The effects of lutein on cardiometabolic health across the life course: a systematic review and meta-analysis\textsuperscript{1,2}

Elisabeth TM Leermakers,\textsuperscript{3,8} Sirwan KL Darweesh,\textsuperscript{3} Cristina P Baena,\textsuperscript{5} Eduardo M Moreira,\textsuperscript{3} Debora Melo van Lent,\textsuperscript{3} Myrte J Tielemans,\textsuperscript{3} Taulant Muka,\textsuperscript{3} Anna Vitezova,\textsuperscript{3} Rajiv Chowdhury,\textsuperscript{6} Wichor M Bramer,\textsuperscript{4} Jessica C Kiefte-de Jong,\textsuperscript{3,7} Janine F Felix,\textsuperscript{3,8} and Oscar H Franco\textsuperscript{3,8}

\footnotesize{\textsuperscript{3}Department of Epidemiology and \textsuperscript{4}Medical Library, Erasmus University Medical Center, Rotterdam, Netherlands; \textsuperscript{5}School of Medicine, Pontificia Universidade Católica do Paraná, Paraná, Brazil; \textsuperscript{6}Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; and \textsuperscript{7}Leiden University College, The Hague, Netherlands}

ABSTRACT

Background: The antioxidant lutein is suggested as being beneficial to cardiometabolic health because of its protective effect against oxidative stress, but evidence has not systematically been evaluated.

Objective: We aimed to evaluate systematically the effects of lutein (intake or concentrations) on cardiometabolic outcomes in different life stages.

Design: This is a systematic review with meta-analysis of literature published in MEDLINE, Embase, Cochrane Central, Web of Science, PubMed, and Google Scholar up to August 2014. Included were trials and cohort, case-control, and cross-sectional studies in which the association between lutein concentrations, dietary intake, or supplements and cardiometabolic outcomes was reported. Two independent investigators reviewed the articles.

Results: Seventy-one relevant articles were identified that included a total of 387,569 participants. Only 1 article investigated the effects of lutein during pregnancy, and 3 studied lutein in children. Furthermore, 31 longitudinal, 33 cross-sectional, and 3 intervention studies were conducted in adults. Meta-analysis showed a lower risk of coronary heart disease (pooled RR: 0.88; 95\% CI: 0.80, 0.98) and stroke (pooled RR: 0.82; 95\% CI: 0.72, 0.93) for the highest compared with the lowest tertile of lutein blood concentration or intake. There was no significant association with type 2 diabetes mellitus (pooled RR: 0.97; 95\% CI: 0.77, 1.22), but higher lutein was associated with a lower risk of metabolic syndrome (pooled RR: 0.75; 95\% CI: 0.60, 0.92) for the highest compared with the lowest tertile. The literature on risk factors for cardiometabolic diseases showed that lutein might be beneficial for atherosclerosis and inflammatory markers, but there were inconsistent associations with blood pressure, adiposity, insulin resistance, and blood lipids.

Conclusions: Our findings suggest that higher dietary intake and higher blood concentrations of lutein are generally associated with better cardiometabolic health. However, evidence mainly comes from observational studies in adults, whereas large-scale intervention studies and studies of lutein during pregnancy and childhood are scarce. Am J Clin Nutr 2016;103:481–94.

Keywords: antioxidant, cardiometabolic health, life course, lutein, systematic review

INTRODUCTION

Lutein is a naturally occurring carotenoid that is synthesized within dark green leafy vegetables such as spinach and kale. Lutein is mostly known for its effect on visual function and its preventive effect against cataracts and macular degeneration (1), potentially through protection against oxidative stress (2). Given its antioxidant properties, it is hypothesized that lutein may also have beneficial effects on metabolic and cardiovascular diseases. Although the larger group of carotenoids has been associated with cardiometabolic protection (3), research has focused mostly on other carotenoids, such as β-carotene (4). Nevertheless, interventional studies with the use of β-carotene supplements have failed to reproduce the beneficial effects that were seen in observational studies (5, 6). Thus, what the substance is behind the previously published beneficial effects of carotenoids has yet to be determined. The xanthophyll lutein is of particular interest because lutein may be a more active antioxidant than β-carotene (7).

Currently, there are no dietary recommendations for lutein intake, and it is important to study the effects of lutein to determine whether such recommendations are required. Several studies have focused on the effects of lutein in the past decades, but the potential effects of lutein on cardiometabolic health at different life stages have not yet been systematically evaluated. Therefore, our objective was to systematically search the available literature for articles describing associations between lutein (from either dietary intake, supplementation, or blood concentrations) and cardiometabolic health across the life

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\textsuperscript{2}Supplemental Tables 1–5 and Supplemental Figure 1 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

\textsuperscript{3}These authors contributed equally to this work.

