Review Article

Vitamin E and risk of age-related cataract: a meta-analysis

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Abstract

Objective: We conducted a meta-analysis to evaluate the relationship between vitamin E and age-related cataract (ARC).

Design: The fixed- or random-effect model was selected based on heterogeneity. Meta-regression was used to explore potential sources of between-study heterogeneity. Publication bias was evaluated using Begg’s test. The dose–response relationship was assessed by a restricted cubic spline model.

Setting: Relevant studies were identified by a search of PubMed and the Cochrane Library to May 2014, without language restrictions.

Subjects: Studies involved samples of people of all ages.

Results: Dietary vitamin E intake, dietary and supplemental vitamin E intake, and high serum tocopherol levels were significantly associated with decreased risk of ARC, the pooled relative risk was 0·73 (95 % CI 0·58, 0·92), 0·86 (95 % CI 0·75, 0·99) and 0·77 (95 % CI 0·66, 0·91), respectively. Supplemental vitamin E intake was non-significantly associated with ARC risk (relative risk = 0·92; 95 % CI 0·78, 1·07). The findings from dose–response analysis showed evidence of a non-linear association between dietary vitamin E intake and ARC. The risk of ARC decreased with dietary vitamin E intake from 7 mg/d (relative risk = 0·94; 95 % CI 0·90, 0·97).

Conclusions: The findings of the meta-analysis indicated that dietary vitamin E intake, dietary and supplemental vitamin E intake, and high level of serum tocopherol might be significantly associated with reduced ARC risk.

Keywords

Vitamin E
Serum tocopherol
Age-related cataract
Meta-analysis

Age-related cataract (ARC) is a common eye disease in the middle-aged and elderly that is characterized by lens opacities and visual impairment due to the oxidation of lens proteins and degenerative changes to the lens caused by ageing(1,2). According to the WHO’s latest assessment, ARC is responsible for 51 % of world blindness, which represents about 20 million people(3). Despite its high prevalence and high cost of treatment, the aetiology of ARC is still unclear. Laboratory and animal data point to a causal role for oxidative mechanisms and suggest a possible beneficial role for antioxidant nutrients, especially vitamin E, in delaying ARC onset and progression(4–6).

Vitamin E, a lipid-soluble antioxidant concentrated in lens fibres and membranes, is postulated to inhibit ARC formation by reducing photoperoxidation of lens lipids and stabilizing lens cell membranes(7,8). A number of epidemiological studies(9–15) generally support an inverse association between vitamin E and the risk of ARC. As yet, however, the protective effect of vitamin E is still controversial because other studies(16–21) show that there is no relationship between vitamin E and the risk of ARC. Therefore, we conducted a meta-analysis to quantitatively assess the associations between dietary vitamin E intake, supplemental vitamin E intake, dietary and supplemental vitamin E intake, and serum tocopherol levels and the risk of ARC.

Materials and methods

We referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting of meta-analyses in the present analysis.

Search strategy

There were two investigators who independently performed a literature search to May 2014 using both PubMed and the Cochrane Library without restrictions using the following search terms: (vitamin E or tocopherol) and (cataract or lens opacities). Moreover, we reviewed the...
reference lists from retrieved articles to search for further relevant studies.

**Inclusion criteria**

Studies were included in the meta-analysis if they met the following criteria: (i) cohort, case–control, cross-sectional studies or randomized controlled trials published as an original study to evaluate the association between vitamin E and ARC; (ii) the exposure of interest was dietary vitamin E intake (i.e. vitamin E from foods), supplemental vitamin E intake (i.e. vitamin E from supplements), dietary and supplemental vitamin E intake (i.e. vitamin E from foods and supplements) or serum tocopherol levels; (iii) the outcome of interest was clearly diagnosed as ARC; and (iv) the relative risk (RR) with 95% confidence interval was provided. If studies had overlapping patients or controls, only the latest or the most complete one was included.

