

## Supplementary Material

### Effects of Cocoa Extract Supplementation and Multivitamin/Multimineral Supplements on Self-Reported Fractures in the Cocoa Supplement and Multivitamins Outcomes Study (COSMOS) Randomized Clinical Trial

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**Supplemental Table 1. Composition of the COSMOS Centrum Silver Supplement**

<b>Vitamin or mineral (units)</b>	<b>Amount</b>	<b>% Daily Value</b> (* Daily Value not established)
Biotin (µg)	30	10
Boron (µg)	-	-
Calcium (mg)	220	22
Chloride (mg)	72	2
Chromium (µg)	50	42
Copper (mg)	0.5	25
Folic Acid (µg)	400	100
Iodine (µg)	150	100
Iron (mg)	-	-
Lutein (µg)	250	*
Lycopene (µg)	300	*
Magnesium (mg)	50	13
Manganese (mg)	2.3	115
Molybdenum (µg)	45	60
Niacin (mg)	20	100
Nickel (µg)	5	*
Pantothenic Acid (mg)	10	100
Phosphorus (mg)	20	2
Potassium (mg)	80	2
Riboflavin (mg)	1.7	100
Selenium (µg)	19	27
Silicon (mg)	2	*
Thiamin (mg)	1.5	100
Vanadium (µg)	10	*
Vitamin A (IU)	2500 40% β-carotene	50
Vitamin B <sub>12</sub> (µg)	25	417
Vitamin B <sub>6</sub> (mg)	3	150
Vitamin C (mg)	60	100
Vitamin D (IU)	1000	250
Vitamin E (IU)	50	167
Vitamin K (µg)	30	38
Zinc (mg)	11	73

**Supplemental Table 2. Baseline characteristics of participants in the overall COSMOS cohort (21,442), according to randomized treatment assignment: Cocoa Extract Supplementation vs. Cocoa Extract Placebo**

Variable	All	Cocoa Extract	Cocoa Extract Placebo
<i>Demographic characteristics</i>			
<b>Age group, no. (%)</b>	N=21,442		
60-69	9224 (43.0%)	4610 (43.0%)	4614 (43.0%)
70-74	5774 (26.9%)	2886 (26.9%)	2888 (26.9%)
75-79	3751 (17.5%)	1876 (17.5%)	1875 (17.5%)
80-84	1761 (8.2%)	882 (8.2%)	879 (8.2%)
≥85	932 (4.4%)	465 (4.3%)	467 (4.4%)
<b>Body Mass Index group, no. (%), kg/m<sup>2</sup></b>	N=21,018		
<25	7070 (33.64%)	3584 (34.12%)	3486 (33.16%)
25 to <30	8230 (39.16%)	4062 (38.67%)	4168 (39.65%)
≥30	5718 (27.21%)	2859 (27.22%)	2859 (27.19%)
<i>Medical Conditions</i>			
<b>Diabetes</b>	N=21,433		
Yes	2864 (13.36%)	1417 (13.22%)	1447 (13.50%)
<b>Multiple Sclerosis</b>	N=21,239		
Yes	66 (0.31%)	32 (0.30%)	34 (0.32%)
<b>Parkinson's Disease</b>	N=21,278		
Yes	81 (0.38%)	33 (0.31%)	48 (0.45%)
<i>Medications (regular use)</i>			
<b>Use of diabetes medication</b>	N=21,433		
Yes	2233 (10.42%)	1099 (10.26%)	1134 (10.58%)
<b>Use of selective serotonin reuptake inhibitors</b>	N=21,116		
Yes	1622 (7.68%)	830 (7.85%)	792 (7.51%)
<b>Use of proton pump inhibitors</b>	N=21,188		
Yes	2424 (11.44%)	1237 (11.66%)	1187 (11.22%)
<b>Use of corticosteroids</b>	N=20,937		
Yes	587 (2.80%)	310 (2.96%)	277 (2.65%)
<b>Use of bone loss/osteoporosis medications*</b>	N=21,095		
Yes	1413 (6.70%)	720 (6.83%)	693 (6.57%)
<b>Use of thyroid hormone</b>	N=21,197		
Yes	3761 (17.74%)	1839 (17.35%)	1922 (18.14%)
<i>Behavioral Characteristics</i>			

