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Long-term antioxidant supplementation has no effect on health-related quality of life: The randomized, double-blind, placebo-controlled, primary prevention SU.VI.MAX trial

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Background The effect of antioxidant vitamin and mineral supplementation on health is one of the most controversial issues in human nutrition. Our objective was to investigate the effect of nutritional doses of a combination of antioxidant vitamins and minerals on health-related quality of life (HRQoL) in a sample of healthy French adults.

Methods SU.VI.MAX is a randomized, double-blind, placebo-controlled, primary prevention trial in which a total of 8112 participants received a single capsule daily containing either placebo or vitamin C 120 mg, vitamin E 30 mg, beta-carotene 6 mg, selenium 100 μg and zinc 20 mg. Participants completed HRQoL questionnaires (SF36 and GHQ12) at baseline and after a mean of 76.0 ± 4.2 months.

Results Scores for physical dimensions tended to decrease over time, whereas those for mental dimensions tended to improve. No differences in changes over time were observed between the supplement and placebo groups. Participants who believed that they received placebo had lower HRQoL scores than did those who thought they had received supplements [SF36 Bodily pain (−3.3), General health (−2.2), Vitality (−1.6) dimensions and physical component summary score (−1.1) in men, and in SF36 Social functioning (−2.3), General health (−1.4) dimensions and physical component summary score (−0.7) in women].

Conclusions Long-term supplementation with antioxidant vitamins and minerals had no beneficial effect on HRQoL in this trial. This is contrary to conventional beliefs and claims that such an effect exists.

Trial Registration ''Primary Prevention Trial of the Health Effects of Antioxidant Vitamins and Minerals.'' NTC n 00272428 http://www.clinicaltrials.gov

Keywords Antioxidants, prevention trial, minerals, vitamins, health-related quality of life

Introduction

The effect of antioxidant vitamin and mineral supplementation on health is one of the most controversial issues in human nutrition. Randomized, placebo-controlled trials of long-term, high-dose administration of antioxidant micronutrients have failed to detect a benefit;[1–5] and two studies involving high-risk participants[2,3] suggested that the treatment may even be harmful. A recent meta-analysis concluded that high-dose ($\geqslant$400 IU/d) vitamin E supplements have a harmful effect on all-cause mortality.[6] Combining 47 low bias risk randomized trials, Bjelakovic *et al.*[7] showed a 5% mortality increase [95% confidence interval (CI) 1.02–1.08] in the group receiving antioxidant supplements.

Nevertheless, the use of antioxidant vitamins and minerals is widespread in the USA,[8–11] and is increasing in European countries.[12–16] Most people who take supplements do so because of the conventional beliefs that vitamins and minerals may have positive effects on health, well-being and quality of life,[16] and because of claims made by the manufacturers of the countless products currently on the market. The lack of controlled data to support the perception of benefit among consumers, and the numerous and diverse claims of manufacturers (particularly those related to perceived health),[17] may be due to the lack, until recently, of reliable tools with which to assess health as anything more than the absence of disease. However, advances in the assessment of health-related quality of life (HRQoL) now make it possible to measure health as perceived by participants themselves (an increasingly common secondary endpoint in clinical trials).

The present paper reports the application of generic measures in the 'SUpplementation en VItamines et Minéraux AntioXydants' (SU.VI.MAX) trial to assess the effect of long-term antioxidant supplementation on HRQoL used as a secondary endpoint. The primary objective of SU.VI.MAX was to test in a randomized, placebo-controlled trial whether an adequate and well-balanced intake of antioxidant nutrients reduces the incidence of cancers and ischaemic CVD in a middle-aged general population. Concerning the main results regarding primary criteria,[18] no effects were observed on ischaemic cardiovascular events, but a decrease in cancer incidence and in global mortality was observed in antioxidant recipient men during the supplementation period compared with the non-recipients. The nutritional doses used indicate that this result could equally well be achieved by dietary changes. The beneficial effect was not observed in women.[18]

Methods

Design and sampling

The methods, background and rationale of SU.VI.MAX are described in detail elsewhere.[18,19] In summary, 14 412 adults (women aged 35–60 years, men 45–60 years) living in France were selected from 79 976 volunteers enrolled after a national multimedia campaign (March–July 1994). Among the exclusion criteria were a history of disease likely to lead to rapid mortality, and supplementary use of relevant vitamins and minerals. Written informed consent was obtained from participants and the trial was approved by the local ethical committee (CCPPRB no. 706 Paris-Cochin Hospital, France) and by the National Committee for protection of Privacy and Civil Liberties (CNIL no. 334641).

