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REVIEW

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Dietary and circulating omega-6 fatty acids and their impact on cardiovascular disease, cancer risk, and mortality: a global meta-analysis of 150 cohorts and meta-regression

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Abstract

Background Despite the significant increase in omega-6 fatty acid consumption, evidence regarding their health impacts remains inconsistent. This study performs an umbrella review and updated meta-analysis to evaluate the association between dietary and circulating omega-6 levels and the risks of cardiovascular diseases (CVDs), cancer, and mortality.

Methods A systematic search was conducted in PubMed, Scopus, and Web of Science until January 2024 to identify eligible meta-analyses of prospective observational studies. The Cochrane risk of bias and GRADE tools were used to assess the risk of bias and certainty of the evidence, respectively.

Results Analysis of 150 publications revealed that higher dietary intake and circulating levels of omega-6 were associated with lower risks of CVDs, cancer incidence, and all-cause mortality in the general population, particularly for coronary heart disease and stroke. While omega-6 intake was linked to lower risks of lung and prostate cancers, it was associated with higher risks of ovarian and endometrial cancers. Subgroup analyses revealed that these protective associations were more pronounced in cohort studies and absent in populations with pre-existing health conditions.

Conclusions Higher dietary intake and circulating levels of omega-6 fatty acids were associated with lower risks of CVDs, cancers, and all-cause mortality. However, the associations vary by cancer type and are less evident in individuals with pre-existing health conditions. These findings highlight the potential benefits of omega-6 fatty acids for public health while underscoring the need for further research to address specific risks and underlying mechanisms.

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Introduction

Cardiovascular diseases (CVDs) and cancers are the leading global causes of morbidity and mortality [1, 2]. Shared biological pathways, such as inflammation and metabolic dysregulation, contribute to the development of both conditions [3]. Emerging evidence highlights that CVDs exacerbate cancer mortality, underscoring the importance of proactively managing shared risk factors, including dietary habits [3–5].

Diet plays a critical role in the development and progression of chronic diseases. Diets high in saturated and trans fats are strongly linked to increased risk [6], while polyunsaturated fatty acids (PUFAs), particularly omega-3 and omega-6, exhibit protective effects [6]. PUFAs reduce inflammation and lower low-density lipoprotein-cholesterol (LDL-C), with potential anticancer benefits through modulation of cell signaling and tumor suppression [6]. Replacing saturated fats with PUFAs, such as those in plant oils, has lowered the risk of coronary heart disease (CHD). However, the long-term health effects of specific plant oils remain contentious, warranting further research [6]. The growing imbalance between omega-6 and omega-3 fatty acid intake underscores the need for a deeper understanding of the health effects of omega-6 fatty acids [7]. Additionally, the health implications of omega-6 remain a topic of considerable debate, creating uncertainties in dietary guidelines and raising concerns that current consumption levels may pose certain health risks [8].

Meanwhile, linoleic acid (LA; ω – 6, 18:2) is the primary dietary omega-6, predominantly sourced from plant oils, chicken, eggs, meat, and nuts [9]. Since the 1960s, the average daily LA intake in Western countries has risen significantly, from 2.7 g to approximately 4.9–21.0 g daily, contributing 4–10% of total dietary calories [10, 11]. In contrast, the daily requirement of LA to prevent essential fatty acid deficiency is only 1–2% of the total energy intake [12]. This more than tenfold increase in LA consumption has prompted extensive research into its metabolic effects, particularly its influence on long-term health outcomes and mortality [13, 14].

Previous meta-analyses have reported an inverse association between higher dietary intake of omega-6 and the risk of CVDs [15, 16]. However, three meta-analyses examining serum omega-6 levels and CVDs yielded inconsistent results [16–18]. A single meta-analysis in 2020 linked higher dietary and serum omega-6 levels to a lower risk of all-cause mortality [19]. While most meta-analyses found an inverse association between dietary omega-6 and various cancers [20–24], one recent study reported a positive link between increased dietary omega-6 intake and colon cancer risk [25]. Of note, the relationship between serum omega-6 levels and cancer remains inconclusive: four meta-analyses [20, 22, 23, 25], two identified a direct association [23, 25], while two reported an inverse relationship [20, 22].

Considering the growing body of research and inconsistencies in previous findings, updated and comprehensive meta-analyses are essential. In this umbrella review, we systematically examined the associations between dietary and circulatory levels of omega-6 fatty acids with the incidence of CVDs, cancers, and mortality. To ensure the robustness of our findings, we performed influence analyses, evaluated the certainty of the evidence (CoE), and explored potential sources of heterogeneity through subgroup analyses and meta-regression.

Methods

This umbrella review adhered to the guidelines outlined in both the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [26] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) handbook [27]. The systematic review protocol for this study was registered in PROSPERO (CRD42024522842).

Systematic search

The authors (RS, MN, and MHR) systematically searched PubMed, Scopus, and Web of Science databases up to January 2024 to identify eligible meta-analyses of prospective observational studies (cohorts and nested case-controls (NCC)). The search utilized combined keywords of the exposure (omega-6) and outcomes (CVDs, cancer, and all-cause mortality). The complete search strategy is outlined in Supplementary Table 1. Additionally, the literature search was complemented by screening the reference lists of all relevant reviews and meta-analyses.

Selection of meta-analyses and original studies

We applied stringent eligibility criteria to identify meta-analyses suitable for our analysis. Studies meeting the following criteria were deemed eligible for inclusion in the present umbrella review:

(1) Meta-analyses of prospective observational studies conducted in populations aged 18 years or older; (2) Assessment of dietary/circulatory levels of total omega-6 or LA using a standard tool (e.g., food frequency questionnaires (FFQ), dietary history, 24-hour dietary recalls, dietary records, or gas chromatography), with reporting of dietary/circulatory total omega-6 or LA as the

exposure; (3) Evaluation of the incidence of CVDs, total and site-specific cancers, all-cause, and cause-specific mortality as outcomes; and (4) Reporting of multivariable-adjusted summary risk estimates and corresponding 95% confidence intervals for each outcome.

Also, we established specific criteria to exclude unsuitable studies from our analysis: (1) Narrative reviews or systematic reviews without meta-analysis; (2) Meta-analyses of interventional studies; and (3) Meta-analyses focused on pregnant and lactating women. Additionally, we excluded primary studies meeting the following criteria from each selected meta-analysis: (1) Cross-sectional or case-control studies and (2) Studies with unadjusted risk estimates.