*To whom correspondence should be addressed. E-mail: e.leermakers@erasmusmc.nl.

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course. Our primary aim was to assess the association between lutein and risk of cardiometabolic diseases and mortality, including coronary heart disease, stroke, metabolic syndrome, and type 2 diabetes mellitus.

Our secondary aim was to evaluate systematically the literature on the associations between lutein and risk factors for cardiometabolic diseases, such as adiposity, insulin resistance, hypertension, atherosclerosis, inflammatory markers, and blood lipids, to gain more insight into the mechanisms underlying possible associations between lutein and cardiometabolic diseases.

**METHODS**

**Search strategy**

An experienced information specialist from the medical library, together with the first author, conducted a systematic search of the current literature from inception up to 26 August 2014 in 4 major electronic databases, including MEDLINE (via OvidSP; http://ovidsp.ovid.com/sp-3.17.0a/ovidweb.cgi), Embase (https://www.embase.com), Cochrane Central (via Wiley; http://onlinelibrary.wiley.com/cochranelibrary/search), and Web of Science (https://apps.webofknowledge.com). Additionally, we searched articles not yet indexed in PubMed and downloaded the most relevant references from Google Scholar. We searched for studies in which associations between lutein, carotenoids, or xanthophylls (through either dietary intake, supplementation, or blood concentrations) and body composition and cardiovascular, inflammatory, or metabolic outcomes were reported at any stage of life, ranging from fetal life through childhood to adulthood. The computer-based searches combined search terms related to the exposure and outcomes of interest, with filters for epidemiologic studies in humans, without any restriction on language or age of subjects. Search terms were searched both as controlled vocabulary (MeSH for MEDLINE and Emtree terms for Embase), and as free-text words in the title and/or abstract. Further details on the search strategy are shown in Supplemental Table 1.

**Study identification and selection**

Working in pairs, 2 reviewers independently reviewed the title and abstract of each reference to determine whether the study should be included. Studies were included if they were interventional or observational (cohort, case-control, or cross-sectional) studies; if they studied the effects of carotenoids, xanthophylls, or lutein (dietary intake, supplementation, or blood concentrations) as exposure; and if the outcomes of interest were related to cardiometabolic health (cardiovascular, metabolic, inflammatory, growth, or adiposity).

Letters, abstracts, reviews, conference proceedings, case reports, and studies not carried out in humans were excluded. To avoid bias from selective reporting of significant results in the abstract, abstracts were included if they reported that carotenoids or xanthophylls were studied, even if lutein was not specifically mentioned. Any disagreements in article selection were resolved through discussion, and a third reviewer was available to resolve any remaining disagreement. Full-text articles were retrieved for the selected papers after initial appraisal and assessed once more by the same 2 independent reviewers to ensure that they satisfied the selection criteria. In case of multiple publications from the same study, only the most recent and/or complete report was included. A flowchart of the selection process can be found in Figure 1.

**Data extraction**

Detailed study-level characteristics were extracted, including study design (such as sample size, duration of follow-up, and country), population characteristics (such as age, sex, and ethnicity), exposure assessment (such as biomarker and diet assessment method), outcome assessment (such as validity of the method), analysis (such as statistical method and measure of association), results (such as effect estimate and SE/CI), and covariates (such as key confounders and additional adjustments).

P values were rounded to 2 decimals. If significant findings were reported without an effect estimate, we reported the direction of effect in the tables with the use of a downward arrow (↓) to indicate a negative association and an upward arrow (↑) to indicate a positive association. From studies that reported multiple results, we included only the results from the most extensive adjusted model and from the most powerful analysis (e.g., linear regression over correlation). When the same cohort published results with different follow-up periods, we included only the results from the longest follow-up period. Data were extracted by one reviewer, and a random 10% of data extraction was checked by an independent reviewer. A summary of study characteristics of the included studies is shown in Table 1. A summary of the main results is shown in Figures 2, 3A–F, and 4A–D. More detailed results of the included studies are presented in Supplemental Tables 2 and 3.