Overall, 13 017 individuals were assigned at random to the supplement or placebo group. Immediately after randomization, 270 were no longer willing to participate, and six were found to be ineligible. The remaining 12 741 participants (5028 men and 7713 women) received a single capsule daily. The supplement group of 2520 men and 3844 women ($n=6364$) were given a combination of vitamin C (120 mg), vitamin E (30 mg), beta-carotene (6 mg), selenium (100 µg, as selenium-enriched yeast) and zinc (20 mg, as gluconate). The placebo group of 2508 men and 3869 women ($n=6377$) were given placebo capsules. Participants were given the capsules annually (either by mail or during a visit) packaged as 52 strips of seven (one strip per week). Random treatment allocation was performed by block-sequence generation, stratified by sex and age-group. Randomization was concealed from participants and all investigators other than the few who were responsible for labelling capsules. The absence of an easy way to distinguish antioxidant from placebo capsules was tested in a pilot study.[20]

Data collection

Biological and clinical data collection is described in detail elsewhere.[18,19] HRQoL was assessed using generic questionnaires: the MOS 36-item short form health survey (SF36)[21] and the 12-item General Health Questionnaire (GHQ-12).[22] The French version of the SF36 is a validated instrument[23] comprising 36 items that explore the following eight dimensions of health, mainly functional status and well-being: physical functioning, role limitations due to physical functioning (role-physical), social functioning, bodily pain, mental health, role limitations due to emotional functioning (role-emotional), vitality and general health perceptions. Standardized physical and mental health component summary scores were calculated according to American norms allowing for international comparisons. The French version of the GHQ-12 is widely used to screen for common mental disorders.[24] The questionnaire consists of 12 items with 4 modalities and a global psychological dimension.

Findings of interest for present purposes were the SF36 and GHQ-12 results at two time points: during the first year of inclusion (baseline) and during the seventh year of follow-up (final). Scores for the two instruments were calculated only if at least half of the

dimension items were present. All scales were scored from 0 (worst) to 100 (best possible HRQoL), allowing comparison of mean scores between the different dimensions. Standardized physical and mental health component summary scores are computed to have means of 50 and standard deviations (SDs) of 10 in the general US population.

A vertical visual analogue scale (0–100) exploring global health[25] was appended to the questionnaires. A transition question, adapted from the SF36 health transition question, requiring the participant to compare her/his health state at the time with that at baseline (from 'incomparably better' to 'incomparably worse') was added to the final measure, as was a question about any major health event experienced during the course of the trial.

All questionnaires were sent to participants by mail, filled out at home and collected during a medical visit.

Compliance was evaluated by asking participants to make a monthly declaration of the number of capsules they had forgotten to take. A questionnaire sent in September 2002 included a request for participants to declare any belief they might have about which group they were in.

Health events

Information about the occurrence of health events, including the main trial endpoints (i.e. death, cancer and ischaemic CVD, which were considered as major health events) was obtained directly from participants, their families, civil registers on vital status, or the results of screening tests and examinations performed during the annual visit. Procedures are described in detail elsewhere.[18]

Statistical analysis

Data were processed on an Alpha-VMS system, and a specific database was developed using SAS® version 8.2 (SAS Inc, Cary, NC).

HRQoL scores are presented as mean ± SD. Relationships between each initial HRQoL mean score and the initial characteristics of the participants [age, sex, body mass index (BMI), smoking habits, level of education, occupation or familial situation, level of beta-carotene] were tested using linear regression or analysis of variance depending on the type of variable.