We selected one meta-analysis for each outcome in every population, exploring the reference lists of all previously published meta-analyses with the same outcome to identify additional eligible studies not included in the chosen meta-analyses. These studies were subsequently included in our review. In cases where multiple meta-analyses were identified for a given outcome in each population, we prioritized the meta-analysis with more primary studies [28]. To ensure the reliability of our results, original studies (cohorts and NCC studies) that were not included in the earlier meta-analyses were also added to this study.

Data extraction

Two authors (RS, MN, and MHR) independently extracted the following data from eligible meta-analyses: first author's name, publication year, exposure, number of primary cohort or NCC studies included in the analysis, number of participants, type of comparison, meta-analysis primary results (pooled estimate, I^2 and publication bias) and follow up range among included studies.

We also extracted the following data from primary studies included in each meta-analysis: first author's name, year of publication, study region, population characteristics, number of cases/ participants, mean age, sex, dietary/biochemical assessment method, exposure, outcome, adjusted relative risks and their corresponding 95% CIs, and follow-up period. Any disagreement was resolved through consensus.

Assessment of methodological quality

Two reviewers, MHR and HA, independently assessed the quality of each meta-analysis, resolving any discrepancies through discussion and consensus. The evaluation was conducted using the Measurement Tool to Assess Systematic Reviews (AMSTAR-2), specifically designed to assess the methodological quality of systematic reviews and meta-analyses [29].

Similarly, two independent reviewers evaluated the quality of primary studies included in each meta-analysis using the ROBINS-I tool for non-randomized studies [30]. This assessment considered several domains, including confounding, participant selection, exposure assessment, misclassification during follow-up, missing data, outcome measurement, and selective reporting of results. Based on these criteria, each domain was assigned a judgment of low, moderate, or serious risk of bias. Any discrepancies between reviewers were resolved through discussion and consensus.

Data synthesis and analysis

We extracted maximally adjusted effect sizes and their corresponding 95% CI from the original studies in each selected meta-analysis. To ensure comprehensive analysis, we combined estimates from the same population presented in different subgroups (e.g., in men and women) or data from the same cohort reported in various studies, using a fixed-effects model, and the combined effect size was used for subsequent analyses. Subsequently, a random-effects model was applied to estimate the relative risks (RR) and their 95% CI, serving as the effect size in the present umbrella review and meta-analysis [31].

We assessed between-study heterogeneity using the I^2 statistic [32]. According to guidelines from the Cochrane Handbook, I^2 statistics were interpreted as follows: 0–40% (might not be important); 30–60% (may represent moderate heterogeneity); 50–90% (may represent substantial heterogeneity); and 75–100% (considerable heterogeneity) [33]. To complement I^2, we also calculated tau2 (τ^2), independent of population size [34]. Potential publication bias was evaluated through visual inspection of funnel plots [33] and using Egger's test [35]. We also employed the trim-and-fill method to adjust for potential publication bias.

The subgroup analyses were performed based on various population characteristics, including the general population and individuals with health concerns (including individuals with high CVDs risk, postmenopausal women, smokers, individuals with CVDs, cancer, diabetes, renal disorders), study region (America, Europe, Asia, and Oceania), study type (cohort and NCC), sex (male, female, both), and measurement type. We also conducted an influence analysis, where each study was excluded to evaluate its impact on the overall estimate. Furthermore, random-effects meta-regression was employed to assess the influence of mean age, follow-up duration, and year of publication on the outcomes when at least ten studies were available. All statistical analyses were conducted using version 17.0 of STATA statistical software (StataCorp), with a significance level set at $P < 0.05$.

Grading of the evidence

The CoE was evaluated using the GRADE tool [36], categorizing evidence certainty as high, moderate, low, or very low. Observational studies, such as prospective cohort studies, are considered low-quality evidence and may be downgraded or upgraded based on predefined criteria. The criteria to downgrade evidence encompass study limitations, inconsistency, indirectness, imprecision, and publication bias. Conversely, the criteria to upgrade the quality of evidence include a substantial magnitude of association, a dose-response gradient, and attenuation by plausible confounding.

Results

Study selection

As illustrated in Fig. 1, our systematic search yielded 26,863 results. Following removing duplicate studies, 20,068 studies initially underwent screening based on title and abstract, with a subsequent full-text review if necessary. The present umbrella review encompassed