**Quality scoring**

We used a predefined quality score (QS) to evaluate the quality of the included studies. The QS is a modified version of previously used scoring systems (79, 80). A score of 0, 1, or 2 points was allocated to each of the following 5 items: study design, study size, exposure assessment, outcome assessment, and adjustment for potential confounders. This allowed a total score between 0 and 10 points, with 10 representing the highest quality.
<table>
<thead>
<tr>
<th>First author (ref), year</th>
<th>Country</th>
<th>Study design</th>
<th>Lutein measure</th>
<th>Follow-up</th>
<th>Total n</th>
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<td>Blood concentration</td>
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<td>Cases with highest IMT; controls with lowest IMT. Nested in population-based cohort</td>
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<td>Ito (37), 2006</td>
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<td>Total n</td>
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<td>Mean age at baseline</td>
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<td>4304</td>
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<td>63 y ²</td>
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<td>55 y Controls: 57 y</td>
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<td>37</td>
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<td>23 y ³</td>
<td>Patients who participated in lutein supplementation trial</td>
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<td>47</td>
<td>60 y</td>
<td>Cases: previous MI, AP, or CHD on angiography Controls: self-reported healthy volunteers</td>
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<tr>
<td>Ribaya-Mercado (54), 1995</td>
<td>United States</td>
<td>Cross-sectional</td>
<td>Blood concentration ²</td>
<td>NA</td>
<td>10</td>
<td>100</td>
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<td>Participants of trial on β-carotene supplementation</td>
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<td>Rowley (55), 2003</td>
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<td>Blood concentration ²</td>
<td>NA</td>
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<td>56</td>
<td>38 y</td>
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<td>Cross-sectional (CC)</td>
<td>Blood concentration ²</td>
<td>NA</td>
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<td>11</td>
<td>50 y</td>
<td>Cases: myocardial infarction Controls: hospital visitors</td>
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<td>966</td>
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<td>59 y</td>
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<td>First author (ref), year</td>
<td>Country</td>
<td>Study design</td>
<td>Lutein measure</td>
<td>Follow-up</td>
<td>Total n</td>
<td>Female, %</td>
<td>Mean age at baseline</td>
<td>Population</td>
<td>Quality score</td>
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<td>Longitudinal</td>
<td>Blood concentration</td>
<td>2.1 y</td>
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<td>0</td>
<td>70 y</td>
<td>Nested CC in a trial of multivitamins, vitamin C, and vitamin E supplements in male health professionals</td>
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<td>Blood concentration</td>
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<td>Netherlands</td>
<td>Cross-sectional</td>
<td>Dietary intake</td>
<td>NA</td>
<td>374</td>
<td>0</td>
<td>60 y</td>
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<td>M: 56 y F: 54 y</td>
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<td>Blood concentration</td>
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<td>73</td>
<td>M: 63 y F: 60 y</td>
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<td>Tavani (67), 2006</td>
<td>Italy</td>
<td>Cross-sectional (CC)</td>
<td>Dietary intake</td>
<td>NA</td>
<td>1442</td>
<td>Cases: 24 Controls: 36</td>
<td>Cases: first episode of nonfatal AMI Controls: hospital-admitted with AMI-unrelated disease</td>
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<td>Dietary intake</td>
<td>4 y³</td>
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<td>42 y</td>
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<td>Longitudinal (CC)</td>
<td>Blood concentration</td>
<td>&lt;11 y</td>
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<td>100</td>
<td>56 y</td>
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<td>Intervention</td>
<td>Supplement</td>
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<td>116</td>
<td>56</td>
<td>55 y</td>
<td>Healthy volunteers</td>
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<td>Wang (72), 2014</td>
<td>United States</td>
<td>Cross-sectional</td>
<td>Blood concentration and diet</td>
<td>NA</td>
<td>2856</td>
<td>54</td>
<td>&gt;20 y</td>
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<td>Blood concentration</td>
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<td>22</td>
<td>100</td>
<td>50–77 y</td>
<td>Postmenopausal women participating in trial (eggs with added cholesterol and lutein) Cases: early atherosclerosis Controls: matched Patients with early atherosclerosis</td>
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<td>China</td>
<td>Cross-sectional</td>
<td>Blood concentration</td>
<td>NA</td>
<td>80</td>
<td>63</td>
<td>56 y</td>
<td>Cases: early atherosclerosis Controls: matched Nested in cohort study</td>
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<td>Xu (75), 2013</td>
<td>China</td>
<td>Intervention</td>
<td>Supplement</td>
<td>3 mo</td>
<td>65</td>
<td>Lutein: 53 Placebo: 64</td>
<td>Lutein: 58 y Placebo: 56 y</td>
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TABLE 1  (Continued)

