**Dietary and Circulating Vitamin C, Vitamin E, β-carotene and Risk of Total Cardiovascular Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Observational Studies**

*Supplementary material including five supplemental tables and eight supplemental figures*

**Supplemental Table 1.** Search strategy to find the relevant articles for inclusion in the meta-analysis of dietary/circulating antioxidants and risk of total cardiovascular mortality.

|  |
| --- |
| **PubMed** |
| 1. vitamin C (All Fields)/ or ascorbate (All Fields)/ or ascorbic acid (All Fields) |
| 2. vitamin E (All Fields)/ or tocopherol (All Fields)/ or tocopherols (All Fields) |
| 3. alpha-tocopherol (All Fields)/ or α-tocopherol (All Fields)/or vitamin A (All Fields) |
| 4. retinol (All Fields)/ or Provitamin A (All Fields)/ or carotene (All Fields)/ or zinc (All Fields) |
| 5. carotenes (All Fields)/ or carotenoid (All Fields)/ or carotenoids (All Fields) |
| 6. alpha-carotene (All Fields)/ or α-carotene (All Fields)/ or β-carotene (All Fields) |
| 7. beta-carotene (All Fields)/ or lycopene (All Fields)/ or lutein (All Fields)/ or zeaxanthin (All Fields) |
| 8. beta-cryptoxanthin (All Fields)/ or β- cryptoxanthin (All Fields)/ or selenium (All Fields) |
| 9. total antioxidant capacity (All Fields)/ or TAC (All Fields) |
| 10. ferric ion reducing antioxidant power (All Fields)/ or FRAP (All Fields) |
| 11.total radical-trapping antioxidant parameter (All Fields)/ or TRAP (All Fields) |
| 12. oxygen radical absorbance capacity (All Fields)/ or ORAC (All Fields) |
| 13. antioxidant (All Fields)/ or antioxidants (All Fields)/ or oxidative stress (All Fields) |
| 14. prospective (All Fields)/or prospectively (All Fields) or longitudinal (All Fields) |
| 15. cohort (All Fields)/or cohorts (All Fields)/or observation (All Fields) |
| 16. observational (All Fields)/or follow up (All Fields)/ or nested (All Fields) |
| 17. death (All Fields)/or mortality (All Fields)/ or survival (All Fields) |
| 18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 |
| 19. 14 or 15 or 16 |
| 20. 17 and 18 |
| 21. 19 and 20 |
| **Scopus** |
| 1. vitamin C (Article title, Abstract, Keywords)/ or \*ascorbate (ti/Ab/Ke) |
| 2. ascorbic acid (ti/Ab/Ke)/ or vitamin E(ti/Ab/Ke)/ or tocopherol(ti/Ab/Ke) |
| 3. tocopherols (ti/Ab/Ke)/or alpha-tocopherol (ti/Ab/Ke)/ or α-tocopherol (ti/Ab/Ke) |
| 4. vitamin A(ti/Ab/Ke)/ or retinol (ti/Ab/Ke)/or Provitamin A(ti/Ab/Ke) |
| 5. carotene (ti/Ab/Ke)/ or carotenes (ti/Ab/Ke)/or carotenoid (ti/Ab/Ke) |
| 7. carotenoids (ti/Ab/Ke)/ or alpha-carotene (ti/Ab/Ke)/or α-carotene (ti/Ab/Ke) |
| 8. β-carotene (ti/Ab/Ke)/ or beta-carotene (ti/Ab/Ke)/or lycopene (ti/Ab/Ke) |
| 9. lutein (ti/Ab/Ke)/ or zeaxanthin (ti/Ab/Ke)/or beta-cryptoxanthin (ti/Ab/Ke) |
| 10. β- cryptoxanthin (ti/Ab/Ke)/ or selenium (ti/Ab/Ke)/or TAC (ti/Ab/Ke) |
| 11. total antioxidant capacity (ti/Ab/Ke)/ or FRAP (ti/Ab/Ke) |
| 12. ferric ion reducing antioxidant power (ti/Ab/Ke)/ or TRAP (ti/Ab/Ke) |
| 13. total radical-trapping antioxidant parameter (ti/Ab/Ke)/ or ORAC (ti/Ab/Ke) |
| 14. oxygen radical absorbance capacity(ti/Ab/Ke) |
| 15. prospective (ti/Ab/Ke)/ or prospectively (ti/Ab/Ke)/ or longitudinal (ti/Ab/Ke) |
| 16. cohort (ti/Ab/Ke)/or cohorts (ti/Ab/Ke)/or observation (ti/Ab/Ke) |
| 17. observational (ti/Ab/Ke)/or follow-up (ti/Ab/Ke)/ or nested (ti/Ab/Ke) |
| 18. death (ti/Ab/Ke)/ or mortality (ti/Ab/Ke)/ or survival (ti/Ab/Ke) |
| 19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 |
| 20. 15 or 16 or 17 |
| 21. 18 and 19 |
| 22. 20 and 21 |