The main hypotheses were tested using an analysis of variance with repeated measures (proc GLM SAS®). This allowed for calculation of a time effect adjusted for group, of a time-by-group effect—the test of interest for the null hypothesis of absence of change over time between the groups (within subject effect), and of a group effect adjusted for time (between subjects effect). The alpha type I error was set at 5%. When appropriated, HRQoL scores mean changes differences are presented with their 95% CI enclosed within brackets.

All analyses were stratified for sex, as HRQoL evolution differed between men and women.

With a repeated measures design, an alpha of 5%, a beta of 80%, an intertemporal correlation of ~0.5 and an SD of the measures of 10, 20, 30, about 1500 men and 2200 women per group allowed to show a score difference of respectively 1 and 0.9, 2.1 and 1.8, 3 and 2.5 between the groups (nQuery® software).

Results

A total of 10 618 participants (4299 males and 6319 females) completed the initial questionnaires: 5316 in the supplement group and 5302 in the placebo group. Among them, 3428 men and 4684 women also completed the final questionnaires. Thus, data from 4081 participants in the supplement group and 4031 in the placebo group were included in the final analysis (Figure 1). The characteristics of the supplement and placebo groups are presented in Table 1.

About 95% of the participants declared having taken at least two-thirds of their capsules throughout the follow-up period of a median of 77 months of supplementation (range: 45–93). There were no differences in capsule consumption between the two groups (86.3% in the supplement group vs 86.6% in the placebo group).

A total of 1243 participants (30.5%) in the supplement group and 1226 (30.4%) in the placebo group reported a health event (including 259 cases of cancer and 122 of ischaemic CVD) between inclusion in the trial and the final HRQoL measure. Major health event occurrence did not differ between the supplement and placebo groups (i.e. people who provided initial and final HRQoL measures): 120 vs 139 cancer, 65 vs 57 ischaemic CVD, respectively. The HRQoL of participants who declared health events differed from that of those who did not. This was true for almost all dimensions (initial values as well as changes differed).

In total, 1048 participants (359 males and 689 females) in the supplement group and 1075 participants (370 males and 705 females) in the placebo group did not fill in initial HRQoL questionnaires. Among those 2123 participants, 125 (65 and 60 in the supplement and placebo groups, respectively) developed cancer or non-fatal ischaemic disease, and 20 participants died (with 50% of deaths during the year following inclusion).

Of the 10 618 participants, 2506 filled in the initial questionnaire but not the final one. Among them, 86 and 88 in the supplement and placebo groups, respectively, developed cancer or non-fatal ischaemic disease, and 13 and 22 died.

Baseline HRQoL

The SF36 questionnaire resulted in high scores for physical functioning (92.9 ± 10.7 among men and