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<tr>
<th>First author (ref), year</th>
<th>Country</th>
<th>Study design</th>
<th>Lutein measure</th>
<th>Follow-up</th>
<th>Total n</th>
<th>Female, %</th>
<th>Age at baseline</th>
<th>Population</th>
<th>Quality score</th>
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<td>2 wk</td>
<td>22</td>
<td>100</td>
<td>23 y</td>
<td>Overweight women participating in a trial of fruit and vegetable consumption</td>
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<td>China</td>
<td>Cross-sectional</td>
<td>Blood concentration</td>
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<td>232</td>
<td>68</td>
<td>56 y</td>
<td>General population</td>
<td>5</td>
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<tr>
<td>Zou (78), 2014</td>
<td>China</td>
<td>Longitudinal</td>
<td>Blood concentration</td>
<td>1 y</td>
<td>45</td>
<td>60</td>
<td>57 y</td>
<td>Participants in a trial (20 mg lutein/d for 12 mo)</td>
<td>6</td>
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</tbody>
</table>

1AMD, age-related macular degeneration; AMI, acute myocardial infarction; AP, angina pectoris; CC, case-control study; CHD, coronary heart disease; CVD, cardiovascular disease; IMT, intima-media thickness; MI, myocardial infarction; NA, not applicable; ref, reference.
2Measured together with zeaxanthin.
3Median.
5Atherosclerosis Risk in Communities Study; Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (the placebo arm); Finnish Mobile Clinic Health Examination Survey; Health Professionals Follow-Up Study; Iowa Women’s Health Study; Nurses’ Health Study, 1980–1986; Nurses’ Health Study, 1986–1996.
6Mean age at diagnosis.

Details on the applied QS are presented in Supplemental Table 4. The assigned score for each item is presented in Supplemental Table 5. In case of multiple outcomes or study designs, the highest QS is presented in Table 1, but an analysis-specific QS is shown in the harvest plots (Figure 3A–F and Figure 4A–D) and in the footnote of Supplemental Table 3.

Meta-analysis

To enable a consistent approach for the meta-analysis, RR estimates for associations between lutein and several outcomes that were differently reported by each study were transformed with the use of methods previously described (81, 82). Estimates were transformed to tertiles, and the transformed estimates thus represent the risk in the highest tertile of lutein, compared with the lowest tertile. In a normal distribution, the means of the highest and lowest tertile lie 2.18 SD apart; therefore, the log RRs per SD were multiplied by 2.18 to obtain risk for highest compared with lowest tertile. The means in the extreme quintiles are 2.8 SD apart; thus, for conversion from quintiles to tertiles, the conversion factor 2.18/2.80 was used. Similarly, scaling factors of 2.18/2.54 were used to convert quartiles, and 2.18/1.59 was used to convert from higher to lower halves. We calculated the SEs of the log RRs with the use of published confidence limits and transformed the SEs in the same way. This method enabled us to meta-analyze the results of the articles on disease risk, namely risk of coronary heart disease, risk of stroke, risk of metabolic syndrome, and type 2 diabetes mellitus. For these outcomes, we contacted authors to retrieve additional information, if meta-analysis was not possible based on the published results.

Heterogeneity between studies was tested by using the F statistic (0–100%), which describes the percentage of variation across studies that is due to heterogeneity rather than chance (83). Analyses were done with the use of random and fixed-effects methods, and the results of both methods are presented.

Subgroup analyses were done to assess whether the results differed by exposure assessment (dietary intake or blood concentrations), or by study design (prospective, cross-sectional, or case-control). Sensitivity analyses were done to assess the influence of each individual study on the pooled RRs by omitting each study one by one. Funnel plots were used to assess the possibility of publication bias.

All analyses were performed with the use of STATA SE 13 (StataCorp).

Harvest plots

For the associations between lutein and risk factors for cardiometabolic diseases, we used harvest plots to summarize reported evidence in a graphic way (84). The harvest plots show the outcomes of interest in all studies and whether they reported significant inverse associations, significant positive associations, or no significant associations. The height of the bar represents the QS, whereas the filling of the bar represents the exposure assessment (i.e., blood concentrations, dietary intake, or supplements). Some outcomes were combined in one figure. More specifically, we combined all measures of blood pressure, (i.e., systolic blood pressure, diastolic blood pressure, and hypertension), all measures of atherosclerosis (i.e., atherosclerosis of carotid arteries, (ilio)femoral arteries, and abdominal aorta), all
measures of insulin resistance (i.e., nonfasting and fasting glucose, insulin, HOMA-IR, and glycated hemoglobin) and all measures of adiposity (i.e., BMI, body fat percentage, and waist circumference).