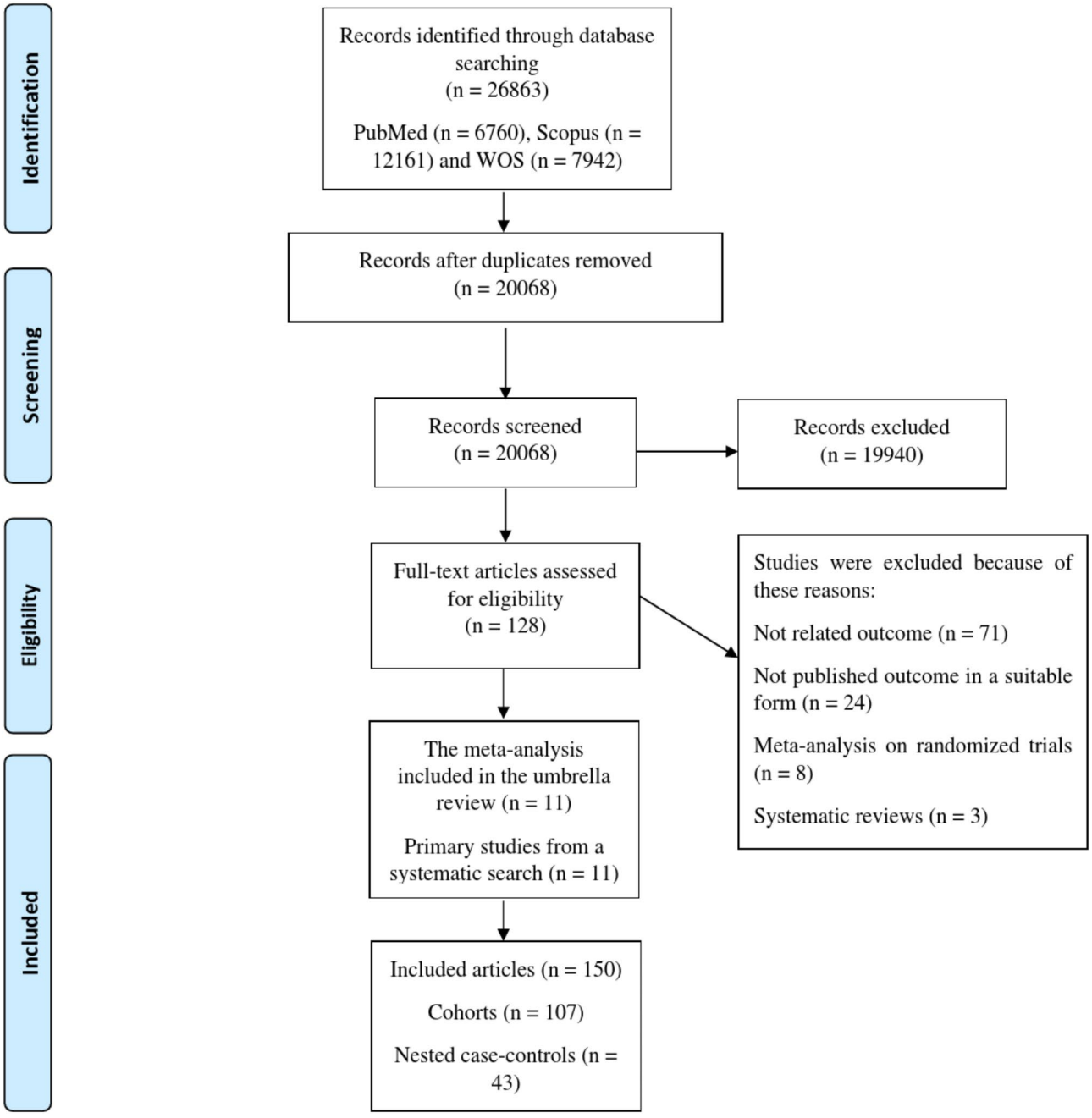

Fig. 1 Flowchart for study selection in the umbrella review and updated meta-analysis

eleven meta-analyses [15–25]. Furthermore, we identified 11 original studies [37–47] that had not been incorporated into previous meta-analyses. Our analysis included 150 publications (107 cohorts and 43 NCCs) comprising 230 studies and 93 distinct cohorts.

As indicated in Table 1, we utilized four meta-analyses [15, 17, 19, 20] as references to select eligible studies. Regarding the association between dietary intake and circulating levels of omega-6 with the incidence of CVDs, we identified 47 studies from the included meta-analyses and 19 studies from the systematic search. Furthermore, concerning the association between dietary intake and circulating levels of omega-6 with cancer incidence, we found 104 studies from the meta-analyses and three studies from the systematic search. Finally, four studies from a systematic search and 53 studies from meta-analyses were included in the association between circulating omega-6 levels and dietary omega-6 intake with all-cause mortality.

Study characteristics

Supplementary Tables 2–4 summarize the key features of the included studies. A total of 111 studies investigated the association between dietary omega-6 intake and the incidence of cancer ($n = 68$), CVDs ($n = 16$), and all-cause mortality ($n = 27$). Additionally, the association between circulating omega-6 levels and the incidence of cancer, CVDs, and all-cause mortality was examined in 50, 39, and 30 studies, respectively.

The majority ($n = 181$) of included studies were conducted on the general population, while 49 focused on individuals with health concerns. Furthermore, 96 studies were performed in America, 91 in Europe, and 43 in Asia and Oceania. One hundred four studies were conducted on both genders, with 61 and 65 explicitly focusing on men and women, respectively. Notably, dietary omega-6 intake was determined using the FFQ in 86 studies, while alternative dietary assessment techniques such as food records and 24-hour recall were employed in 25 studies. Furthermore, the amount of circulating omega-6 in total plasma/serum/whole blood, phospholipids, erythrocytes, and cholesteryl esters has been measured in 54, 40, 14, and 11 studies, and the follow-up periods of the included studies ranged from one to thirty-two years.

Meta-analysis

Association between highest vs. lowest dietary and circulatory levels of omega-6 with all-cause mortality

As depicted in Figs. 2-a and 3-a, the comparison between the highest and lowest levels of dietary omega-6 intake (RR: 0.88; 95% CI: 0.83, 0.94; I^2: 62.4) and circulating omega-6 levels (RR: 0.89; 95% CI: 0.84, 0.94; I^2: 70.5) revealed a lower risk of all-cause mortality. Moreover, as shown in Supplementary Table 5, higher dietary omega-6

Table 1 Basic characteristics of included meta-analysis, investigating the association between higher versus lower intake and Circulating levels of omega-6 fatty acids with the incidence of cardiovascular diseases, cancer, and related mortality

Author, year	Comparison	Participants	NO. primary studies	NO. of studies from other metaanalyses	NO. of studies from a systematic search	Outcome	Omega-6 types	RR (95% CI)	I^2	*P*heterogeneity	Eager's *p*-value	Follow-up range
Farvid 2014 [15]	High vs. low	310,602	14	1	1	CVDs	Intake	0.86 (0.78, 0.92)	35.5	0.091	0.250	5.3–23
Ren 2022 [17]	High vs. low	31,926	20	12	18	CVDs	Circulatory	0.98 (0.79, 1.20)	55.4	-	-	1.0–31
Kim 2020 [20]	High vs. low	-	54	13	1	Cancer	Intake	1.02 (0.99, 1.05)	44.3	0.001	0.240	5.3–27
Kim 2020 [20]	High vs. low	-	36	1	2	Cancer	Circulatory	0.92 (0.86, 0.98)	13.8	0.256	0.220	1.9–13
Li 2020 [19]	High vs. low	811,069	22	1	4	All-cause mortality	Intake	0.87 (0.81, 0.94)	67.9	0.001	0.160	4.9–30
Li 2020 [19]	High vs. low	811,069	30	0	0	All-cause mortality	Circulatory	0.91 (0.87, 0.95)	64.1	0.001	0.490	1.5–31

Table 2 Meta-regression analysis for the association between dietary and circulatory levels of omega-6 with the incidence of CVDs, cancer and related mortality

