

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

Study, Year (Reference)	Study Design	Type of Supplementation	Frequency and Duration of Use	Adverse Effect	Occurrence of Adverse Effects, n (%)		Relative Risk (99% CI)	P Value	Comment
					Treatment Group	Placebo Group			
REACT, 2002 (27)	RCT	β -Carotene, 18 mg + vitamin C, 750 mg + all-rac 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 and 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

Appendix Table 4—Continued

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					Treatment Group	Placebo Group			
				Hospitalization due to mild to moderate symptoms (e.g., chest pain or discomfort, vasovagal episode, fever)	135 (7.4)	181 (10.1)	–	0.005	
				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) for antioxidants vs. no antioxidants	0.35	Similar results when comparing antioxidants and placebo
MONMD, 1996 (26)	RCT	β -Carotene, 20 000 IU + vitamin E, 200 IU + vitamin C, 750 mg + zinc picolinate, 12.5 mg + selenium, 50 μ g + vitamin B ₂ , 25 mg + chromium, 100 μ 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 = β -carotene, 50 mg/d; C = α -tocopherol, 800 IU/d; D = selenium, 400 μ 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

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					Treatment Group	Placebo Group			
				Allergic dermatitis	1	–	–	–	These dropout cases (1 with allergic dermatitis and 2 with continued gastric pain) may have occurred for reasons related to supplement use, but the types of supplements used were not reported
				Gastric pain	2				
Grouhi and Sussman 2000 (32)	Case report	Niacin, 240 mg (from multivitamin, B-complex, and anti-nausea tablets)	NS	Pseudoallergic toxic reaction	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 ₂ + copper sulfate + zinc sulfate + selenium dioxide monohydrate	NS	Fixed drug eruption (a pattern of cutaneous drug reaction which occurs at the same site or sites 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.