**Supplemental Table 2.** Subgroup analysis of vitamin C intake (highest versus lowest category) and risk of total cardiovascular mortality.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Number of studies | RR (95%CI) | I2 (%), *P*heterogeneity1 | *P*between2 |
| All studies |  | 10 | 0.79 (0.68-0.89) | 45.7, 0.06 | - |
| Sex |  |  |  |  |  |
| Men |  | 3 | 0.93 (0.85-1.00) | 61.7, 0.07 |  |
| Women |  | 3 | 0.91 (0.84-0.99) | 67.8, 0.05 |
| Region |  |  |  |  |  |
| US |  | 2 | 0.73 (0.02-1.44) | 89.4, 0.001 | 0.32 |
| Europe |  | 5 | 0.84 (0.70-0.98) | 6.8, 0.37 |
| Asia |  | 3 | 0.80 (0.72-0.88) | 0, 0.74 |
| Baseline mean age |  |  |  |  |  |
| < 60 years |  | 6 | 0.82 (0.72-0.91) | 31.0, 0.20 | 0.18 |
| > 60 years |  | 4 | 0.72 (0.45-1.00) | 60.2, 0.06 |
| Follow-up duration |  |  |  |  |  |
| < 10 years |  | 4 | 0.83 (0.75-0.92) | 0, 0.70 | 0.16 |
| > 10 years |  | 6 | 0.73 (0.54-0.93) | 62.2, 0.02 |
| Number of cases |  |  |  |  |  |
| < 500 |  | 6 | 0.75 (0.51-0.98) | 62.9, 0.02 | 0.25 |
| > 500 |  | 4 | 0.82 (0.75-0.89) | 0, 0.62 |
| Dietary assessment method |  |  |  |  |  |
| FFQ |  | 7 | 0.83 (0.76-0.90) | 0, 0.54 | 0.06 |
| Other |  | 3 | 0.69 (0.36-1.01) | 70.6, 0.03 |
| Assessment of intake |  |  |  |  |  |
| From food only |  | 7 | 0.83 (0.76-0.90) | 0, 0.67 | 0.004 |
| From food and supplement |  | 3 | 0.55 (0.26-0.85) | 54.5, 0.11 |
| Exclusion of baseline CVDs | Yes | 3 | 0.77 (0.57-0.96) | 38.4, 0.20 | 0.78 |
|  | No | 7 | 0.79 (0.65-0.94) | 54.7, 0.04 |
| Adjustments |  |  |  |  |  |
| Body mass index | Yes | 8 | 0.82 (0.75-0.90) | 5.5, 0.39 | 0.06 |
|  | No | 2 | 0.62 (0.16-1.08) | 81.8, 0.02 |
| Physical activity | Yes | 6 | 0.80 (0.72-0.87) | 0, 0.59 | 0.83 |
|  | No | 4 | 0.81 (0.53-1.09) | 76.5, 0.005 |
| Smoking status | Yes | 8 | 0.82 (0.75-0.90) | 5.5, 0.39 | 0.06 |
|  | No | 2 | 0.62 (0.16-1.08) | 81.8, 0.02 |
| Energy intake | Yes | 8 | 0.82 (0.75-0.90) | 5.5, 0.39 | 0.06 |
|  | No | 2 | 0.62 (0.16-1.08) | 81.8, 0.02 |
| Vitamin supplementation | Yes | 4 | 0.78 (0.67-0.90) | 0, 0.92 | 0.71 |
|  | No | 6 | 0.77 (0.60-0.95) | 68.7, 0.007 |
| 1 *P*-heterogeneity within subgroups with the use of a random-effects model.  2 *P*-heterogeneity between subgroups with the use of a fixed-effects model.  Abbreviations: CVD, cardiovascular disease; FFQ, food frequency questionnaire; RR, relative risk. | | | | | |