Variables	Number of studies	Coefficient	*P*-Value	τ 2
Dietary intake of omega-6				
CVDs incidence				0.013
Mean age	16	0.007	0.360	0.024
Follow-up duration	16	-0.003	0.719	0.028
Year of publication	16	-0.004	0.601	0.030
Cancer incidence				0.001
Mean age	52	-0.006	0.067	0.003
Follow-up duration	62	-0.003	0.265	0.000
Year of publication	68	0.001	0.545	0.001
All-cause mortality				0.006
Mean age	25	-0.001	0.563	0.005
Follow-up duration	27	-0.003	0.264	0.003
Year of publication	27	0.005	0.081	0.002
Circulating levels of omega-6				
CVDs incidence				0.003
Mean age	46	0.004	0.123	0.005
Follow-up duration	46	-0.004	0.060	0.005
Year of publication	50	0.001	0.683	0.008
Cancer incidence				0.016
Mean age	37	-0.000	0.990	0.030
Follow-up duration	30	-0.018	0.248	0.032
Year of publication	39	0.015	**0.035**	**0.024**
All-cause mortality				0.009
Mean age	27	0.001	0.576	0.013
Follow-up duration	30	-0.003	0.420	0.018
Year of publication	30	-0.000	0.901	0.019

intake was associated with a lower risk of CVDs (RR: 0.88; 95% CI: 0.82, 0.93; I^2: 26.4) and cancer (RR: 0.89; 95% CI: 0.85, 0.92; I^2: 0.00) mortality. While higher circulating omega-6 levels were associated with lower CVD mortality risk (RR: 0.85; 95% CI: 0.79, 0.92; I^2: 30.9), no significant association was observed between circulating omega-6 levels with risk of cancer mortality (RR: 0.90; 95% CI: 0.79, 1.01; I^2: 39.2).

Association between highest vs. lowest dietary and circulatory levels of omega-6 with cancer incidence

Figures 2-b and 3-b indicate the risk of cancer incidence concerning dietary intake and circulating levels of omega-6, respectively. While higher levels of omega-6 intake did not exhibit a significant association with cancer incidence (RR: 1.01; 95% CI: 0.97, 1.04; I^2: 28.1), higher circulating omega-6 levels were linked to a lower risk of cancer (RR: 0.88; 95% CI: 0.80, 0.96; I^2: 46.3). Furthermore, Supplementary Table 6 provides insight into the association between dietary and circulating omega-6 levels and various types of cancer. Notably, higher dietary intake and circulating omega-6 levels were associated with a lower risk of lung cancer (RR: 0.84; 95% CI: 0.71, 0.99; I^2: -) and prostate cancer (RR: 0.86; 95% CI: 0.76, 0.96; I2: 18.5), respectively. However, higher omega-6 intake was associated with a higher risk of endometrial and ovarian cancer (RR: 1.15; 95% CI: 1.01, 1.30; I^2: 0.00).

Association between highest vs. lowest dietary and circulatory levels of omega-6 with CVDs incidence

As indicated in Figs. 2-c and 3-c, while higher levels of dietary omega-6 intake were not associated with CVD incidence (RR: 0.92; 95% CI: 0.83, 1.02; I^2: 53.9), higher circulating omega-6 levels were significantly linked to a lower risk of CVD incidence (RR: 0.92; 95% CI: 0.89, 0.96; I^2: 42.0). Additionally, Supplementary Table 7 presents the association between dietary and circulating omega-6 levels with various types of CVDs. Although higher levels of dietary and circulating omega-6 did not exhibit a significant relationship with the incidence of total CVDs and atrial fibrillation, higher circulating omega-6 levels were associated with a lower risk of CHD (RR: 0.93; 95% CI: 0.88, 0.98; I2: 43.5) and stroke (RR: 0.86; 95% CI: 0.79, 0.94; I^2: 36.2).

Subgroup analyses

Supplementary Tables 7–9 summarize the subgroup analysis based on population characteristics, study region, study type, sex, and measurement type. Study characteristics, study region, and sex were known as a source of heterogeneity. Studies conducted on the general population indicated a lower risk of CVDs, cancer, and all-cause mortality when comparing the highest versus lowest dietary and circulating omega-6 levels. However, no significant relationship was observed in populations with health concerns. Furthermore, findings from both cohort and NCC studies indicated that higher circulating levels of omega-6 were associated with a lower incidence of CVDs and cancer, with cohort studies showing a more pronounced association.

Although cohort studies did not indicate a significant association between higher omega-6 intake and cancer incidence, the results from NCC studies suggested that higher omega-6 intake is linked to a higher risk of cancer (RR: 1.19; 95% CI: 1.00, 1.41; I^2: 0.00). Additionally, in contrast to NCC studies, cohort studies revealed that higher circulating levels of omega-6 were associated with a lower risk of mortality (RR: 0.87; 95% CI: 0.82, 0.92; I^2: 70.8).

Meta-regression

As indicated in Table 3 and Supplementary Fig. 7, we conducted a meta-regression based on mean age, follow-up duration, and year of publication per 1 unit increase in mentioned factors. The year of publication was recognized as a source of heterogeneity in the relationship between the circulating levels of omega-6 and the