We only present harvest plots if >3 studies reported on the same outcome.

RESULTS

Study selection

Overall, 4377 unique references were identified from the search strategy (Figure 1), of which 4045 articles were excluded based on title and abstract. Full texts of the remaining 332 articles were further screened by 2 independent reviewers, and 71 articles were included for data extraction.

Characteristics of studies included

The characteristics of the 71 studies included in this systematic review are shown in Table 1. These studies contained a total of 387,569 participants (range: 10–112,348) with mean ages ranging from birth to 82 y old. Because some studies were performed within the same cohort, the study populations partially overlapped. Of the 71 included articles, the vast majority (66 articles) were published after the year 2000. In children, we identified 1 intervention study (9), 1 longitudinal study (11), and 2 cross-sectional studies (8, 10), of which 1 also studied maternal lutein concentrations (10). The remaining 67 studies all focused on adults, predominantly on middle-aged and elderly, of which 31 were longitudinal studies, 33 were cross-sectional, and only 3 were intervention studies.

The assigned QS ranged from 1 to 10, with a mean QS of 6.5. Of the 71 studies, 21 studies received a score of ≥8, and 18 studies had a score of <8.

From the total 71 studies, 26 studies were performed in Europe and 25 in the United States. The other studies were from Japan (n = 6), China (n = 5), Australia (n = 3), and Korea, Singapore, Costa Rica, Thailand, Uganda, and the Philippines (1 each).

Associations between lutein and coronary heart disease

In total, measures of association from 10 studies on lutein and coronary heart disease were pooled, with a total number of 203,630 participants (including 8239 cases) (26, 27, 30, 38, 42, 43, 46, 50, 61, 67) (Figure 2). Six studies were longitudinal, with follow-up periods from 1.85 to 14 y (27, 30, 42, 43, 50, 61); the other 4 were cross-sectional (26, 38, 46, 67). The pooled results show that the highest tertile of lutein was associated with a lower risk of coronary heart disease.
heart disease (RR: 0.88; 95% CI: 0.80, 0.98), compared with the lowest tertile (concentrations and intake combined). A pooled analysis including only studies with clinical endpoints of coronary heart disease (therefore excluding the studies with angina pectoris as an outcome) showed no change in results (RR: 0.89; 95% CI: 0.80, 0.998).

Two studies could not be included in the meta-analysis because they only compared lutein concentrations between cases and controls. One of these studies (QS 4) found lower concentrations of lutein in the cases (56), whereas the other study (QS 3) found no significant difference (53). A third study that could not be pooled (QS 8) did not find an association.

FIGURE 3 Harvest plots of the evidence of an association between lutein and cardiovascular disease risk factors, including blood pressure (A), atherosclerosis (B), C-reactive protein (C), IL-6 (D), adiposity (E), and insulin resistance (F). In the 2010 study by Suzuki et al. (65), the inverse association between lutein and IL-6 was significant in women only. In the 2011 study by Suzuki et al. (66), the inverse association between lutein and adiposity was significant in women only.
between lutein and risk of mortality from coronary heart disease (HR: 0.82; 95% CI: 0.42, 1.58 per unit increase in lutein concentrations) (37).

**Associations between lutein and stroke**

Results of 3 longitudinal studies that reported on the associations between lutein and stroke were pooled (13, 31, 32). The number of controls largely overlap, but the total number of unique cases was 1398. Pooled results showed that the highest tertile of lutein was associated with a lower risk of stroke (RR: 0.82; 95% CI: 0.72, 0.93) compared with the lowest tertile (Figure 2).

One study (QS 8) could not be included in the meta-analysis because it did not report information on the distribution of lutein concentrations, but this study reported results in the same direction (stroke-specific mortality HR: 0.72; 95% CI: 0.37, 0.93) compared with the lowest tertile (Figure 2).

One study (QS 8) could not be included in the meta-analysis because it did not report information on the distribution of lutein concentrations, but this study reported results in the same direction (stroke-specific mortality HR: 0.72; 95% CI: 0.37, 0.93) compared with the lowest tertile (Figure 2).

