

Appendix Table 4. Adverse Effects of Multivitamin and Mineral Supplement Use

| Study, Year<br>(Reference)                              | Study Design | Type of<br>Supplementation                                                                                 | Frequency and Adverse Effect<br>Duration of<br>Use | Occurrence of Adverse Effects, <i>n</i><br>(%)                       |                                                                                                                                    | Relative Risk<br>(99% CI)                              | <i>P</i> Value   | Comment |                                                                                                                                                                                                                                                            |
|---------------------------------------------------------|--------------|------------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|------------------|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                         |              |                                                                                                            |                                                    | Treatment Group                                                      | Placebo Group                                                                                                                      |                                                        |                  |         |                                                                                                                                                                                                                                                            |
| REACT, 2002<br>(27)                                     | RCT          | β-Carotene, 18 mg + vitamin C, 750 mg + <i>all-rac</i> α-tocopherol acetate, 600 mg vs. placebo (corn oil) | 3 divided doses daily (with meals) for 3 y         | Intercurrent illness                                                 | 107                                                                                                                                | 84                                                     | –                | NS      | Persons who completed the study and those who dropped out did not differ; proportions of early dropouts and late dropouts were very similar; frequency of side effects (defined by the World Health Organization) did not differ between randomized groups |
|                                                         |              |                                                                                                            |                                                    | Death                                                                | 9 (coronary thrombosis, renal-cell cancer, throat cancer, carcinomatosis, esophagitis, sudden death, aneurysm, pulmonary fibrosis) | 3 (coronary thrombosis, bile duct cancer, lung cancer) | –                | 0.07    |                                                                                                                                                                                                                                                            |
|                                                         |              |                                                                                                            |                                                    | Skin yellowing                                                       | –                                                                                                                                  | –                                                      | –                | –       |                                                                                                                                                                                                                                                            |
| AREDS cataract study, 2001 (28)                         | RCT          | Vitamin C, 500 mg + vitamin E, 400 IU + β-carotene, 15 mg vs. placebo                                      | 2 divided doses (with meals) for 6.3 y             | Hospitalization (due to mild to moderate symptoms)                   | 173 (7.3)                                                                                                                          | 221 (9.3)                                              | –                | 0.01    | No clinically or statistically significant difference in changes in cholesterol level or hematocrit                                                                                                                                                        |
|                                                         |              |                                                                                                            |                                                    | Primary adverse effect (caused by skin subcutaneous tissue problems) | 56 (2.4)                                                                                                                           | 21 (0.9)                                               | –                | <0.001  |                                                                                                                                                                                                                                                            |
|                                                         |              |                                                                                                            |                                                    | Change in skin color                                                 | 203 (8.6)                                                                                                                          | 146 (6.1)                                              |                  | <0.01   |                                                                                                                                                                                                                                                            |
|                                                         |              |                                                                                                            |                                                    | Chest pain                                                           | 467 (19.8)                                                                                                                         | 541 (22.8)                                             |                  | 0.01    |                                                                                                                                                                                                                                                            |
|                                                         |              |                                                                                                            |                                                    | Death                                                                | 251                                                                                                                                | 240                                                    | 1.06 (0.84-1.33) | 0.53    |                                                                                                                                                                                                                                                            |
| AREDS age-related macular degeneration study, 2001 (29) | RCT          | Antioxidants (vitamin C, 500 mg + vitamin E, 400 IU + β-carotene, 15 mg) vs. no antioxidants               | 2 divided doses (with meals) for 6.3 y             | Yellow skin                                                          | 151 (8.3)                                                                                                                          | 106 (6.0)                                              | –                | 0.008   | No clinically or statistically significant difference in changes in cholesterol level or hematocrit                                                                                                                                                        |
|                                                         |              |                                                                                                            |                                                    | Hospitalization due to mild to moderate                              | 135 (7.4)                                                                                                                          | 181 (10.1)                                             | –                | 0.005   |                                                                                                                                                                                                                                                            |