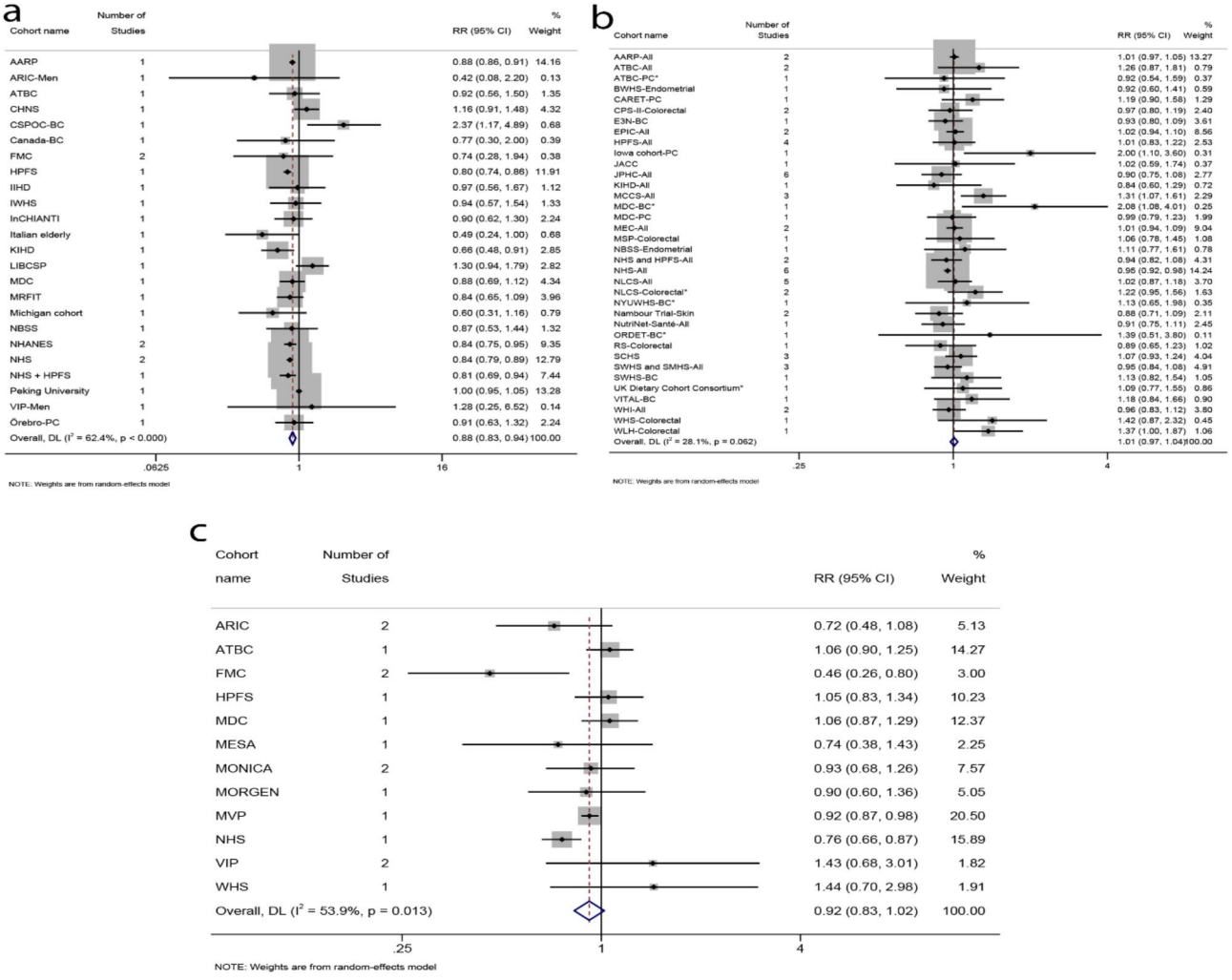

Fig. 2 Forrest plots of cohorts and nested case-control studies (*) illustrating the pooled estimation for the association between highest vs. lowest dietary intake of omega-6 with (**a**) all-cause mortality, (**b**) cancer incidence, and (**c**) cardiovascular disease incidence

incidence of cancer, so the pooled estimate changed by 0.015 units per year (*P* value = 0.035).

Publication bias

Supplementary Figs. 1–6 represent the funnel plots investigating the potential for publication bias among included studies. Significant publication bias was observed for the association between dietary and circulating omega-6 levels with cancer incidence (Eagers *p*-value: 0.012) and all-cause mortality (Eagers *p*-value: 0.007), respectively. Consequently, we utilized the trim-and-fill method to address potential publication bias.

Regarding the association between circulating levels of omega-6 and all-cause mortality, the fill-and-trim analysis revealed no new studies, and the random-effects model trimming estimation remained consistent with the pooled estimate (RR: 0.88; 95% CI: 0.84, 0.93). However, concerning the association between dietary omega-6 intake and cancer incidence, the initial fill-and-trim analysis identified 11 additional studies beyond those included. The results of the fill-and-trim analysis indicated that although a higher compared to a lower intake of omega-6 was associated with a lower risk of developing cancer, this association did not reach statistical significance (RR: 0.98; 95% CI: 0.94, 1.01). Given this minimal difference (0.03), which does not impact the observed relationship, this level of publication bias is not considered problematic.

Influence analysis

According to influence analysis, excluding none of the studies had a significant impact on the association between dietary and circulating levels of omega-6 with cancer incidence and all-cause mortality. Additionally, excluding none of the studies had a considerable effect on the pooled estimation of the association between circulating omega-6 with CVDs incidence (range: 0.91–0.92). However, by excluding the impact of the study by