**Data extraction**

Data were independently extracted by two investigators who reached a consensus on all of the items. Information extracted from each study was as follows: first author’s name, year of publication, area in which the study was conducted, study design, age, gender and number of cases and controls (participants for cohort studies), the highest and the lowest levels of vitamin E intake or serum tocopherol, and multivariate-adjusted RR (we present all results with RR for simplicity) with corresponding 95% CI for the highest vs. the lowest category of dietary vitamin E intake, supplemental vitamin E intake, dietary and supplemental vitamin E intake, or serum tocopherol level, respectively. For dose–response analysis, the number of cases and participants (person-years) and the RR (95% CI) for each category of dietary vitamin E intake were also extracted. The median or mean level of dietary vitamin E intake for each category was assigned to the corresponding RR for every study. If the upper or lower boundary of the exposure category was open-ended, we assumed that the boundary had the same amplitude as the adjacent category.

**Statistical analysis**

Two (highest vs. lowest, dose–response) types of meta-analysis were performed. For highest vs. lowest analyses, the pooled measure was calculated as the inverse variance-weighted mean of the logarithm of the multivariate-adjusted RR with 95% CI to evaluate the relationship between ARC risk and vitamin E status. Statistical heterogeneity among studies was assessed by using the Q and I² statistics\(^{(22)}\). If substantial heterogeneity was present (I² > 50%)\(^{(23)}\), the DerSimonian and Laird\(^{(24)}\) random-effect model was adopted as the pooling method; otherwise, the fixed-effect model was used as the pooling method. A sensitivity analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study. Meta-regression with restricted maximum likelihood estimation was performed to explore the potentially important covariates that might have substantial impacts on between-study heterogeneity. Publication bias was estimated using Begg’s test\(^{(25)}\) and the funnel plot\(^{(26)}\).

For dose–response analysis, a two-stage, random-effects, dose–response meta-analysis\(^{(27)}\) was performed. In the first stage, a restricted cubic spline model with three knots at the 10th, 50th and 90th centiles\(^{(28)}\) of the dietary vitamin E intake was estimated using generalised least square regression, taking into account the correlation within each set of published RR\(^{(27)}\). Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis\(^{(29)}\). A P value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0.

All statistical analyses were conducted with the statistical software package Stata 12.0. A two-tailed \(P < 0.05\) was considered statistically significant.

**Results**

**Literature search and study characteristics**

The search strategy identified 256 articles from PubMed and forty-two articles from the Cochrane Library. Seventy-four articles were reviewed in full text after screening by reviewing titles and abstracts. Upon closer examination, forty-seven articles were excluded for the following reasons: thirty-six articles were irrelevant to the interest of the exposure or the outcome, seven articles\(^{(30–36)}\) did not provide OR/RR and its 95% CI, three articles\(^{(37–39)}\) were duplicated studies and one article\(^{(40)}\) was a review. Finally, twenty-seven articles\(^{(6,10–15,17–19,21–41,56)}\) were included in the present meta-analysis. The detailed literature search for article inclusion is shown in Fig. 1; the baseline characteristics of the study participants and the design characteristics in the published articles are shown in Tables 1 and 2.

**Quantitative synthesis**

The main results are summarized in Table 3.

**Dietary vitamin E intake and risk of age-related cataract**

The association between dietary vitamin E intake and ARC risk was examined in eight articles\(^{(15–17,43,45,50,53,56)}\) with eight studies including 15,021 participants and 2258 cases. The highest vs. the lowest dietary vitamin E intake was statistically significantly associated with the risk of ARC (RR = 0.73; 95% CI 0.58–0.92; \(I² = 69.1\%\); \(P_{\text{heterogeneity}} = 0.002\); Fig. 2).

**Dose–response analysis**

Data from three studies\(^{(15,53,56)}\) were included in dose–response analysis. Evidence of a non-linear relationship...
Supplemental vitamin E intake and risk of age-related cataract

The association between supplemental vitamin E intake and ARC risk was examined in ten articles (10–16, 19–21, 24, 47, 49, 52) with ten studies including 358,007 participants and 5147 cases. Compared with the lowest category, the pooled RR of ARC for the highest category was 0.92 (95% CI 0.78–1.07; $I^2 = 74.2\%$; $P_{\text{heterogeneity}} < 0.001$); no statistically significant association was observed between supplemental vitamin E intake and risk of ARC.