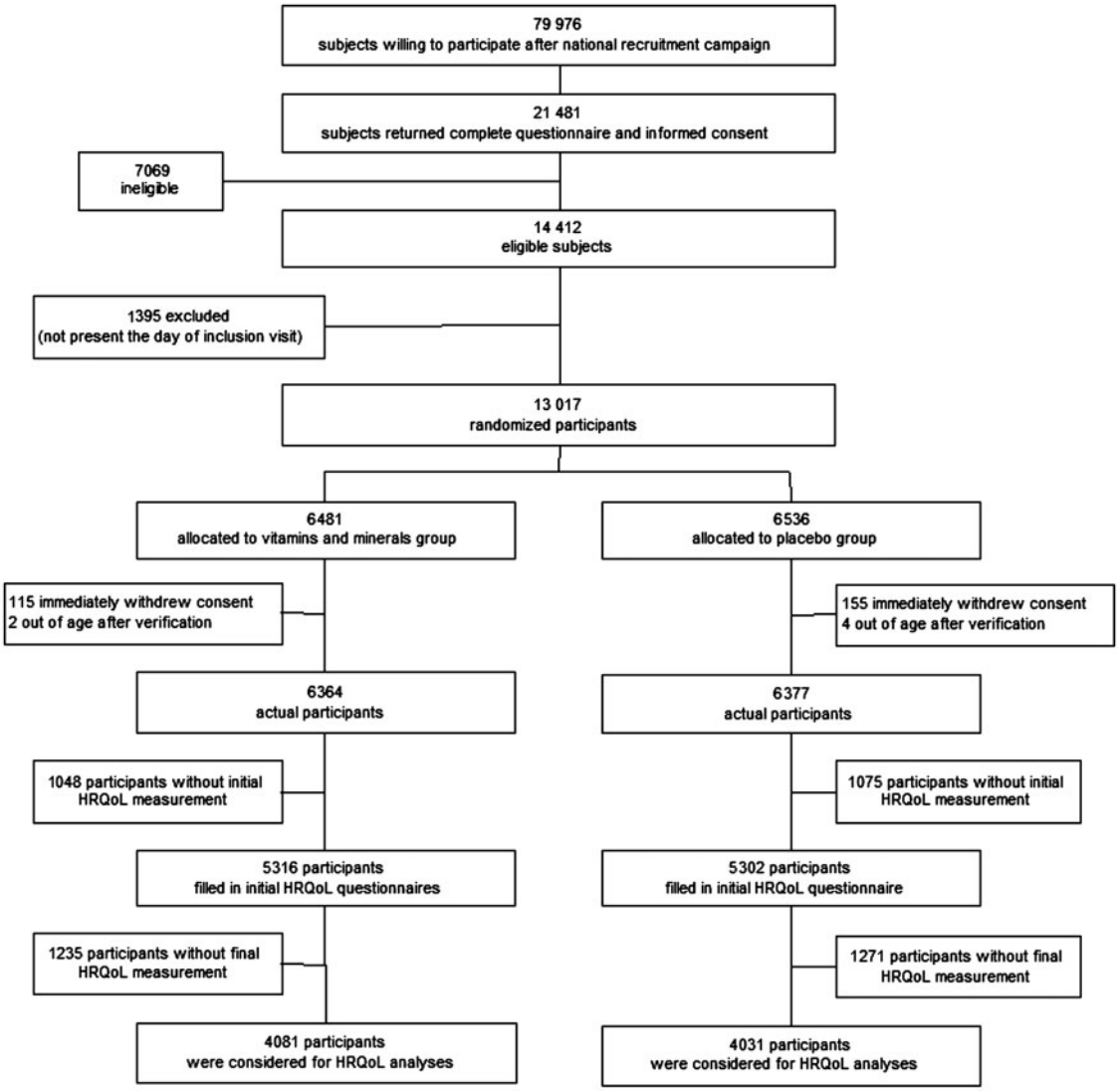

Figure 1 Flowchart of participant involvement

89.0 ± 14.2 among women), whereas those for the mental health dimension were comparatively low (71.1 ± 16.0 among men and 67.4 ± 17.6 among women). The vitality dimension produced the lowest scores among both men (63.7 ± 15.7) and women (57.5 ± 17.7). The mean physical summary scale was >50 (+2.6) with a standard deviation <10 (−4), and the mean mental summary scale was <50 (−1.1) with a standard deviation close to 10 (+0.4).

The GHQ12 score (71.1 ± 11.5 and 67.5 ± 13.9 among men and women, respectively) was close to the SF36 mental health dimension.

All scores were, as expected, consistently related to sex (lower among women), age, BMI and smoking habits. Physical dimensions were also positively correlated with the initial serum level of beta-carotene ($P = 0.0006$ for SF36-physical functioning and $P = 0.06$ for SF36-bodily pain) after adjustment for the other above predictors. Mental and social dimensions were related to level of education, occupation and familial situation (in any case, the HRQoL differences between modalities were <5 points).

Changes over time in HRQoL

The mean time between the two HRQoL measures was 76.0 (±4.2) months. Initial and final scores were linearly correlated for all dimensions; correlation coefficients ranged from 0.24 for SF36 role-physical to 0.63 for SF36 general health perceptions.

HRQoL scores changed in men and women, and with each instrument. The only exceptions were the SF36 role-physical, role-emotional and general health dimensions among men, and the SF36 role-physical dimension among women. All these changes were consistent between instruments and by sex.