**Associations between lutein and mortality from cardiovascular diseases**

Besides the abovementioned analysis of lutein in relation to stroke-specific mortality or mortality specific to coronary heart disease (37), 5 studies reported on lutein in relation to mortality from a combined outcome of any cardiovascular disease (QS 6–9) (14, 37, 44, 59). Mean follow-up time ranged from 4.25 to 15 y and sample sizes ranged from 216 to 13,293. None of the studies found significant associations, but the effect estimates were mostly in the direction of higher lutein being associated with a lower risk of mortality from cardiovascular disease (14, 37, 44, 59), except for one study (19).

Two studies from a US cohort (one in male subjects and one in female subjects) were not included in the meta-analyses because they reported only on a combined outcome of any cardiovascular disease, including both fatal and nonfatal events. Both studies found no significant associations (37, 58).

**Associations between lutein and type 2 diabetes mellitus**

The meta-analysis of the results of lutein in relation to type 2 diabetes mellitus is presented in Figure 2. Four studies were included (33, 40, 45, 70), all of which were longitudinal observational studies with follow-up periods between 10 and 23 y, including in total 35,242 participants (including 1661 cases). The pooled results showed no significant association between lutein and risk of diabetes (RR: 0.97; 95% CI: 0.77, 1.22, highest compared with lowest tertile of lutein).

**Associations between lutein and metabolic syndrome**

Of the 6 studies on metabolic syndrome, one was in adolescents (8) and the others were in adults (16, 21, 60, 63, 66). All studies were cross-sectional, with a total of 8133 participants.
(including 1773 cases). The highest tertile of lutein was associated with a lower risk of metabolic syndrome (RR: 0.75; 95% CI: 0.60, 0.92) compared with the lowest tertile (Figure 2).

Additional analyses

There was no significant heterogeneity between groups for any of the outcomes included in the meta-analyses. Subgroup analyses by exposure assessment (dietary intake or blood concentrations) or by study design (prospective, cross-sectional, or case-control) showed no differences in results. Sensitivity analyses performed by omitting each study one by one showed that none of the individual studies significantly affected the results. Funnel plots to assess the possibility of publication bias did not show any obvious asymmetry (Supplemental Figure 1).

Associations between lutein and cardiovascular disease risk factors

The harvest plots of the association between lutein and blood pressure and between lutein and atherosclerosis are shown in Figure 3. From the 6 studies on blood pressure, 2 studies observed a significant inverse association (35, 63), and these studies were of somewhat higher quality than those reporting no significant association (21, 60, 66) or a positive association (61) (Figure 3A).

Of the 10 studies on atherosclerosis, 5 studies found no significant associations (23, 36, 39, 41, 48), and 5 studies of a similar quality found a significant inverse association (24, 51, 74, 77, 78) (Figure 3B).

Three studies reported on other cardiovascular disease risk factors. The largest study (n = 26,872; QS 8) observed that intake of lutein (assessed retrospectively 2 y before the outcome) was significantly associated with a lower risk of intermittent claudication (68). The other 2 studies found no significant associations between lutein concentrations and pulse wave velocity (QS 7) (47), and between lutein concentrations of arterial stiffness (QS 5) (77).

We identified 15 articles on inflammatory markers, which reported on C-reactive protein (CRP) (10 articles), IL-6 (5 articles), leukocytes (3 articles), TNF-α (2 articles), fibrinogen (2 articles), interferon-γ (1 article), and IL-1 (1 article). The harvest plot for CRP shows that, of 10 studies, 3 found a significant inverse association (34, 71, 72), including 1 intervention study (71). The other 7 studies (12, 18, 29, 55, 64, 65, 69), which also included 1 intervention study (29), found no significant associations (Figure 3C).

The harvest plot for IL-6 shows that 2 studies observed significant inverse associations (64, 65), whereas 3 studies (including an intervention study) did not (22, 74, 75) (Figure 3D).

Of 3 studies on leukocytes, 2 studies (QS 5 and 8) found significant inverse associations (15, 34), and 1 study (QS 5) found a nonsignificant inverse association (69). Of 2 studies on TNF-α (both QS 6), 1 study found an inverse association (22), whereas the other did not (65). The 2 studies on fibrinogen (QS 5 and 9) did not find significant associations (34, 69), and neither did the study on interferon-γ (QS 5) (74). The only study (QS 6) on IL-1 found a significant inverse association between lutein blood concentrations and IL-1β in LPS-activated peripheral blood mononuclear cells (76).