Dietary and supplemental vitamin E intake and risk of age-related cataract

Three articles (18, 49, 53) with four studies including 8512 participants and 874 cases provided the result for dietary and supplemental vitamin E intake and ARC risk. The highest v: the lowest dietary and supplemental vitamin E intake was statistically significantly associated with the risk of ARC (RR = 0.86; 95% CI 0.75–0.99; $I^2 = 47.1\%$; $P_{\text{heterogeneity}} = 0.129$).

Serum tocopherol levels and the risk of age-related cataract

A forest plot of the seventeen included studies from fourteen articles (31–35, 38, 42, 46, 48–51, 54–56) with 17,194 participants and 4,179 cases is shown in Fig. 4. The highest v: the lowest level of serum tocopherol was statistically significantly associated with the risk of ARC (RR = 0.77; 95% CI 0.66–0.91; $I^2 = 52.1\%$; $P_{\text{heterogeneity}} = 0.007$). A significant association was found in case-control studies (RR = 0.67; 95% CI 0.51–0.89; $I^2 = 0.0\%$; $P_{\text{heterogeneity}} = 0.56$), while no significant association was found in cohort studies (RR = 0.83; 95% CI 0.62–1.12; $I^2 = 57.5\%$; $P_{\text{heterogeneity}} = 0.051$) and cross-sectional studies (RR = 0.77; 95% CI 0.56–1.07; $I^2 = 61.2\%$; $P_{\text{heterogeneity}} = 0.017$). For ARC subtypes, a significant association was found in nuclear (RR = 0.64; 95% CI 0.50–0.81; $I^2 = 44.1\%$; $P_{\text{heterogeneity}} = 0.097$) but not in cortical (RR = 0.95; 95% CI 0.72–1.25; $I^2 = 52.7\%$; $P_{\text{heterogeneity}} = 0.061$) and posterior subcapsular cataract (RR = 1.13; 95% CI 0.76–1.69; $I^2 = 34.5\%$; $P_{\text{heterogeneity}} = 0.192$).

Sources of heterogeneity and sensitivity analysis

To explore the heterogeneity, meta-regression was performed for covariate analysis for individual results. However, for the covariates publication year, study design, study conducted area and gender, the univariate meta-regression analysis showed that no covariate was significantly associated with between-study heterogeneity. Sensitivity analysis showed that no individual study had excessive influence on the above-mentioned pooled effect.

Publication bias

Visual inspection of the funnel plot and Begg’s test showed no evidence of significant publication bias for the studies of dietary vitamin E intake ($P = 0.174$), supplemental vitamin E intake ($P = 0.283$), dietary and supplemental vitamin E intake ($P = 1.000$), or serum tocopherol levels ($P = 0.807$; Fig. 5) on ARC.

Discussion

Mechanisms of ARC are still disputed, but oxidative damage of lens proteins is believed to play an important part in the process (59). Antioxidants such as vitamin E may modify antioxidant defence and the development of ARC. Vitamin E can inhibit lipid peroxidation (57) and stabilize lens cell membranes (58). Vitamin E may also affect ascorbate regeneration and enhance glutathione recycling, perhaps helping to maintain concentrations of reduced glutathione in the lens and aqueous humor (59).
**Table 1** Characteristics of the studies on vitamin E intake and age-related cataract included in the present meta-analysis