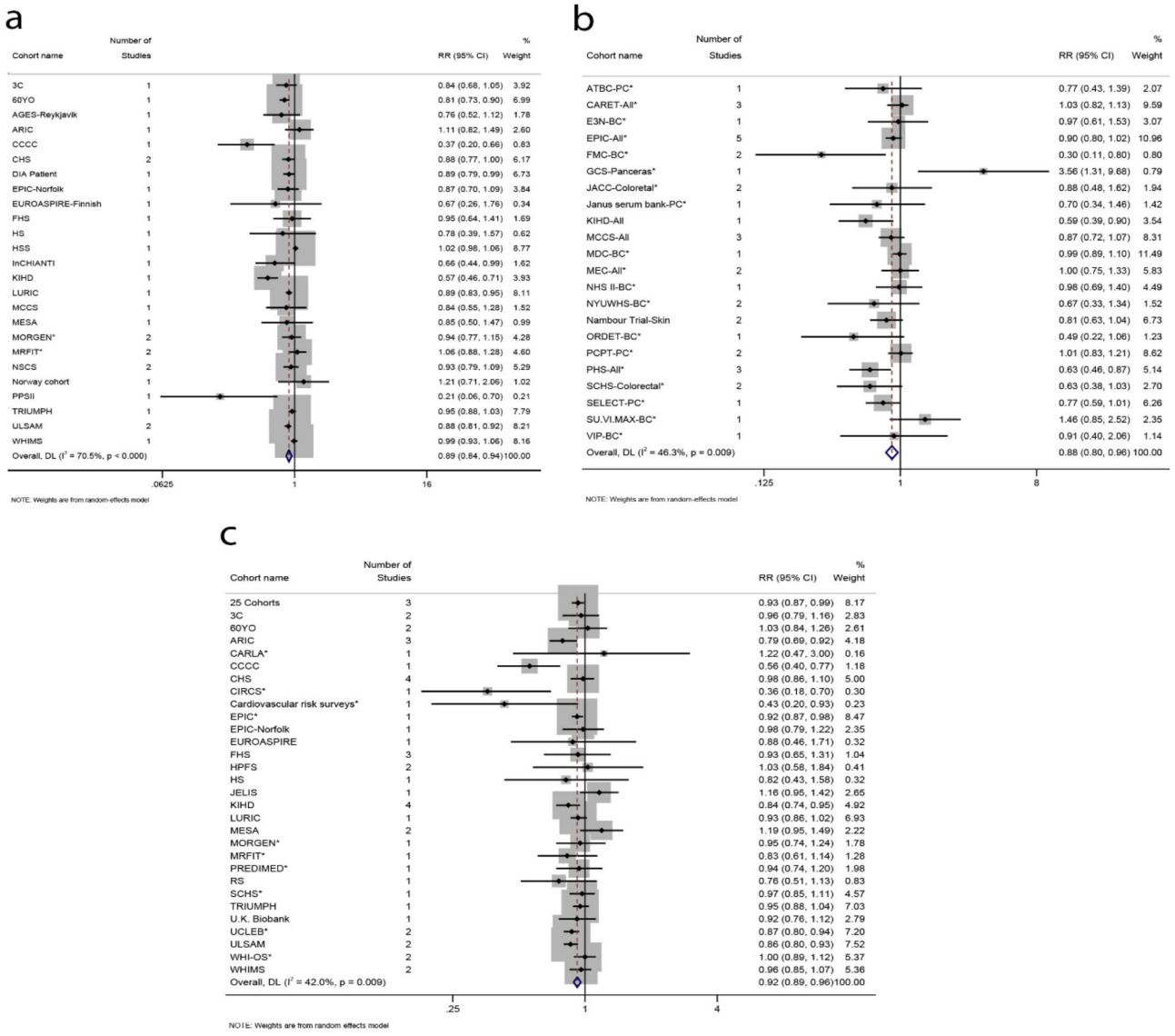

Fig. 3 Forrest plots of cohorts and nested case-control studies (*) illustrating the pooled estimation for the association between highest vs. lowest circulatory levels of omega-6 with (**a**) all-cause mortality, (**b**) cancer incidence, and (**c**) cardiovascular disease incidence

Pietinen et al. [48], there was a significant association between dietary omega-6 intake with CVDs incidence (RR: 0.89; 95% CI: 0.80, 0.99).

Methodological quality

Table 3 summarizes the methodological quality of the included meta-analyses. Of the 11 meta-analyses reviewed [15–25], six [16, 17, 20–22, 25] were rated as having low methodological quality, while the remaining five [15, 18, 19, 23, 24] were rated as critically low. The main factors contributing to lower quality were the lack of a predefined protocol before conducting the meta-analyses and insufficient evaluation of how the risk of bias may have influenced the aggregated results.

Supplementary Table 11 presents the risk of bias assessment for the included studies using the ROBINS-I tool. Key factors contributing to a reduction in study quality from moderate to serious were biases related to confounding, exposure assessment methods, follow-up misclassification, and missing data. Serious issues in exposure assessment and follow-up misclassification resulted in a serious risk of bias in 12% of the studies ($n = 18$), while less severe concerns led to a moderate risk of bias in the remaining studies.

Grading the evidence

Supplementary Table 12 presents the GRADE assessment results, which range from very low to moderate certainty. The association between dietary omega-6 intake

Table 3 The methodological quality of included meta-analyses using AMSTAR2

Author, year (ref)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall
Jayedi, 2023 [16]	Y	Y	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	low
Lu, 2023 [25]	Y	Y	Y	PY	Y	Y	PY	PY	Y	N	Y	N	N	Y	Y	Y	low
Yousefi, 2023 [22]	Y	Y	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	low
Ren, 2022 [17]	Y	N	Y	PY	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	low
Liu, 2021 [21]	Y	N	Y	PY	N	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	low
Kim, 2020 [20]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	low
Li, 2020 [19]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Critically low
Zhang, 2020 [18]	Y	N	Y	PY	N	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Critically low
Zhou, 2016 [23]	Y	N	Y	PY	Y	N	PY	PY	N	N	Y	Y	N	Y	Y	Y	Critically low
Farvid, 2014 [15]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Critically low
Zock, 1998 [24]	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	Y	Y	Critically low

ref, references (main text); **PY**, partially yes. **Q1**: Did the research questions and inclusion criteria for the review include the components of PICO?; **Q2**: 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?; **Q3**, Did the review authors explain their selection of the study designs for inclusion in the review?; **Q4**, Did the review authors use a comprehensive literature search strategy?; **Q5**, Did the review authors perform study selection in duplicate?; **Q6**, Did the review authors perform data extraction in duplicate?; **Q7**, Did the review authors provide a list of excluded studies and justify the exclusions?; **Q8**, Did the review authors describe the included studies in adequate detail?; **Q9**, Did the review authors use a satisfactory technique for assessing the risk of bias?; **Q10**, Did the review authors report on the sources of funding?; **Q11**, Did the review authors use appropriate methods for statistical combination of results?; **Q12**, Did the review authors assess the potential impact of RoB in individual studies on the results?; **Q13**, Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?; **Q14**, Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity?; **Q15**, Did the review authors carry out an adequate investigation of publication bias?; **Q16**, Did the review authors report any potential sources of conflict of interest?

and CVD mortality showed moderate certainty of evidence. In contrast, other associations were rated as low to very low certainty, primarily due to serious concerns about the risk of bias, inconsistencies across studies, and non-significant results, particularly for cancer and CVD incidence.

For circulating omega-6 levels, the certainty of evidence was generally moderate despite some concerns about the risk of bias. However, an exception was observed for cancer-specific mortality, where the certainty was downgraded to very low due to non-significant results, indirectness, and additional limitations related to the risk of bias and consistency.

Discussion

Our findings indicate that higher omega-6 intake is associated with a lower risk of CVDs and all-cause mortality. However, while higher omega-6 intake was linked to a lower risk of lung and prostate cancers, it was associated with an increased risk of ovarian and endometrial cancers. Higher circulating omega-6 levels were also associated with a lower risk of CVDs, particularly CHD and stroke, as well as lower cancer incidence and all-cause mortality. Subgroup analyses in the general population showed that both dietary and circulating omega-6 levels were inversely associated with all-cause mortality, CVDs, and cancer incidence. However, no such associations were observed in populations with pre-existing health conditions. In both cohort and NCC studies, higher circulating omega-6 levels were linked to a lower incidence of cancer and CVDs, with more potent effects observed in cohort studies. Notably, only in cohort studies was an increase in circulating omega-6 levels associated with lower all-cause mortality rates.