Three studies reported on the relation between lutein and child body composition. One study (QS 6) found no significant associations between either maternal blood concentrations or cord blood concentrations of lutein and birth weight, birth length, or head circumference (10). An intervention study in the Philippines (QS 8) also did not find differences in growth measures between children receiving lutein-fortified infant formula and those receiving regular formula (9); however, a study in HIV-infected infants (QS 5) found lutein concentrations at 3.5 mo to be significantly associated with higher attained weight and height at 9 mo but not with weight or height velocity (11).

The harvest plot of the association between lutein and adiposity, measured as body fat percentage, BMI, or abdominal adiposity with the use of waist circumference is shown in Figure 3E. Of a total of 8 studies, 3 studies showed a significant inverse association (63, 66, 73), but 4 studies (15, 21, 60, 71), including a high quality intervention study (71), did not. However, one of the studies that did not find an association with waist circumference, BMI, or visceral fat did find that higher dietary intake of lutein was associated with lower amounts of subcutaneous fat (60). Also, one of the studies observed that the inverse association between lutein concentrations and waist circumference was only significant in women, but not in men (66).

The harvest plot of the associations between lutein and measures of insulin resistance (glucose, insulin, HOMA, and glycated hemoglobin) is shown in Figure 3F. We identified 13 studies, of which 2 reported a significant inverse association (20, 26) and the others found no significant associations (15, 17, 21, 28, 33, 49, 60, 62, 63, 66, 75).

Harvest plots of the associations between lutein and blood lipids are shown in Figure 4.

For total cholesterol, 1 study found a positive association (61), but 1 intervention study (71) and 3 observational studies (15, 49, 52) found no association (Figure 4A).

Of 11 studies on HDL cholesterol, 1 found an inverse association (49), whereas 5 studies found that higher lutein concentrations were associated with higher HDL cholesterol concentrations (21, 52, 63, 66, 72). However, another 5 studies (15, 60, 71, 74, 75), of which 2 were intervention studies (71, 75), found no significant associations (Figure 4B).

For LDL cholesterol, 2 intervention studies (71, 75) and 4 observational studies (15, 49, 52, 74) found no significant associations. Only one study found a significant association, with higher blood concentrations of lutein being associated with lower LDL cholesterol (72) (Figure 4C).

Nine studies on triglycerides that also included 2 intervention studies (71, 75) all found no significant associations (21, 49, 52, 60, 63, 66, 74) (Figure 4D).

One study (QS 4) was not included in the harvest plots for blood lipids, because it assessed plasma total lipids (cholesterol and triglycerides combined). This study found no significant association (54).

DISCUSSION

In this systematic review with meta-analysis, we showed that higher lutein was associated with a lower risk of coronary heart disease, stroke, and metabolic syndrome, but not with risk of type 2 diabetes mellitus. Although several studies suggested that lutein was associated with a lower risk of cardiovascular disease mortality, none of them were statistically significant. The literature on risk factors of cardiometabolic diseases suggested that
lutein might prevent atherosclerosis and reduce inflammatory markers, but there were inconsistent associations with blood pressure, adiposity, insulin resistance, and blood lipids. The majority of the studies were observational and performed in adults, and the effects of lutein on cardiometabolic health in children remains largely unaddressed.

Several biological mechanisms have been proposed for the potential beneficial effect of lutein on cardiometabolic health, including vascular changes, antioxidant effects, and effects on immune response and inflammation. These combinatory mechanisms suggest that lutein could act as a beneficial factor on overall health, as well as on specific organ systems.

It has been suggested that oxidative stress (e.g., induced by smoking), can lead to insulin resistance (85, 86). As an antioxidant, lutein can reduce oxidative stress, and might thus decrease insulin resistance, which might explain the inverse association between lutein and metabolic syndrome. However, if the protective effect of lutein on metabolic syndrome is indeed through increasing insulin sensitivity, it is striking that there was no association with type 2 diabetes mellitus; hence, this mechanism seems unlikely. It could be hypothesized that the association of lutein with metabolic syndrome arises because lutein may influence other components of metabolic syndrome. However, in our systematic review, we found no consistent associations with blood pressure, triglycerides, and adiposity. Because lutein is absorbed along with fat in the gastrointestinal tract and transported through chylomicrons, a relation between lutein and lipid concentrations can be expected (52). In this systematic review, several observational studies showed lutein to be related to lipid concentrations, in particular, higher HDL concentrations (21, 52, 63, 66), but the 2 intervention studies did not show any effect from lutein supplementation on lipid concentrations (71, 75). Furthermore, none of the observational studies on triglycerides showed a significant association, and results for adiposity were inconsistent, suggesting that it is unlikely that the association between lutein and metabolic syndrome is driven by these factors. The methodologic quality of the studies, however, should also be considered when interpreting the meta-analysis of metabolic syndrome and diabetes. Most importantly, all studies on metabolic syndrome were cross-sectional, which puts them at a higher risk of reverse causation. This would mean that lower concentrations of lutein are a consequence of disease processes, rather than a cause. This might be of particular concern in diseases in which oxidative stress can play a role, because blood concentrations of antioxidants are being used to counteract oxidative stress. Depletion of lutein concentrations might thus occur in patients with obesity or metabolic syndrome, which has indeed been suggested by several studies (87–89). The studies on type 2 diabetes mellitus were all prospective, with fairly long follow-up periods (>10 y), which make them less susceptible to reverse causation.