Variable	All	Cocoa Extract	Cocoa Extract Placebo
<b>Sleep, hrs</b>	N=21,123		
<5	358 (1.69%)	175 (1.66%)	183 (1.73%)
5	1264 (5.98%)	638 (6.05%)	626 (5.92%)
6	4153 (19.66%)	2035 (19.28%)	2118 (20.04%)
7	8053 (38.12%)	4112 (38.97%)	3941 (37.28%)
8	5609 (26.55%)	2735 (25.92%)	2874 (27.19%)
9	1476 (6.99%)	749 (7.10%)	727 (6.88%)
≥10	210 (0.99%)	109 (1.03%)	101 (0.96%)
<b>Physical Activity</b>			
<b>Flights of stairs climbed daily</b>	N=21,019		
None	5124 (24.38%)	2533 (24.14%)	2591 (24.62%)
1-2 flights	4647 (22.11%)	2314 (22.05%)	2333 (22.17%)
3-4 flights	3414 (16.24%)	1703 (16.23%)	1711 (16.26%)
5-9 flights	4051 (19.27%)	2022 (19.27%)	2029 (19.28%)
10-14 flights	2334 (11.10%)	1190 (11.34%)	1144 (10.87%)
15 or more	1449 (6.89%)	732 (6.98%)	717 (6.81%)
<b>Usual walking pace</b>	N=21,166		
Don't walk regularly	2381 (11.25%)	1161 (10.98%)	1220 (11.51%)
Easy (less than 2 mph)	3791 (17.91%)	1871 (17.70%)	1920 (18.12%)
Normal 2-2.9 mph	9585 (45.28%)	4792 (45.33%)	4793 (45.24%)
Brisk 3-3.9 mph	4919 (23.24%)	2489 (23.55%)	2430 (22.94%)
Very brisk 4 mph or faster	490 (2.32%)	258 (2.44%)	232 (2.19%)
<b>Physical Function limitations in past 2 weeks</b>			
<b>Climbing a flight of stairs without stopping (N=21,007)</b>			
Extremely	420 (2.00%)	214 (2.04%)	206 (1.96%)
Quite a bit	459 (2.18%)	226 (2.15%)	233 (2.22%)
Moderately	803 (3.82%)	399 (3.80%)	404 (3.85%)
Slightly	2138 (10.18%)	1048 (9.98%)	1090 (10.38%)
Not at all	17187 (81.82%)	8618 (82.04%)	8569 (81.59%)
<b>Dressing yourself (N=21,103)</b>			
Extremely	23 (0.11%)	10 (0.09%)	13 (0.12%)
Quite a bit	31 (0.15%)	15 (0.14%)	16 (0.15%)

Variable	All	Cocoa Extract	Cocoa Extract Placebo
Moderately	91 (0.43%)	44 (0.42%)	47 (0.45%)
Slightly	378 (1.79%)	183 (1.73%)	195 (1.85%)
Not at all	20580 (97.52%)	10299 (97.61%)	10281 (97.43%)
<b>Hurrying (as if to catch a bus) or jogging (N=20,954)</b>			
Extremely	913 (4.36%)	454 (4.33%)	459 (4.38%)
Quite a bit	856 (4.09%)	416 (3.97%)	440 (4.20%)
Moderately	1048 (5.00%)	532 (5.08%)	516 (4.93%)
Slightly	2574 (12.28%)	1312 (12.52%)	1262 (12.05%)
Not at all	15563 (74.27%)	7768 (74.11%)	7795 (74.44%)
<b>Showering and bathing (N=21,111)</b>			
Extremely	33 (0.16%)	16 (0.15%)	17 (0.16%)
Quite a bit	43 (0.20%)	20 (0.19%)	23 (0.22%)
Moderately	138 (0.65%)	71 (0.67%)	67 (0.63%)
Slightly	456 (2.16%)	219 (2.07%)	237 (2.25%)
Not at all	20441 (96.83%)	10229 (96.91%)	10212 (96.74%)
<b>Walking one block on level ground (N=21,043)</b>			
Extremely	239 (1.14%)	117 (1.11%)	122 (1.16%)
Quite a bit	293 (1.39%)	148 (1.41%)	145 (1.38%)
Moderately	478 (2.27%)	242 (2.30%)	236 (2.24%)
Slightly	1204 (5.72%)	585 (5.56%)	619 (5.88%)
Not at all	18829 (89.48%)	9425 (89.62%)	9404 (89.34%)
<b>Doing yard work, housework, or carrying groceries (N=21,058)</b>			
Extremely	248 (1.18%)	125 (1.19%)	123 (1.17%)
Quite a bit	419 (1.99%)	188 (1.78%)	231 (2.19%)
Moderately	941 (4.47%)	473 (4.49%)	468 (4.45%)
Slightly	2718 (12.91%)	1399 (13.28%)	1319 (12.53%)
Not at all	16732 (79.46%)	8348 (79.26%)	8384 (79.66%)
<b>General Health, Self-reported</b>	N=20,975		
Excellent	5633 (26.86%)	2859 (27.25%)	2774 (26.46%)
Very Good/Good	14709 (70.13%)	7321 (69.79%)	7388 (70.46%)
Fair/Poor	633 (3.02%)	310 (2.96%)	323 (3.08%)