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|                        |     |                                                                                                                                                                                                                                  |                           | symptoms (e.g., chest pain or discomfort, vasovagal episode, fever) |              |              |                   |       |                                                                                                                                                                                                                                                                      |  |
|                        |     |                                                                                                                                                                                                                                  |                           | Hospitalization due to infections                                   | 29 (1.6)     | 15 (0.8)     | –                 | 0.04  |                                                                                                                                                                                                                                                                      |  |
|                        |     |                                                                                                                                                                                                                                  |                           | Skin and subcutaneous tissue conditions                             | 41 (2.2)     | 18 (1.0)     | –                 | 0.003 |                                                                                                                                                                                                                                                                      |  |
|                        |     |                                                                                                                                                                                                                                  |                           | Circulatory adverse experience                                      | 6 (0.3)      | 15 (0.8)     | –                 | 0.04  |                                                                                                                                                                                                                                                                      |  |
|                        |     |                                                                                                                                                                                                                                  |                           | Mortality                                                           | 216          | 194          | 1.10 (0.85 –1.42) | 0.35  | Similar results when comparing antioxidants and placebo.                                                                                                                                                                                                             |  |
| MONMD, 1996 (26)       | RCT | $\beta$ -Carotene, 20 000 IU + vitamin E, 200 IU + vitamin C, 750 mg + zinc picolinate, 12.5 mg + selenium, 50 mcg + vitamin B <sub>2</sub> , 25 mg + chromium, 100 $\mu$ g + non-vitamin/mineral nutrients vs. placebo (starch) | 2 divided doses for 18 mo | Diffuse whole-body maculopapular rash                               | 1            | –            | –                 | –     | Possible adverse reaction or cross-reaction with hypertensive medication (hydrochlorothiazide and atenolol)                                                                                                                                                          |  |
|                        |     |                                                                                                                                                                                                                                  |                           | Transient diarrhea                                                  | –            | –            | –                 | –     | No significant difference between randomized groups in changes in diarrhea, constipation, nausea, vomiting, and dyspeptic symptoms                                                                                                                                   |  |
| Xuan et al., 1991 (31) | RCT | Placebo, A, B, AB, C, AC, BC, ABC, D, AD, BD, ABD, CD, ACD, BCD, and ABCD, where A = retinol, 25 000 IU/d; B = $\beta$ -carotene, 50 mg/d; C = $\alpha$ -tocopherol, 800 IU/d; D = selenium, 400 $\mu$ g/d                       | Once daily for 6 mo       | See comments                                                        | See comments | See comments | –                 | –     | 83% ever smoked; median age, 54 y; Symptoms (muscle cramps, diarrhea, decreased appetite, runny nose, joint pain, lip chapping, yellowing of skin, broken nails, hair loss, tingling in limbs, headache, lethargy) were generally improved in the intervention group |  |
|                        |     |                                                                                                                                                                                                                                  |                           | Allergic dermatitis                                                 | 1            | –            | –                 | –     | These dropout cases (1 with allergic dermatitis and 2 with continued gastric pain)                                                                                                                                                                                   |  |

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|                          |             |                                                                                                                                           |                     |                                                                                                                                            |                              |   |   |   | may have occurred for reasons related to supplement use, but the types of supplements used were not reported                                                                                            |
| Grouhi et al., 2000 (32) | Case report | Niacin, 240 mg (from multivitamin, B-complex, and anti-nausea tablets)                                                                    | NS                  | Gastric pain<br>Pseudoallergic toxic reaction                                                                                              | 2<br>1 (nonsmoker, age 40 y) | – | – | – | Multivitamin contained calcium, 100 mg; vitamin E, 800 IU; vitamin C, 300 mg; niacin, 40 mg; and selenium, 200 µg; the case patient also took echinacea, barley green, licorice root, and Chinese herbs |
| Gulati et al., 1999 (33) | Case report | Vitamin A acetate + vitamin E acetate + vitamin C + vitamin B <sub>2</sub> + copper sulfate + zinc sulfate + selenium dioxide monohydrate | NS                  | Fixed drug eruption (a pattern of cutaneous drug reaction which occurs at the same sites(s) each time the particular drug is administered) | 1 (Indian, age 58 y)         | – | – | – |                                                                                                                                                                                                         |
| Ohtake et al., 2005 (34) | Case report | Vitamin C, 6000 mg + calcium lactate, 1000 mg + vitamin D, 250 IU + laxatives                                                             | Once daily for 10 y | Severe proximal tubular dysfunction, calcified lesion, hypokalemic nephropathy                                                             | 1 (Japanese, age 48 y)       | – | – | – | Hypokalemic nephropathy probably was due to long-term use of laxatives, but the calcified lesion probably was due to massive oxalate load after excessive ingestion of vitamin C                        |

\*AREDS = Age-Related Eye Disease Study; MONMD = Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study; NS = not significant; RCT = randomized, controlled trial; REACT = Roche European American Cataract Trial.