**Supplemental Table 3.** Subgroup analysis of circulating C (highest versus lowest category) and risk of total cardiovascular mortality.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Number of studies | RR (95%CI) | *I*2 (%), *P*heterogeneity1 | *P*between2 |
| All studies |  | 6 | 0.60 (0.42-0.78) | 64.7, 0.01 | - |
| Region |  |  |  |  |  |
| US |  | 3 | 0.75 (0.61-0.89) | 0, 0.51 | 0.002 |
| Europe |  | 3 | 0.46 (0.26-0.67) | 41.6, 0.18 |
| Baseline mean age |  |  |  |  |  |
| < 60 years |  | 3 | 0.62 (0.30-0.94) | 85.7, 0.001 | 0.83 |
| > 60 years |  | 3 | 0.58 (0.38-0.78) | 0, 0.95 |
| Follow-up duration |  |  |  |  |  |
| < 10 years |  | 2 | 0.37 (0.17-0.58) | 13.2, 0.28 | 0.001 |
| > 10 years |  | 4 | 0.72 (0.60-0.84) | 0, 0.54 |
| Number of cases |  |  |  |  |  |
| < 500 |  | 4 | 0.46 (0.30-0.62) | 17.2, 0.31 | 0.002 |
| > 500 |  | 2 | 0.78 (0.63-0.92) | 0, 0.86 |
| Adjustments |  |  |  |  |  |
| Body mass index | Yes | 4 | 0.61 (0.35-0.88) | 78.6, 0.003 | 0.88 |
|  | No | 2 | 0.58 (0.36-0.81) | 0, 0.74 |
| Physical activity | Yes | 2 | 0.74 (0.58-0.90) | 0, 0.38 | 0.02 |
|  | No | 4 | 0.55 (0.32-0.78) | 63.5, 0.04 |
| Smoking status | Yes | 4 | 0.61 (0.35-0.88) | 78.6, 0.003 | 0.88 |
|  | No | 2 | 0.58 (0.36-0.81) | 0, 0.74 |
| Vitamin supplementation | Yes | 3 | 0.55 (0.22-0.88) | 83.3, 0.003 | 0.39 |
|  | No | 3 | 0.66 (0.49-0.84) | 0, 0.49 |
| 1 *P*-heterogeneity within subgroups with the use of a random-effects model.  2 *P*-heterogeneity between subgroups with the use of a fixed-effects model.  Abbreviations: FFQ, food frequency questionnaire; RR, relative risk. | | | | | |

**Supplemental Table 4.** Subgroup analysis of vitamin E intake (highest versus lowest category) and risk of total cardiovascular mortality.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Number of studies | RR (95%CI) | I2 (%), *P*heterogeneity1 | *P*between2 |
| All studies |  | 8 | 0.92 (0.79-1.03) | 51.3, 0.04 | - |
| Region |  |  |  |  |  |
| US |  | 1 | 1.07 (0.74-1.41) | - | 0.26 |
| Europe |  | 4 | 0.83 (0.55-1.11) | 71.0, 0.01 |
| Asia |  | 3 | 0.94 (0.84-1.03) | 4.0, 0.35 |
| Baseline mean age |  |  |  |  |  |
| < 60 years |  | 5 | 0.95 (0.87-1.04) | 0, 0.57 | 0.01 |
| > 60 years |  | 3 | 0.76 (0.41-1.11) | 70.3, 0.03 |
| Follow-up duration |  |  |  |  |  |
| < 10 years |  | 3 | 0.86 (0.56-1.16) | 80.0, 0.007 | 0.80 |
| > 10 years |  | 5 | 0.91 (0.81-1.01) | 7.8, 0.36 |
| Number of cases |  |  |  |  |  |
| < 500 |  | 4 | 0.84 (0.54-1.13) | 69.4, 0.02 | 0.07 |
| > 500 |  | 4 | 0.95 (0.86-1.03) | 0, 0.48 |
| Dietary assessment method |  |  |  |  |  |
| FFQ |  | 6 | 0.91 (0.78-1.04) | 57.0, 0.04 | 0.75 |
| other |  | 2 | 0.91 (0.52-1.30) | 61.1, 0.11 |
| Adjustments |  |  |  |  |  |
| Body mass index | Yes | 7 | 0.89 (0.77-1.02) | 54.5, 0.04 | 0.27 |
|  | No | 1 | 1.13 (0.74-1.52) | - |
| Physical activity | Yes | 5 | 0.84 (0.69-1.00) | 64.0, 0.03 | 0.12 |
|  | No | 3 | 1.05 (0.88-1.21) | 0, 0.86 |
| Smoking status | Yes | 6 | 0.91 (0.78-1.04) | 57.0, 0.04 | 0.59 |
|  | No | 2 | 0.91 (0.52-1.30) | 61.1, 0.11 |
| Energy intake | Yes | 7 | 0.89 (0.77-1.02) | 54.5, 0.04 | 0.27 |
|  | No | 1 | 1.13 (0.74-1.52) | - |
| 1 *P*-heterogeneity within subgroups with the use of a random-effects model.  2 *P*-heterogeneity between subgroups with the use of a fixed-effects model.  Abbreviations: FFQ, food frequency questionnaire; RR, relative risk. | | | | | |