**Supplemental Table 3. Baseline characteristics of participants in the overall COSMOS cohort (21,442), according to randomized treatment assignment: Multivitamin/Multimineral Supplementation vs. Placebo**

Variable	All <sup>1</sup>	Multivitamin/Multimineral Supplementation	Placebo
<i>Demographic characteristics</i>			
<b>Age group, no. (%)</b>			
60-69	9224 (43.0%)	4611 (43.0%)	4613 (43.0%)
70-74	5774 (27.0%)	2886 (26.9%)	2888 (26.9%)
75-79	3751 (17.5%)	1875 (17.5%)	1876 (17.5%)
80-84	1761 (8.2%)	889 (8.3%)	872 (8.1%)
≥85	932 (4.4%)	459 (4.3%)	473 (4.4%)
<b>Body Mass Index group, no. (%), kg/m<sup>2</sup></b>			
<25	7070 (33.6%)	3533 (33.7%)	3537 (33.6%)
25 to <30	8230 (39.16%)	4166 (39.7%)	4064 (38.6%)
≥30	5718 (27.21%)	2800 (26.7%)	2918 (27.7%)
<i>Medical Conditions</i>			
<b>Diabetes</b>	N=21433		
Yes	2864 (13.4%)	1415 (13.2%)	1449 (13.5%)
<b>Multiple Sclerosis</b>	N=21239		
Yes	66 (0.3%)	38 (0.4%)	28 (0.3%)
<b>Parkinson's Disease</b>	N=21278		
Yes	81 (0.4%)	32 (0.3%)	49 (0.5%)
<i>Medications (regular use)</i>			
<b>Use of diabetes medication</b>	N=21433		
Yes	2233 (10.4%)	1098 (10.3%)	1135 (10.6%)
<b>Use of selective serotonin reuptake inhibitors</b>	N=21,116		
Yes	1622 (7.7%)	767 (7.3%)	855 (8.1%)
<b>Use of proton pump inhibitors</b>	N=21,188		
Yes	2424 (11.4%)	1178 (11.1%)	1246 (11.8%)
<b>Use of corticosteroids</b>	N=20,937		
Yes	587 (2.8%)	265 (2.5%)	322 (3.1%)

<sup>1</sup> Information was lacking regarding ethnicity in 863 participants, body mass index in 424 participants, and leisure time physical activity in 258 participants.

Variable	All <sup>1</sup>	Multivitamin/Multimineral Supplementation	Placebo
<b>Use of prescription osteoporosis medications<sup>2</sup></b>	N=21,095		
Yes	1413 (6.7%)	685 (6.5%)	728 (6.9%)
<b>Use of thyroid hormone</b>	N=21,197		
Yes	3761 (17.7%)	1881 (17.8%)	1880 (17.7%)
<b><i>Behavioral Characteristics</i></b>			
<b>Sleep, hrs</b>	N=21123		
<5	358 (1.7%)	181 (1.7%)	177 (1.7%)
5	1264 (6.0%)	647 (6.1%)	617 (5.9%)
6	4153 (19.7%)	2073 (19.6%)	2080 (19.7%)
7	8053 (38.1%)	3991 (37.8%)	4062 (38.5%)
8	5609 (26.6%)	2825 (26.7%)	2784 (26.4%)
9	1476 (7.0%)	750 (7.1%)	726 (6.9%)
≥10	210 (1.0%)	105 (1.0%)	105 (1.0%)
<b><i>Physical Activity</i></b>			
<b>Flights of stairs climbed daily</b>	N=21019		
None	5124 (24.4%)	2558 (24.3%)	2566 (24.4%)
1-2 flights	4647 (22.1%)	2307 (21.9%)	2340 (22.3%)
3-4 flights	3414 (16.2%)	1715 (16.3%)	1699 (16.2%)
5-9 flights	4051 (19.3%)	2020 (19.2%)	2031 (19.3%)
10-14 flights	2334 (11.1%)	1185 (11.3%)	1149 (10.9%)
15 or more	1449 (6.9%)	735 (7.0%)	714 (6.8%)
<b>Usual walking pace</b>	N=21166		
Don't walk regularly	2381 (11.3%)	1193 (11.3%)	1188 (11.2%)
Easy (less than 2 mph)	3791 (18.0%)	1901 (18.0%)	1890 (17.9%)
Normal 2-2.9 mph	9585 (45.3%)	4771 (45.1%)	4814 (45.5%)
Brisk 3-3.9 mph	4919 (23.2%)	2484 (23.5%)	2435 (23.0%)
Very brisk 4 mph or faster	490 (2.3%)	238 (2.3%)	252 (2.4%)
<b>Physical Function limitations in past 2 weeks</b>			
<b>Climbing a flight of stairs without stopping</b>	N=21007		
Extremely	420 (2.0%)	215 (2.1%)	205 (2.0%)

