (0.314)
	Carotenoids intake	5	0.822 (0.771–0.877)	0 (0.987)
	Carotenoids supplement	1	1.090 (1.010–1.117)	NA (NA)
Myocardial infarction/ischaemic heart disease	Blood	1	0.57 (0.47–0.69)	NA (NA)
	Carotenoids intake	1	0.85 (0.77–0.93)	NA (NA)
	Carotenoids supplement	2	1.023 (0.949–1.103)	0.535 (0.143)

CI, confidence interval; OR, odds ratio; NA, not available.

dence and CVD mortality, coronary heart disease, stroke, myocardial infarction and ischemic heart disease. These findings indicate potential protective effects of carotenoid consumption on CVD despite methodological variations across included studies.

The present umbrella review provided sufficient proof that reinforces evidence for the carotenoids to play a protective impact against the development of CVD. Aune *et al*. [35] reported negative correlations between carotenoid consumption and the hazard of several health outcomes, including coronary heart disease, stroke, and mortality. Bahonar *et al*. [50] observed in a 165-patient cohort study that plasma total carotenoid concentrations above median levels was related to a 71% decrease in the hazard of CVD mortality (HR = 0.29, 95% CI: 0.12–0.71). Leermakers *et al*. [38] demonstrated protective effects of dietary lutein on coronary heart disease (RR = 0.88; 95% CI: 0.80–0.98) and stroke (RR = 0.82; 95% CI: 0.72–0.93). Song *et al*. (2017) [37] demonstrated a statistically notable negative correlation between lycopene exposure and CVD risk (RR = 0.83, 95% CI: 0.76–0.90), with consistent results in dietary (RR = 0.87; 95% CI: 0.79–0.96) and biomarker-based (RR = 0.74; 95% CI: 0.62–0.87) analyses. Moreover, diet-related lycopene consumption showed protective effects for mitigating coronary heart disease risk (RR = 0.87; 95% CI: 0.76–0.98) and stroke (RR = 0.83; 95% CI: 0.69–0.96) [37]. Further study confirmed these findings in a pooled data analysis of 116,127 study participants, demonstrating a 19.3% decrease in the hazard of stroke with lycopene intake (RR = 0.807; 95% CI: 0.680–0.957) [39].

Despite the protective evidence, conflicting findings exist regarding carotenoid-CVD associations. Yang *et al*. [32] reported β-carotene supplementation modestly raised overall CVD incidence (RR = 1.04; 95% CI: 1.00–1.08) and was consistently linked to raised CVD mortality (RR = 1.12; 95% CI: 1.04–1.19), particularly among smokers. Another epidemiology study showed similar evidence, β-carotene was notably correlation with a raised hazard of CVD mortality (OR = 1.10; 95% CI: 1.02–1.19) [30]. Leppälä *et al*. [51] demonstrated a statistically notable correlation between β-carotene and subarachnoid hemorrhage risk (RR = 2.30; 95% CI: 1.20–4.40). The Alpha-Tocopherol, Beta-Carotene Cancer (ATBC) Prevention Study further reported harmful effects of β-carotene on stroke incidence (RR = 1.11; 95% CI: 0.980–1.25) and mortality (RR = 1.06; 95% CI: 0.780–1.44) [52]. Tierney *et al*. [53] highlighted substantial discrepancies in lycopene intervention outcomes, particularly regarding dosage and delivery mode.

Dietary carotenoids possess a physiologically balanced combination of moderate bioavailability, complex synergistic components, and natural dosage, which collectively underpin their protective effects against CVD and chronic illnesses [54]. By contrast, carotenoid supplements—characterized by high bioavailability, simplified composition, and supraphysiological doses—may disrupt redox balance and metabolic regulation, with particularly pronounced impacts in high-risk populations [13]. This discrepancy stems from the inherent difference between natural occurrence and artificial formulation, and the food matrix plays a central role in mediating these variations. Synergistic nutrients in natural foods can enhance the bioactivity of carotenoids while mitigating potential pro-oxidant effects; furthermore, the sustained and moderate plasma concentrations resulting from dietary intake are compatible with the body's antioxidant defense system. Although supplements offer advantages such as high bioavailability and targeted delivery, they lack this protective mechanism, rendering them prone to inducing oxidative stress or interfering with physiological processes at high doses [55,56].