<table>
<thead>
<tr>
<th>Study/study ID*</th>
<th>Country</th>
<th>Study design</th>
<th>Age range (years)</th>
<th>Sample size</th>
<th>No. of cases</th>
<th>ARC outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
<th>Adjustment for covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson et al. (1991)</td>
<td>USA</td>
<td>Case–control</td>
<td>50+</td>
<td>175</td>
<td>175</td>
<td>Any type</td>
<td>Supplement: 0.44</td>
<td>0.24, 0.77</td>
<td>0.04</td>
<td>Age and gender</td>
</tr>
<tr>
<td>Hankinson et al. (1992)</td>
<td>USA</td>
<td>Cohort</td>
<td>45–67</td>
<td>50 828</td>
<td>493</td>
<td>Any type</td>
<td>Dietary: 0.88</td>
<td>0.65, 1.18</td>
<td>0.40</td>
<td>Age, smoking, family history, diabetes and BMI</td>
</tr>
<tr>
<td>Tavani et al. (1996)</td>
<td>Italy</td>
<td>Case–control</td>
<td>20–80</td>
<td>706</td>
<td>207</td>
<td>Any type</td>
<td>Dietary: 0.50</td>
<td>0.30, 1.00</td>
<td>&lt;0.05</td>
<td>Age, gender, education, smoking, diabetes, BMI and energy intake</td>
</tr>
<tr>
<td>Teikari et al. (1998)</td>
<td>Finland</td>
<td>RCT</td>
<td>51–69</td>
<td>159 199</td>
<td>7286</td>
<td>Any type</td>
<td>Supplement: 0.91</td>
<td>0.74, 1.11</td>
<td></td>
<td>Age, diabetes, BMI, education and alcohol</td>
</tr>
<tr>
<td>McCarty et al. (1999)</td>
<td>Australia</td>
<td>Case–control</td>
<td>40+</td>
<td>764</td>
<td>177</td>
<td>Nuclear</td>
<td>Supplement: 0.43</td>
<td>0.19, 0.99</td>
<td>&lt;0.05</td>
<td>Age, energy intake, smoking, alcohol consumed per week and percentage of energy intake as linoleic acid</td>
</tr>
<tr>
<td>Lyle et al. (1999)</td>
<td>USA</td>
<td>Cohort</td>
<td>43–84</td>
<td>1354</td>
<td>245</td>
<td>Nuclear</td>
<td>Dietary: 0.70</td>
<td>0.40, 1.10</td>
<td>0.22</td>
<td>Age, gender, education and occupation</td>
</tr>
<tr>
<td>Nadalin et al. (1999)</td>
<td>Australia</td>
<td>RCT</td>
<td>55–80</td>
<td>1630</td>
<td>578</td>
<td>Cortical</td>
<td>Supplement: 0.44</td>
<td>0.25, 0.77</td>
<td></td>
<td>Age and gender</td>
</tr>
<tr>
<td>Jacques et al. (2001)</td>
<td>USA</td>
<td>Case–control</td>
<td>53–73</td>
<td>478</td>
<td>163</td>
<td>Nuclear</td>
<td>Supplement: 0.49</td>
<td>0.22, 0.90</td>
<td>0.03</td>
<td>Age, smoking, alcohol use, BMI and hypertension</td>
</tr>
<tr>
<td>Valero et al. (2002)</td>
<td>USA</td>
<td>Case–control</td>
<td>55–74</td>
<td>692</td>
<td>343</td>
<td>Any type</td>
<td>Dietary: 0.77</td>
<td>0.84, 1.24</td>
<td>0.09</td>
<td>Age, gender and energy intake</td>
</tr>
<tr>
<td>Taylor et al. (2002)</td>