<sup>2</sup> alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, raloxifene, or calcitonin

Variable	All <sup>1</sup>	Multivitamin/Multimineral Supplementation	Placebo
Quite a bit	459 (2.2%)	234 (2.2%)	225 (2.1%)
Moderately	803 (3.8%)	390 (3.7%)	413 (3.9%)
Slightly	2138 (10.2%)	1037 (9.9%)	1101 (10.5%)
Not at all	17187 (81.8%)	8623 (82.1%)	8564 (81.5%)
<b>Dressing yourself</b>	(N=21,103)		
Extremely	23 (0.1%)	16 (0.2%)	7 (0.1%)
Quite a bit	31 (0.2%)	18 (0.2%)	13 (0.1%)
Moderately	91 (0.4%)	44 (0.4%)	47 (0.5%)
Slightly	378 (1.8%)	191 (1.8%)	187 (1.8%)
Not at all	20580 (97.5%)	10284 (97.5%)	10296 (97.6%)
<b>Hurrying (as if to catch a bus) or jogging</b>	(N=20,954)		
Extremely	913 (4.4%)	459 (4.4%)	454 (4.3%)
Quite a bit	856 (4.1%)	432 (4.1%)	424 (4.1%)
Moderately	1048 (5.0%)	499 (4.8%)	549 (5.2%)
Slightly	2574 (12.3%)	1252 (12.0%)	1322 (12.6%)
Not at all	15563 (74.3%)	7837 (74.8%)	7726 (73.8%)
<b>Showering and bathing</b>	(N=21,111)		
Extremely	33 (0.2%)	22 (0.2%)	11 (0.1%)
Quite a bit	43 (0.2%)	24 (0.2%)	19 (0.2%)
Moderately	138 (0.7%)	71 (0.7%)	67 (0.6%)
Slightly	456 (2.2%)	224 (2.1%)	232 (2.2%)
Not at all	20441 (96.8%)	10218 (96.8%)	10223 (96.9%)
<b>Walking one block on level ground</b>	(N=21,043)		
Extremely	239 (1.1%)	124 (1.2%)	115 (1.1%)
Quite a bit	293 (1.4%)	152 (1.5%)	141 (1.3%)
Moderately	478 (2.3%)	239 (2.3%)	239 (2.3%)
Slightly	1204 (5.7%)	573 (5.5%)	631 (6.0%)
Not at all	18829 (89.5%)	9429 (89.7%)	9400 (89.3%)
<b>Doing yard work, housework, or carrying groceries</b>	(N=21,058)		
Extremely	248 (1.2%)	129 (1.2%)	119 (1.1%)
Quite a bit	419 (2.0%)	217 (2.1%)	202 (1.9%)
Moderately	941 (4.5%)	466 (4.4%)	475 (4.5%)
Slightly	2718 (12.9%)	1320 (12.5%)	1398 (13.3%)
Not at all	16732 (79.5%)	8399 (79.8%)	8333 (79.2%)