Carotenoids may have the potential to reduce CVD risk through a range of biological mechanisms, specifically by lowering blood pressure, dampening the levels of pro-inflammatory cytokines, lessening inflammatory markers (e.g., C-reactive protein) and enhancing insulin sensitivity within critical metabolic tissues including the liver,

skeletal muscles, and adipose tissue [19]. Furthermore, carotenoids can have the capacity to influence gene expression levels linked to key cellular metabolic pathways [57]. The protective actions of carotenoids against chronic illnesses stem from their versatile characteristics, which include anti-inflammatory, anticoagulant, antiviral, and antioxidant capacities, as well as directly modulate immune responses [58]. Linnewiel-Hermoni *et al*. (2014) [59] documented that carotenoid interventions significantly reduced C-reactive protein (Weighted Mean Difference (WMD) = –0.54 mg/L, 95% CI: –0.71 to –0.37, $p < 0.001$) and interleukin-6 (IL-6) (WMD = –0.54 pg/mL, 95% CI: –1.01 to –0.06, $p = 0.025$), with specific decrease observed for lutein/zeaxanthin (WMD = –0.30 mg/L, $p < 0.001$) and β-cryptoxanthin (WMD = –0.35 mg/L, $p < 0.001$) on C-reactive protein. Furthermore, lycopene has been shown to reduce inducible nitric oxide synthase and IL-6 mRNA expression, inhibit Inhibitor of κB (IκB) phosphorylation/degradation and Nuclear Factor-κB (NF-κB) translocation, and prevent Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) and p38 Mitogen-Activated Protein Kinase (p38 MAP) kinase phosphorylation, thereby exerting anti-inflammatory effects [60,61]. Collectively, lycopene supplementation enhances endothelial function, reduces inflammatory markers, and exerts protective effects against CVD progression [62].

The antioxidant effect of carotenoids, considered health-promoting agents against atherosclerotic CVD, is one of the potential mechanisms [63]. Milani *et al*. [19] proposed that lycopene may have a preventive effect against CVD in humans, given that it exhibits notable antioxidant activity in vitro, suppresses cholesterol synthesis, and enhances the degradation of low-density lipoprotein (LDL). Carotenoids quench molecular singlet oxygen and scavenge reactive oxygen species, particularly peroxyl radicals [64]. Moreover, carotenoids promote the localization of Nuclear factor erythroid 2-related factor 2 (Nrf-2) in the cell nucleus and the activation of phase II enzymes to decrease oxidative stress [65]. Through the capacity to neutralize free radicals, carotenoids promote the clearance of cells under oxidative stress, thereby mitigating their deleterious effects. Collectively, carotenoids mediate protective effects against CVD through modulation of lipid profiles, inhibition of lipid peroxidation, and enhancement of antioxidant defense systems, thereby counteracting vascular inflammation, stabilizing membrane integrity during atherosclerotic processes, and reducing CVD risk [66].

The US Preventive Services Task Force emphasized that single carotenoid supplementation may exert complex physiological effects in smokers, with potential dose-dependent deleterious outcomes on CVD risk due to pro-oxidant activity [30]. Concurrently, exceeding tolerable upper intake levels poses universal health risks for the general population [67]. Future studies should systematically examine co-administration of concomitant substances and dose-response relationships associated with adverse health effects, while determining safe carotenoid consumption thresholds through strict human trials.

Our present umbrella review comprehensively collects and evaluates all previously published meta-analyses and systematic reviews to reach a conclusion on the effectiveness of carotenoids in CVD prevention with the highest quality of evidence and minimized bias. However, our current investigation has several limitations that require further consideration. Firstly, the interaction between modifiers such as smoking may bias the calculated effect sizes, which we should take into consideration. Secondly, a systematic selection of studies included in previously published meta-analyses was performed, representing a potential limitation due to possible exclusion of non-identified studies. Thirdly, we were unable to evaluate whether carotenoids supplementation would be beneficial against CVD for populations who are deficient in carotenoids at baseline. Fourthly, in our present umbrella review, multiple meta-analyses incorporated the uniform primary observation-focused research. Fifthly, while total included studies and research are population-based that encompassing cohort studies, case-control studies, and randomized controlled trials (RCTs), they employ distinct research designs and data processing strategies, which could introduce variability into the findings. Sixth, a major limitation involves the inability to establish dose-response relationships between carotenoid exposure and CVD outcomes due to insufficient data availability and substantial inter-study dose variations. Additionally, limited evidence exists regarding individual carotenoid subtypes in specific CVD contexts, thereby introducing potential bias in pooled effect estimates.

5. Conclusion

This umbrella meta-analysis represents the most comprehensive assessment to date of carotenoid-CVD associations, revealing significant inverse relationships between multiple carotenoids and reduced incidence and mortality of CVD. Despite these findings, current evidence remains inconclusive regarding definitive protective effects, highlighting the need for future studies to mitigate potential biases through stratified subgroup analyses and improve evidence consistency via standardized outcome reporting.

Availability of Data and Materials

Data will be made available on request.

Author Contributions

DG: Writing—original draft, Writing—review & editing, Software, Methodology, Formal analysis, Conceptualization, Data curation. HX: Writing—review & editing, Methodology, Formal analysis, Project administration, Funding acquisition. BH: Software, Data curation. PT: Software, Methodology. YY: Data curation. YZ: Software,

Methodology. DP: Methodology, Data curation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR46996.

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