<td>USA</td>
<td>Case–control</td>
<td>53–73</td>
<td>462</td>
<td>86</td>
<td>Cortical</td>
<td>Dietary and supplement: 1.21</td>
<td>0.75, 1.95</td>
<td></td>
<td>Age, smoking, alcohol use, BMI and hypertension</td>
</tr>
<tr>
<td>McNeil et al. (2004)</td>
<td>Australia</td>
<td>RCT</td>
<td>55–80</td>
<td>1192</td>
<td>222</td>
<td>Any type</td>
<td>Supplement: 1.30</td>
<td>1.00, 1.60</td>
<td>0.06</td>
<td>Age, gender, smoking status and BMI</td>
</tr>
<tr>
<td>Christen et al. (2008)</td>
<td>USA</td>
<td>Cohort</td>
<td>45+</td>
<td>7171</td>
<td>369</td>
<td>Any type</td>
<td>Dietary: 0.92</td>
<td>0.08, 1.06</td>
<td>0.39</td>
<td>Age, smoking, alcohol use, BMI and hypertension</td>
</tr>
<tr>
<td>Study/study ID*</td>
<td>Country</td>
<td>Study design</td>
<td>Age range (years)</td>
<td>Sample size</td>
<td>No. of cases</td>
<td>ARC outcome</td>
<td>RR</td>
<td>95 % CI</td>
<td>P value</td>
<td>Adjustment for covariates</td>
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<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Christen et al. (2008)(52)</td>
<td>USA</td>
<td>RCT</td>
<td>45+</td>
<td>2376</td>
<td>1159</td>
<td>Any type</td>
<td>Supplement: 0·96</td>
<td>0·88, 1·04</td>
<td>0·92</td>
<td>Age, aspirin and β-carotene treatment assignment</td>
</tr>
<tr>
<td>Christen et al. (2010)(20)</td>
<td>USA</td>
<td>RCT</td>
<td>50+</td>
<td>1174</td>
<td>579</td>
<td>Any type</td>
<td>Supplement: 0·99</td>
<td>0·88, 1·11</td>
<td>0·46</td>
<td>Age, PHS cohort, vitamin C, carotene and multivitamin treatment assignment</td>
</tr>
<tr>
<td>Selin et al. (2013)(21)</td>
<td>Sweden</td>
<td>Case–control</td>
<td>50+</td>
<td>144</td>
<td>32</td>
<td>Any type</td>
<td>Supplement: 1·57</td>
<td>1·10, 2·22</td>
<td></td>
<td>Age, smoking, abdominal obesity, education, hypertension, corticosteroid use, alcohol, and fruit and vegetable intake</td>
</tr>
<tr>
<td>Theodoropoulou et al. (2013)(16)</td>
<td>Greece</td>
<td>Case–control</td>
<td>45–85</td>
<td>314</td>
<td>314</td>
<td>Any type</td>
<td>Dietary: 0·50</td>
<td>0·38, 0·66</td>
<td>&lt;0·001</td>
<td>Age, gender, smoking, BMI, education and energy intake</td>
</tr>
<tr>
<td>Pastor-Valero (2013)(56)</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>65+</td>
<td>593</td>
<td>433</td>
<td>Any type</td>
<td>Dietary: 0·49</td>
<td>0·27, 0·95</td>
<td>0·94</td>
<td>Age, sex, BMI, energy intake, marital status, smoking, alcohol consumption, physical activity, use of supplements and history of diabetes</td>
</tr>
</tbody>
</table>