**Supplemental Table 4. Locations of Prevalent Fractures Prior to Trial Enrollment**

Fracture location	Cocoa extract group (n = 10,719)	Cocoa extract placebo group (n = 10,723)	Multivitamin/Multimineral (MVM) Group (10,720)	MVM Placebo group (n = 10,722)
	n (%)	n (%)	n (%)	n (%)
Hip	135 (6.3)	116 (5.5%)	124 (6.0%)	127 (5.8%)
Clinical spine	111 (5.2%)	82 (3.9%)	83 (4.0%)	110 (5.1%)
Lower arm	412 (19.1%)	409 (19.5%)	392 (18.9%)	429 (19.7%)
Upper arm	185 (8.6%)	180 (8.6%)	192 (9.3%)	173 (8.0%)
Lower leg	277 (12.9%)	310 (14.8%)	298 (14.4%)	289 (13.3%)
Upper leg	60 (2.8%)	78 (3.7%)	68 (3.3%)	70 (3.2%)
Foot	582 (27.0%)	579 (27.7%)	559 (27.0%)	602 (27.7%)
Other	861 (40.0%)	803 (38.4)	825 (39.8%)	839 (38.6%)

**Supplemental Table 5. Effects of Multivitamin/Multimineral Supplementation (vs. Placebo) on Incident Fracture by Tertile of Alternative Healthy Eating Index Score, According to Fracture Location**

		# Events	HR (95% CI)
<b>Clinical</b>			
	Lowest tertile	561	0.99 (0.84-1.17)
	Middle tertile	629	1.02 (0.87-1.20)
	Highest tertile	660	1.27 (1.09-1.48)
<b>Hip</b>			
	Lowest tertile	52	0.85 (0.49-1.48)
	Middle tertile	59	1.05 (0.63-1.75)
	Highest tertile	57	1.61 (0.94-2.76)
<b>Nonvertebral</b>			
	Lowest tertile	528	1.01 (0.85-1.20)
	Middle tertile	581	1.01 (0.85-1.18)
	Highest tertile	624	1.27 (1.08-1.49)
<b>Clinical Spine</b>			
	Lowest tertile	40	0.89 (0.48-1.67)
	Middle tertile	57	1.13 (0.67-1.90)
	Highest tertile	51	1.45 (0.82-2.54)
<b>Forearm/wrist</b>			
	Lowest tertile	90	0.92 (0.60-1.39)
	Middle tertile	106	0.87 (0.59-1.27)
	Highest tertile	107	1.41 (0.96-2.07)
<b>Major osteoporotic</b>			
	Lowest tertile	229	0.90 (0.69-1.16)
	Middle tertile	282	1.02 (0.81-1.29)
	Highest tertile	279	1.41 (1.11-1.78)
<b>Pelvic</b>			
	Lowest tertile	20	0.43 (0.16-1.11)
	Middle tertile	29	0.61 (0.29-1.29)
	Highest tertile	34	1.06 (0.54-2.08)

**Supplemental Table 6. Effects of Multivitamin/Multimineral Supplementation (vs. Placebo) on Incident Fracture by Self-Rated General Health, According to Fracture Location**

			<b>Hazard Ratio (95% Confidence Interval)</b>
<b>Clinical</b>			
	Excellent	462	0.95 (0.80-1.15)
	Very good/good	1482	1.13 (1.02-1.25)
	Fair/poor	78	1.66 (1.04-2.65)
<b>Hip</b>			
	Excellent	34	0.85 (0.44-1.69)
	Very good/good	133	1.06 (0.76-1.49)
	Fair/poor	11	2.80 (0.72-10.87)
<b>Nonvertebral</b>			
	Excellent	431	0.96 (0.79-1.16)
	Very good/good	1393	1.13 (1.02-1.26)
	Fair/poor	70	1.72 (1.06-2.84)
<b>Clinical Spine</b>			
	Excellent	29	1.03 (0.50-2.13)
	Very good/good	118	1.30 (0.90-1.87)
	Fair/poor	13	1.85 (0.57-6.02)
<b>Forearm/wrist</b>			
	Excellent	78	1.09 (0.70-1.70)
	Very good/good	237	1.06 (0.82-1.37)
	Fair/poor	9	0.93 (0.25-3.55)
<b>Major osteoporotic</b>			
	Excellent	186	1.01 (0.76-1.35)
	Very good/good	629	1.11 (0.95-1.30)
	Fair/poor	39	1.87 (0.96-3.65)
<b>Pelvic</b>			
	Excellent	22	0.87 (0.38-2.03)
	Very good/good	63	0.66 (0.40-1.09)
	Fair/poor	4	-- <sup>3</sup>

<sup>3</sup> Number of cases inadequate for reliable estimation of hazard ratio.