Table 1 General and biological characteristics of the sample at baseline ($n=8112$), by sex and group

	Men		Women	
	Supplement ($n=1730$)	Placebo ($n=1698$)	Supplement ($n=2351$)	Placebo ($n=2333$)
Age in years [mean (SD)]	52.1 (4.7)	52.1 (4.7)	47.9 (6.5)	47.8 (6.6)
Occupation, *n* (%)				
Farmer, self-employed	128 (7.4)	143 (8.4)	98 (4.2)	99 (4.2)
Higher managerial and professional	608 (35.1)	550 (32.4)	395 (16.8)	361 (15.5)
Lower administration and manual	657 (38.0)	663 (39.0)	1262 (53.7)	1282 (55.0)
Not in employment	337 (19.5)	342 (20.1)	596 (25.4)	591 (25.3)
Level of education, *n* (%)				
Elementary school	397 (22.9)	438 (25.8)	471 (20.0)	477 (20.4)
Secondary school	462 (26.7)	450 (26.5)	586 (24.9)	625 (26.8)
University or equivalent	871 (50.3)	810 (47.7)	1294 (55.0)	1231 (52.8)
Family situation, *n* (%)				
Living with others	1548 (89.5)	1535 (90.4)	1885 (80.2)	1876 (80.4)
Living alone	182 (10.5)	163 (9.6)	466 (19.8)	457 (19.6)
Smoking habits, *n* (%)				
Non-smoker	595 (35.6)	594 (36.4)	1310 (57.4)	1312 (58.2)
Former smoker	847 (50.7)	823 (50.4)	654 (28.6)	657 (29.1)
Current smoker	228 (13.7)	217 (13.3)	319 (14.0)	285 (12.6)
BMI [in kg/m^2 mean (SD)]	25.0 (2.9)	25.0 (2.8)	22.7 (3.4)	22.9 (2.8)
Serum cholesterol [in mmol/l mean (SD)]	6.2 (1.0)	6.2 (1.0)	5.9 (1.0)	5.9 (1.0)
Fasting glucose [in mmol/l mean (SD)]	5.9 (0.9)	6.0 (0.9)	5.5 (0.8)	5.5 (0.7)
Beta-carotene [in μmol/l mean (SD)]	0.5 (0.3)	0.5 (0.4)	0.7 (0.6)	0.7 (0.4)
Alpha-tocopherol [in μmol/l mean (SD)]	32.2 (8.4)	32.1 (8.1)	31.3 (8.0)	31.1 (7.6)
Vitamin C [in μg/ml mean (SD)]	8.9 (5.1)	8.9 (4.4)	10.5 (4.6)	10.6 (5.4)
Selenium [in μmol/l mean (SD)]	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Zinc [in μmol/l mean (SD)]	13.5 (1.8)	13.5 (1.9)	12.8 (1.9)	12.9 (1.8)

Although statistically significant, they were weak, ranging from −0.06 for the SF36 physical functioning to −2.6 (men) for the SF36 bodily pain and 2.3 (women) for the SF36 social functioning (Table 2).

About 60% of participants reported not having perceived a change in health during the follow-up period; fewer than 20% declared an improvement overall, but women did so more often than men.

Changes in HRQoL were comparable in magnitude in the supplement and placebo groups: among women, the only difference in change was in SF36 vitality (+2.1 vs +0.9, respectively; $P=0.01$). All changes were consistent with responses to the transition question, which did not differ between the two groups.

When all participants who declared a health event were excluded, the results did not change. Limiting the analysis to compliant participants who had taken at least two-thirds of their capsules had no effect on the results. Re-running the analysis with the baseline level of beta-carotene as an adjustment variable (including an interaction term between group and the level of beta-carotene) did not change the results. Moreover, limiting the analysis to participants with lower baseline beta-carotene levels had no effect on the results.

About half of the participants (47.6%) said they had no idea to which group they had been assigned (Table 3).