ARC, age-related cataract; RR, relative risk; RCT, randomized controlled trial; PSC, posterior subcapsular cataract; PHS, Physicians’ Health Study.

*Study ID is used in Fig. 2.
Table 2 Characteristics of the studies on serum tocopherol levels and age-related cataract included in the present meta-analysis

<table>
<thead>
<tr>
<th>Study/study ID*</th>
<th>Country</th>
<th>Study design</th>
<th>Age range (years)</th>
<th>Sample size</th>
<th>No. of cases</th>
<th>ARC outcome</th>
<th>RR</th>
<th>95 % CI</th>
<th>P value</th>
<th>Adjustment for covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knekt et al. (1992)(41)</td>
<td>Finland</td>
<td>Case–control</td>
<td>47–83</td>
<td>1419</td>
<td>–</td>
<td>Any type</td>
<td>0·53</td>
<td>0·24–1·11</td>
<td></td>
<td>Age, gender, smoking, diastolic blood pressure, serum cholesterol, BMI and occupation</td>
</tr>
<tr>
<td>Vitale et al. (1993)(42)</td>
<td>USA</td>
<td>Case–control</td>
<td>40+</td>
<td>1260</td>
<td>660</td>
<td>Nuclear</td>
<td>0·52</td>
<td>0·26–1·07</td>
<td></td>
<td>Age, gender and diabetes</td>
</tr>
<tr>
<td>Leske et al. (1995)(11)</td>
<td>US</td>
<td>Case–control</td>
<td>40–79</td>
<td>830</td>
<td>421</td>
<td>Any type</td>
<td>0·68</td>
<td>0·42–1·03</td>
<td></td>
<td>Age and gender</td>
</tr>
<tr>
<td>Rouhiainen et al. (1996)(12)</td>
<td>Finland</td>
<td>Cohort</td>
<td>44–63</td>
<td>410</td>
<td>–</td>
<td>Cortical</td>
<td>0·93</td>
<td>0·87–0·99</td>
<td>0·03</td>
<td>Not available</td>
</tr>
<tr>
<td>Leske et al. (1998)(13)</td>
<td>USA</td>
<td>Cohort</td>
<td>40+</td>
<td>744</td>
<td>–</td>
<td>Nuclear</td>
<td>0·58</td>
<td>0·36–0·94</td>
<td>0·03</td>
<td>Age, energy intake, smoking, alcohol consumed per week and (in the vitamin E model) percentage of energy intake as linoleic acid</td>
</tr>
<tr>
<td>Lyle et al. (1999)(46)</td>
<td>USA</td>
<td>Case–control</td>
<td>50–86</td>
<td>652</td>
<td>252</td>
<td>Any type</td>
<td>0·50</td>
<td>0·20–1·10</td>
<td>0·07</td>
<td>Age, smoking, history of heavy alcohol consumption, serum cholesterol concentration and BMI</td>
</tr>
<tr>
<td>Gale et al. (2001)(48)</td>
<td>England</td>
<td>Cross-sectional</td>
<td>66–75</td>
<td>412</td>
<td>53</td>
<td>Nuclear</td>
<td>0·60</td>
<td>0·30–1·30</td>
<td>0·67</td>
<td>Age, gender, social class, BMI, glycylated Hb, serum cholesterol, smoking, use of steroids in previous 5 years and alcohol intake</td>
</tr>
<tr>
<td>Jacques et al. (2001)(49)</td>
<td>USA</td>
<td>Cohort</td>
<td>53–73</td>
<td>478</td>
<td>163</td>
<td>Nuclear</td>
<td>0·48</td>
<td>0·25–0·95</td>
<td>0·08</td>
<td>Age, smoking, alcohol use, BMI and hypertension</td>
</tr>
<tr>
<td>Valero et al. (2002)(50)</td>
<td>USA</td>
<td>Case–control</td>
<td>55–74</td>
<td>692</td>
<td>343</td>
<td>Any type</td>
<td>0·93</td>
<td>0·56–1·52</td>
<td>0·28</td>
<td>Age, gender and energy intake</td>
</tr>
<tr>
<td>Taylor et al. (2002)(18)</td>
<td>USA</td>
<td>Cohort</td>
<td>53–73</td>
<td>462</td>
<td>112</td>
<td>Cortical</td>
<td>1·32</td>
<td>0·81–2·14</td>
<td></td>
<td>Age, smoking, alcohol use, BMI and hypertension</td>
</tr>
<tr>
<td>Ferrigno et al. (2005)(51)</td>
<td>Italy</td>
<td>Cross-sectional</td>
<td>55–75</td>
<td>1020</td>
<td>710</td>
<td>Any type</td>
<td>1·86</td>
<td>1·08–3·08</td>
<td></td>
<td>Age, gender, alcohol use, smoking, family history, diabetes and hypertension</td>
</tr>
<tr>
<td>Dherani et al. (2008)(54)</td>
<td>India</td>
<td>Cross-sectional</td>
<td>50+</td>
<td>1112</td>
<td>821</td>
<td>Any type</td>
<td>0·58</td>
<td>0·36–0·94</td>
<td>0·03</td>
<td>Age, sex, smoking, BMI and average systolic and blood pressure</td>
</tr>
<tr>
<td>Ravindran et al. (2011)(55)</td>
<td>India</td>
<td>Cross-sectional</td>
<td>60+</td>
<td>5638</td>
<td>4098</td>
<td>Any type</td>
<td>0·91</td>
<td>0·72–1·14</td>
<td>0·30</td>
<td>Age, sex, tobacco use, BMI, diastolic blood pressure, outdoor exposure, diabetes and socio-economic status</td>
</tr>
<tr>
<td>Pastor-Valero (2013)(56)</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>65+</td>
<td>593</td>
<td>433</td>
<td>Any type</td>
<td>0·51</td>
<td>0·27–0·96</td>
<td>0·03</td>
<td>Age, sex, BMI, energy intake, marital status, smoking, alcohol consumption, physical activity, use of supplements and history of diabetes</td>
</tr>
</tbody>
</table>

ARC, age-related cataract; RR, relative risk; PSC, posterior subcapsular cataract.

*Study ID is used in Fig. 4.
In recent years, a large body of literature has been performed to evaluate the relationship between vitamin E and risk of ARC based on populations. The results of those studies were conflicting. Generally each individual study had a relatively small number of participants and was underpowered for detecting the effect, thus a meta-analysis should be the appropriate approach to obtain a more definitive conclusion. Our meta-analysis, of twenty-seven articles including 245,531 individuals from different countries, afforded us a much higher possibility to reach reasonable conclusions regarding the association of dietary vitamin E intake, supplemental vitamin E intake, dietary and supplemental vitamin E intake, or serum tocopherol levels and ARC risk.