Our meta-analysis also showed that higher lutein intake or concentrations were associated with a lower risk of coronary heart disease and stroke. Besides the abovementioned relation between lutein and blood lipids, other mechanisms might apply. With respect to the established preventive effect of lutein on age-related macular degeneration, the attention has shifted from a local effect in the eye toward a possible systemic anti-inflammatory function (1). Indeed, in our systematic review, we observed that lutein was associated with lower concentrations of several inflammatory markers, with the strongest evidence for CRP. CRP has been consistently associated with cardiovascular diseases (90); however, this might not be a causal risk factor but, rather, a marker of disease (91). The mechanisms by which lutein affects the immune response may, however, differ from its antioxidant effects (92). Animal studies have shown that lutein enhances the antibody response to T cell–dependent antigens (93), and stimulates both cellular and humoral immunity (94–96). Another explanation might be that lutein affects the vascular wall, because there is some evidence that lutein can reduce the wall thickening of the small arteries (97, 98). We identified 10 studies on atherosclerosis, of which 5 showed that higher blood concentrations of lutein were associated with less atherosclerosis. Because both inflammatory activity and atherosclerosis play a role in the development of cardiovascular diseases, these might thus be the underlying mechanisms for the association between lutein and cardiovascular disease. Based on the findings from our review, we cannot clearly identify the mechanisms involved. Further studies, both experimental and observational and looking at both chronic disease and acute events, are needed to elucidate the pathways by which lutein exerts its effect on cardiometabolic health.

Some methodologic considerations need to be taken into account when considering our results. First of all, although there was no significant heterogeneity in the meta-analysis, it should be noted that we included studies that used blood concentrations of lutein as exposure, as well as studies that used dietary intake of lutein. When measuring dietary intake, there is no absolute measure of how much is absorbed into the body, and the correlation between intake of lutein and blood concentrations might be low (99). Blood concentrations may thus provide a more direct measurement, because they are closer to the physiologic pathways and less prone to measurement error than is self-reported dietary intake. However, the use of blood concentrations may lead to reverse causality if the disease itself can deplete lutein concentrations in the body (87–89). Furthermore, with both measurements, results might be confounded by other carotenoids, because most studies were observational and were not able to adjust for other carotenoids. In addition, lutein might be a marker of a healthier diet, and results thus may be confounded by other factors associated with a healthier lifestyle, such as physical activity. Therefore, given the limited number of intervention studies, causality of the observed associations cannot be established.

This review also has several strengths. An important strength is the systematic search in multiple databases by an experienced biomedical information specialist. Second, we reviewed studies on all carotenoids to identify articles that did not mention lutein in the title or abstract, which could occur especially with null findings. Furthermore, we used different indexes of lutein status, which allows for a complete overview of the literature on lutein. In addition, we included risk factors and intermediate markers, as well as hard endpoints. This enabled us to perform a meta-analysis on the risk of certain diseases, but also gives some insight into the potential mechanisms underlying the associations. However, because the results of the intermediate markers, such as atherosclerosis and inflammatory markers, were presented with the use of harvest plots, no summary estimate is derived and a strong conclusion thus cannot be drawn.
In conclusion, to date, lutein mostly has been investigated in observational studies. These studies showed that higher dietary intake of lutein and higher blood concentrations are associated with a lower risk of coronary heart disease and stroke, possibly through less atherosclerosis and lower inflammatory activity. However, further studies and randomized, controlled trials are required to evaluate the causality of these associations. A potential inverse association between lutein and metabolic syndrome should be studied further in high-quality longitudinal studies, because thus far this has only been shown cross-sectionally. In addition, more research is needed on the effects of lutein during fetal life, infancy, and childhood, in order to enable conclusions on the effect of lutein along the full life course.

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