**Supplemental Table 5.** Subgroup analysis of circulating β-carotene (highest versus lowest category) and risk of total cardiovascular mortality.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Number of studies | RR (95%CI) | I2 (%), *P*heterogeneity1 | *P*between2 |
| All studies |  | 6 | 0.68 (0.52-0.83) | 50.1, 0.07 | - |
| Region |  |  |  |  |  |
| US |  | 2 | 0.75 (0.42-1.08) | 63.2, 0.10 | 0.44 |
| Europe |  | 4 | 0.65 (0.45-0.83) | 55.3, 0.08 |
| Baseline mean age |  |  |  |  |  |
| < 60 years |  | 3 | 0.64 (0.39-0.89) | 67.8, 0.04 | 0.22 |
| > 60 years |  | 3 | 0.75 (0.57-0.92) | 13.8, 0.31 |
| Follow-up duration |  |  |  |  |  |
| < 10 years |  | 2 | 0.58 (0.30-0.86) | 0, 0.89 | 0.37 |
| > 10 years |  | 4 | 0.70 (0.50-0.89) | 67.4, 0.03 |
| Number of cases |  |  |  |  |  |
| < 500 |  | 5 | 0.63 (0.47-0.79) | 43.7, 0.13 | - |
| > 500 |  | 1 | 0.91 (0.65-1.18) | - |
| Adjustments |  |  |  |  |  |
| Body mass index | Yes | 4 | 0.64 (0.41-0.88) | 40.6, 0.11 | 0.46 |
|  | No | 2 | 0.71 (0.47-0.96) | 70.5, 0.07 |
| Physical activity | Yes | 3 | 0.67 (0.33-1.01) | 65.0, 0.06 | 0.83 |
|  | No | 3 | 0.68 (0.50-0.87) | 53.0, 0.19 |
| Smoking status | Yes | 4 | 0.64 (0.41-0.88) | 50.6, 0.11 | 0.46 |
|  | No | 2 | 0.71 (0.47-0.96) | 70.5, 0.07 |
| 1 *P*-heterogeneity within subgroups with the use of a random-effects model.  2 *P*-heterogeneity between subgroups with the use of a fixed-effects model.  Abbreviations: FFQ, food frequency questionnaire; RR, relative risk. | | | | | |

Studies included in quantitative synthesis (meta-analysis)  
(n = 18)

Records excluded   
(n =14995)

Records screened   
(n = 15141)

Records after duplicates removed   
(n = 15141)

## Identification

## Eligibility

## Included

## Screening

Additional records identified through other sources   
(n = 6)

Records identified through database searching   
(n = 17296)

Full-text articles excluded, with reasons   
(n = 129)

72 for not relevant exposure/outcomes 16 clinical trials 15 reviews 13 in patients 4 with composite outcomes 4 duplicates 3 without risk estimates 1 combined exposures 1 abstract

Full-text articles assessed for eligibility   
(n = 146)

Studies included in qualitative synthesis   
(n = 17)

**Supplemental Fig. 1.** Search strategy to find the potential relevant studies for inclusion in the meta-analysis of dietary and circulating antioxidants and risk of total cardiovascular mortality.

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**Supplemental Fig. 2**. Relative risk of cardiovascular mortality for the highest compared with the lowest category of dietary vitamin C intake. ES, effect size; M, Shanghai Men's Health Study; W, Shanghai Women's Health Study.

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**Supplemental Fig. 3**. Funnel plot of the relative risks of 10 studies on dietary vitamin C and risk of cardiovascular mortality. Begg’s test *P*=0.86, Egger’s test *P*=0.33. Log RR: natural logarithm of relative risk. S.E: standard error.

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**Supplemental Fig. 4**. Relative risk of cardiovascular mortality for the highest compared with the lowest category of circulating vitamin C concentration. ES, effect size.

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**Supplemental Fig. 5**. Relative risk of cardiovascular mortality for the highest compared with the lowest category of dietary vitamin E intake. ES, effect size; M, Shanghai Men's Health Study; W, Shanghai Women's Health Study.

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**Supplemental Fig. 6**. Relative risk of cardiovascular mortality for the highest compared with the lowest category of circulating α-tocopherol concentration. ES, effect size.

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**Supplemental Fig. 7**. Relative risk of cardiovascular mortality for the highest compared with the lowest category of dietary β-carotene intake. ES, effect size.

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**Supplemental Fig. 8**. Relative risk of cardiovascular mortality for the highest compared with the lowest category of circulating β-carotene concentration. ES, effect size.