Overall, we found that dietary vitamin E intake, dietary and supplemental vitamin E intake, and high serum tocopherol levels were significantly associated with arc.

### Table 3 Pooled relative risks of the relationship between vitamin E and age-related cataract, and corresponding 95% confidence intervals

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of studies</th>
<th>Pooled RR*</th>
<th>95% CI</th>
<th>$P$ value for testing pooled RR</th>
<th>$I^2$ statistic (%)</th>
<th>$P$ value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary vitamin E intake</td>
<td>8</td>
<td>0.73</td>
<td>0.58, 0.92</td>
<td>0.007</td>
<td>69.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Supplemental vitamin E intake</td>
<td>10</td>
<td>0.92</td>
<td>0.78, 1.07</td>
<td>0.286</td>
<td>74.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dietary and supplement vitamin E intake</td>
<td>4</td>
<td>0.86</td>
<td>0.75, 0.99</td>
<td>0.029</td>
<td>47.1</td>
<td>0.129</td>
</tr>
<tr>
<td>Serum tocopherol</td>
<td>17</td>
<td>0.77</td>
<td>0.66, 0.91</td>
<td>0.002</td>
<td>52.1</td>
<td>0.007</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>5</td>
<td>0.83</td>
<td>0.62, 1.12</td>
<td>0.231</td>
<td>57.5</td>
<td>0.051</td>
</tr>
<tr>
<td>Case−control</td>
<td>5</td>
<td>0.67</td>
<td>0.51, 0.89</td>
<td>0.005</td>
<td>0.0</td>
<td>0.564</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>7</td>
<td>0.77</td>
<td>0.56, 1.07</td>
<td>0.118</td>
<td>61.2</td>
<td>0.017</td>
</tr>
<tr>
<td>ARC subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear</td>
<td>7</td>
<td>0.64</td>
<td>0.50, 0.81</td>
<td>0.006</td>
<td>44.1</td>
<td>0.097</td>
</tr>
<tr>
<td>Cortical</td>
<td>6</td>
<td>0.95</td>
<td>0.72, 1.25</td>
<td>0.716</td>
<td>52.7</td>
<td>0.061</td>
</tr>
<tr>
<td>PSC</td>
<td>5</td>
<td>1.13</td>
<td>0.76, 1.69</td>
<td>0.602</td>
<td>34.5</td>
<td>0.192</td>
</tr>
</tbody>
</table>

RR, relative risk; ARC, age-related cataract; PSC, posterior subcapsular cataract.

*When $I^2 \leq 50\%$, pooled RR (95% CI) was for fixed-effects model; otherwise, it was for random-effects model.

**Fig. 2** Forest plot for the pooled relative risk (RR) of dietary vitamin E intake and age-related cataract. The study-specific RR and 95% CI are represented by the grey square and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the diamond presents the pooled RR risk and its width represents the pooled 95% CI. D+L denotes the random-effect model; I−V denotes the fixed-effect model.

**Fig. 3** The dose–response analysis between dietary vitamin E intake and risk of age-related cataract. --- and --- represent the estimated relative risk (RR) and its 95% CI, respectively, from the spline model; ----- represents the linear model.

In recent years, a large body of literature has been performed to evaluate the relationship between vitamin E and risk of ARC based on populations. The results of those studies were conflicting. Generally each individual study had a relatively small number of participants and was underpowered for detecting the effect, thus a meta-analysis should be the appropriate approach to obtain a more definitive conclusion. Our meta-analysis, of twenty-seven articles including 245,531 individuals from different countries, afforded us a much higher possibility to reach reasonable conclusions regarding the association of dietary vitamin E intake, supplemental vitamin E intake, dietary and supplemental vitamin E intake, or serum tocopherol levels and ARC risk.