Consistent with our results, Wu et al. reported that elevated circulating levels of LA were linked to reduced overall and CVD-specific mortality in older adults [8]. However, concerns persist regarding potential health risks associated with omega-6 fatty acids. For example, a large prospective cohort study revealed a significant association between the omega-6/omega-3 PUFA ratio in circulation and increased mortality risk from all causes, cancer and CVDs [49].

Specifically, concerns have been raised about LA and its metabolite, arachidonic acid (AA), potentially promoting thrombosis and inflammation [50]. These concerns primarily stem from the hypothesis that omega-6 fatty acids compete with omega-3s for shared enzymatic pathways, which could reduce the production of beneficial omega-3-derived bioactive metabolites [51]. Notably, the lowest risk appears when omega-6 and omega-3 fatty acids are present at high levels, highlighting the importance of maintaining a balanced intake of these essential fatty acids [8].

Similar to prior meta-analyses of prospective cohorts and earlier clinical trials that demonstrated a reduced risk of CVDs with higher omega-6 intake [52, 53], our findings also reveal a significant association between circulating omega-6 levels and CVD risk. Supporting this, Nagai et al. reported that lower circulating omega-6 levels at admission were significantly associated with worse clinical outcomes in patients with acute decompensated heart failure (ADHF) [54]. However, conflicting evidence exists, such as a meta-analysis by Chowdhury et al., which found no significant association between dietary omega-6 intake and CVD mortality [55].

Guidelines on omega-6 dietary intake for CVD prevention remain inconsistent [56]. For instance, secondary analyses of clinical trials involving LA-rich corn oil have suggested a potential increase in CHD and overall mortality risk [50, 57]. Furthermore, Mazidi et al., using Mendelian randomization, found elevated AA levels to be directly associated with an increased risk of myocardial infarction, CHD, and large artery stroke [58]. Despite these mixed findings, aggregated data from clinical trials and cohort studies indicate a moderate benefit of n-6 PUFA intake, particularly LA, in reducing CHD risk. This is observed regardless of whether LA replaces saturated fats or carbohydrates [53, 59, 60].

Our findings regarding the association between higher circulating omega-6 levels and a reduced risk of overall cancer align with Wallingford et al., who reported an inverse relationship between total omega-6 levels and the occurrence of basal cell carcinoma tumors [61]. Similarly, a population-based cohort study observed minor inverse relationships between plasma omega-6 levels and overall cancer incidence, as well as several site-specific cancers, though notable exceptions included prostate cancer [62]. Another study found that while omega-6 did not significantly influence prostate cancer risk, a high intake of LA reduced prostate cancer risk [63]. The UK Biobank cohort further confirmed the association between circulating omega-6 levels and cancer risk [49].

However, we found a higher risk of endometrial and ovarian cancers associated with increased omega-6 intake. High dietary intake of ω-6 PUFAs may promote tumor malignancy through histological changes linked to tumor differentiation, increased cell proliferation, angiogenesis, pro-inflammatory oxylipins, and activation of molecular aggressiveness targets such as NF-κB p65, YY1, COX-2, and TGF-β [64]. However, it is important to consider the study characteristics underlying these findings, as factors such as the source of omega-6 intake and its interaction with other dietary components may also influence these outcomes.

Yammine et al. reported that higher intakes of omega-6, primarily derived from deep-frying fats, may be associated with an increased risk of endometrial cancer [42]. Similarly, Bertone et al. identified an association between increased omega-6 intake and a higher risk of ovarian cancer; however, this association appeared to extend to the majority of fats consumed, implying that overall fat intake may have a significant impact on ovarian cancer risk [65]. The studies indicated that the repeated rupture of ovarian follicles during ovulation could expose the ovarian epithelium to hormones within the surrounding fluid, with heightened estrogen levels potentially elevating the risk of tumor development [66]. Moreover, high-fat consumption may increase circulating estrogen levels, promoting cellular damage and proliferation [67].

Subgroup analyses further revealed meaningful associations between omega-6 fatty acid levels and risks of all-cause mortality, cancer, and cardiovascular diseases, predominantly evident within the general population. Conversely, no substantial associations were identified among individuals with pre-existing health conditions. These discrepancies may be attributed to variations in ethnicity and baseline health status [68].

The health effects of omega-6 fatty acid consumption appear to be a double-edged sword, with outcomes highly dependent on the balance of fatty acids consumed and the individual's health status and underlying conditions. Omega-6 fatty acids are metabolized by various enzyme families, including cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 (CYP), resulting in the formation of oxylipins. Generally, oxylipins derived from omega-6 exhibit more pronounced biological effects [69]. It is essential to recognize that the oxylipin profiles present in the body vary according to the composition of fatty acids ingested [69].

LA derivatives, including hydroxy-octadecadienoic acids (HODEs) and dihydroxyoctadecenoic acid (DiHOMEs), are associated with various health conditions. For example, 9-HODE and 13-HODE play a significant role in the progression of atherosclerosis, while 13-oxo-ODE is recognized for its anti-inflammatory properties [12, 69]. Additionally, COX enzymes catalyze the conversion of AA to prostaglandin H2 (PGH2), which serves as a precursor for numerous prostaglandins and thromboxane A2 [70]. These metabolites are implicated in processes related to inflammation, obesity, and cancer [12, 69]. Moreover, AA is a precursor for the synthesis of anti-inflammatory and pro-resolving lipoxins (LXA4, LXB4) [71] and 4-series leukotrienes, such as LTC4, in addition to hepoxilins, which are involved in regulating neutrophil activity [72].

Epidemiological studies indicate that maintaining a high omega-3 to omega-6 fatty acid ratio may contribute to a reduction in cancer risk [73]. Multiomic research utilizing transgenic mouse models has highlighted the significance of the omega-6 to omega-3 fatty acid ratio across various tissues, implying its involvement in the

pathogenesis of chronic conditions like cancer and inflammation [69]. This ratio may also have implications for the microbiome [69]. However, perspectives diverge regarding the role of omega-6 PUFAs in human health. Marangoni et al. (2020) advocate for an increased intake of LA, citing its cardiometabolic advantages, which include lipid-lowering properties and enhanced glucose homeostasis [74].

A meta-analysis indicates that substituting 5% of dietary energy derived from complex carbohydrates or saturated fats with an equivalent amount of omega-6 results in a reduction in plasma total cholesterol by 0.11 mmol/L and LDL-C by 0.39 mmol/L [75]. Experimental studies have demonstrated that dietary LA enhances the hepatic expression of LDL receptors [76]. Furthermore, omega-6 PUFAs were associated with decreased hepatic lipogenesis and increased lipid catabolism in vitro, likely due to the inhibition of sterol regulatory element binding protein 1c (SREBP-1c) activity [77]. Additionally, a study involving individuals with abdominal obesity found that a diet rich in omega-6 PUFAs significantly reduced plasma levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) compared to a diet high in saturated fats [78]. In individuals who have dyslipidemia and insulin resistance, replacing saturated fats with omega-6 PUFAs decreases the production and quantity of LDL particles by reducing the synthesis of apolipoprotein. B100 [79].

From a nutrition policy perspective, our results suggest that, in the general population, the intake of omega-6—an essential fatty acid—does not pose a health risk. Therefore, dietary guidelines should prioritize reducing the intake of harmful fats, such as trans fatty acids and saturated fatty acids, while also considering the overall composition of fatty acids consumed, the balance between different fatty acids, and other dietary factors, such as antioxidant intake, rather than limiting omega-6 consumption.

Of note, there may be a threshold of omega-6 intake beyond which risk changes, suggesting that dose-response studies are essential to clarify the shape of the relationship between omega-6 and health outcomes. Clinical trials could explore the effects of replacing other dietary components with omega-6 fatty acids, while observational studies using substitution analysis could further assess these associations on health outcomes. Additionally, inconsistencies in the evidence may stem from factors such as the lack of differentiation between fatty acid types, imprecise intake measurement, and insufficient consideration of dietary background and disease severity—factors contributing to heterogeneity and reducing the certainty of findings. Additionally, future studies could explore the effects of sources of omega-6, the impact of omega-6 within various dietary patterns, and different food matrices on health outcomes. These issues are particularly relevant for developing countries and regions such as Asia, Africa, and Oceania, where research is limited. Conducting collaborative international high-quality studies in these areas could help fill the knowledge gap and provide more comprehensive conclusions.

Our study has several notable strengths. First, it provides a comprehensive assessment of the health effects of omega-6 fatty acids, examining cardiovascular disease, cancer, and mortality as primary outcomes. Additionally, it uniquely considers both dietary intake and circulating levels of omega-6 fatty acids together. Second, we minimized biases and overestimations often associated with cross-sectional and case-control studies by focusing on cohort studies. Finally, we evaluated the robustness of our findings using quantitative methods, including influence analysis, subgroup analysis, and meta-regression and reported the CoE. However, the study also has limitations. A significant publication bias was observed for some outcomes. However, our study accounted for publication bias in two ways. First, the trim-and-fill analysis indicated that incorporating potential missing studies would not significantly alter the observed effect sizes. Second, in assessing the CoE, publication bias in the association between omega-6 intake and cancer incidence led to a downgrading of the evidence, reducing its certainty to 'Very Low.' This level of publication bias suggests that future studies may yield findings that differ from the current results. Despite efforts to reduce heterogeneity through subgroup analyses and meta-regression, high heterogeneity persisted in specific analyses. Lastly, while significant associations were observed for the studied outcomes, the CoE was weak for some findings. Future research should address these limitations, explore these associations more thoroughly, and enhance the overall CoE.

Conclusion

Based on our review, higher dietary intake and circulating levels of omega-6 fatty acids appear to have a predominantly protective role in reducing the risk of CVDs, certain cancers, and all-cause mortality in the general population. Specifically, higher omega-6 levels were associated with lower risks of CHD, stroke, and lung and prostate cancers. However, the increased risks of ovarian and endometrial cancers highlight the complexity of these relationships and the need for caution when interpreting these findings. Subgroup analyses indicate that the protective effects are more evident in cohort studies and individuals without pre-existing health conditions. These results suggest that eating omega-6 fatty acids could benefit public health as a balanced diet. However, the low CoE for some outcomes limits the generalizability of the findings. Further, well-designed studies

with appropriate methodologies and targeted research questions are needed to clarify the relationship between omega-6 and health outcomes.

Abbreviations

AA	Arachidonic Acid
ADHF	Acute Decompensated Heart Failure
AMSTAR-2	Critical Appraisal Tool for Systematic Reviews that Include Randomized or Non-randomized Studies of Healthcare Interventions
CHD	Coronary Heart Disease
CIs	Confidence Intervals
CoE	Certainty of The Evidence
CoI	Conflicts of Interest;
COX	Cyclooxygenases;
CVDs	Cardiovascular Diseases;
CYP	Cytochrome P450;
DiHOMEs	Dihydroxyoctadecenoic acid;
FFQ	Food Frequency Questionnaires;
GRADE	Grading of Recommendations Assessment, Development, and Evaluation;
HODEs	Hydroxy-octadecadienoic acids;
LA	Linoleic Acid;
LDL-C	Low-Density Lipoprotein-Cholesterol;
LDLR	Hepatic LDL-C Receptor;
LOX	Lipoxygenases;
NCC	Nested Case-Control;
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9;
PGH2	Prostaglandin H2;
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses;
PUFAs	Polyunsaturated Fatty Acids;
RR	Relative Risks;
SREBP-1c	Sterol Regulatory Element Binding Protein 1c

Supplementary Information

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Supplementary Material 1

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RS: Conceptualization, Methodology, Formal analysis, Investigation, Validation, Writing - Review & Editing. MN: Conceptualization, Methodology, Formal analysis, Investigation, Validation, Writing - Review & Editing. MHR: Data Curation, Methodology, Writing - Review & Editing. SJ: Writing - Original Draft, Writing - Review & Editing. HA: Methodology, Writing - Original Draft. MA: Writing - Review & Editing. FT: Formal analysis, Validation, Writing - Review & Editing. MV: Supervision. All authors read and approved the final version of the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

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