Overall, we found that dietary vitamin E intake, dietary and supplemental vitamin E intake, and high serum tocopherol levels were significantly associated with arc.
decreased risk of ARC. The findings from the dose–response analysis showed evidence of a non-linear association between dietary vitamin E intake and ARC. The risk of ARC decreased with dietary vitamin E intake from 7 mg/d. In addition, a protective role was found in the stratified analyses for serum tocopherol on nuclear cataract; and high serum tocopherol was found to have a positive effect on ARC in case–control studies. However, the association of supplemental vitamin E intake with ARC risk reduction was not statistically significant. Several reasons might be taken into consideration. First, the dose of supplementation used differed in the different original studies, and the use of high-dose vitamin E supplements may be associated with increased risk of ARC. Second, in the total of ten included studies on supplemental vitamin E intake and ARC risk, five were randomized controlled trials\textsuperscript{19,20,44,47,52} that were based on populations with different nutritional status. In addition, in two randomized controlled trials\textsuperscript{19,47} the subjects were volunteers, thus volunteer bias might be introduced. Third, in three of five randomized controlled trials\textsuperscript{19,44,47} and one cohort study\textsuperscript{13}, the intervention periods of less than 5 years are too short to influence the natural history of cataract development. Furthermore, ARC develops slowly over many years and might even require a long-term prevention rather than treatment; thus, perhaps it is better to start the preventive interventions at an earlier age within one’s lifetime.

The findings of our study have important clinical and public health implications with respect to ARC prevention. According to the dose–response analysis, a statistically significant decreased risk of developing ARC was shown with increasing dietary vitamin E intake from 7 mg/d.

Our meta-analysis suggested that vitamin E might have a significant beneficial effect on the prevention of ARC, especially nuclear cataract, in the analyses of serum tocopherol on ARC subtypes. This might be due to the fact that different cataract types are related to different risk factors and different pathophysiological processes\textsuperscript{60,61}. Cumulative oxidative stress might be more likely to result in depletion of the endogenous antioxidant defence.
system in the nucleus of the lens, which would reduce antioxidants uptake in this region and lead to inability to repair the damage (62–64).

Between-study heterogeneity is common in meta-analysis and it is essential to explore the potential sources of between-study heterogeneity. Hence, we conducted a meta-regression analysis on variables including publication year, study design, study conducted area and gender to explore the potential sources of between-study heterogeneity. However, these factors were not found to be sources of heterogeneity in our meta-analysis, but other possibilities related to ARC, such as variations in lifestyle and dietary practices, cannot be ruled out. The presence of heterogeneity indicates the need for consensus definitions for ARC and its subtypes in future studies.

To interpret our study results properly, it is necessary to understand several limitations. First, the potential contributions to the epidemiological criteria for causality are different in the various observational studies included in the present meta-analysis. With the exception of consistency, to which all designs contribute, and biological plausibility, to which no designs contribute directly, all three types of observational studies in our meta-analysis contribute to some but not all criteria including temporality, strength or dose–response, experimental confirmation and specificity. A prospective design meets the criteria of temporality and is less affected by biases than case–control and cross-sectional designs, so it is in the highest order of the strength of evidence in observational studies; while the other two designs usually have no temporality and are susceptible to biases, and the strength of evidence from these studies is weaker as a result. On the other hand, observational studies are closer to the real-life environment, which is more credible when making its corollary to reality, but the results are more susceptible to interference. In our meta-analysis, combined results from the three types of study design in serum tocopherol were inconsistent; stronger association was found in the combined results from case–control studies. However, an overstated association could be expected from the case–control studies because of recall or selection bias, and early symptoms in patients may have resulted in a change in dietary habits. Second, a meta-analysis is not able to solve problems with confounding factors that could be inherent in the included studies. Although most studies adjusted for other known risk factors for ARC, residual or unknown confounding cannot be excluded as a potential explanation for the observed findings. Third, the number of studies involved in the meta-analysis was insufficient and we could only perform dose–response analysis on dietary vitamin E intake. Finally, in a meta-analysis of published studies, it is possible that an observed association might suffer from publication bias because studies with null results tend not to be published. However, no significant publication bias was detected in our meta-analysis.

Conclusion

In summary, results from the present meta-analysis suggest that increasing dietary vitamin E intake, dietary and supplemental vitamin E intake, and high level of serum tocopherol might be significantly associated with reduced ARC risk.

Acknowledgements

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