Women were more likely than men to have an idea. Comparable proportions (about a quarter each) thought they were taking placebo (27.4%) or vitamins and minerals (25%). There was no relationship with the true allocation. Limiting the analysis to participants who did not have an opinion about group status had no effect on the results. Participants who thought they had been allocated to the placebo group had lower scores at initial and final evaluation than those who believed they were receiving supplements. Participants who reported having no idea about

Table 2 Mean initial HRQoL and change (final-initial) by sex and group

	Men ($n = 3428$)						Women ($n = 4684$)					
	Supplement		Placebo		*P*-value		Supplement		Placebo		*P*-value	
	Initial	Change	Initial	Change	Time	Group[a]	Initial	Change	Initial	Change	Time	Group[a]
SF36												
Physical functioning	92.9	−1.1	92.8	−0.4	0.000	0.067	89.0	−0.1	89.1	−0.7	0.046	0.093
Role-physical	88.0	−1.3	88.2	−0.2	0.145	0.279	81.4	0.4	82.5	−0.1	0.781	0.619
Bodily pain	76.0	−2.6	75.9	−1.8	0.000	0.306	70.5	−1.0	70.6	−1.3	0.000	0.677
Mental health	70.6	1.7	71.6	1.7	0.000	0.996	64.6	2.1	64.8	1.3	0.000	0.093
Role-emotional	86.3	−0.2	86.3	1.1	0.417	0.242	78.7	2.0	79.6	0.6	0.023	0.220
Social functioning	82.3	1.6	83.8	0.6	0.002	0.146	76.9	2.3	77.4	1.6	0.000	0.281
Vitality	63.5	1.3	63.9	1.3	0.000	0.897	57.3	2.1	57.7	0.9	0.000	0.014
General health	72.4	−0.5	72.5	−0.1	0.207	0.505	73.0	−1.3	72.6	−1.7	0.000	0.382
Physical summary scale	52.6	−0.9	52.5	−0.6	0.000	0.126	51.7	−0.6	51.7	−0.7	0.000	0.914
Mental summary scale	48.5	1.0	49.1	0.9	0.000	0.728	45.5	1.4	45.7	0.9	0.000	0.088
GHQ12	70.8	1.9	71.4	1.4	0.000	0.220	67.4	1.6	67.6	1.0	0.000	0.210
Global health (VAS)	75.1	−1.1	76.1	−1.1	0.000	0.916	74.3	−0.7	73.6	−0.4	0.014	0.485
Transition question (%)						0.18[b]						0.11[b]
No change		57.9		61.0				53.6		56.3		
Better		16.0		14.5				20.3		18.2		
Worse		26.1		24.6				26.2		25.5		

0 = Worst HRQoL; 100 = Best HRQoL.
[a]Time*group interaction effect testing the null hypothesis of absence of change in evolution between groups.
[b]Pearson chi-square testing the null hypothesis of absence of a difference in the distribution between groups.

their group exhibited intermediate values (Table 3). Figure 2 represents, in men and in women, the differences between HRQoL mean changes between baseline and follow-up among participants who thought they were in the placebo group and participants who believed they were in the supplement group (Figure 2).

Whatever the dimension, HRQoL changes over time were more favourable in participants who believed they were receiving supplements (with the exceptions of the GHQ score and SF36 role-emotional in men and SF36 role-emotional in women), with differences in SF36 bodily pain [−3.3 (−5.4 to −1.3)], general health [−2.2 (−3.5 to −0.8)], vitality [−1.6 (−3.1 to −0.1)] dimensions and physical component summary score [−1.1 (−1.8 to −0.8)] in men, and in SF36 social functioning [−2.3 (−4.2 to −0.5)], general health [−1.4 (−2.7 to −0.2)] dimensions and physical component summary score [−0.7 (−1.3 to −0.04)] in women. The transition question revealed major differences: about one-third of the participants who thought they were in the placebo group felt worse, compared with only one-sixth of those under the impression that they were in the supplement group (Table 3).

Discussion

The results of this trial indicate that supplementation for 7.5 years with nutritional doses of antioxidant vitamins and minerals does not improve well-being or HRQoL in a general adult population. This finding is in contrast with the reduction in the risk of total cancer in men revealed on the same data.[18] No other large prevention trial has used HRQoL as an endpoint in the context of antioxidant supplementation.

Randomization can be expected to have ensured that the groups did not differ with regard to factors with a bearing on HRQoL, whether identified or not. Compliance was good, with levels comparable to those observed in other studies of similar design.[1,2,5] An increase in biochemical markers after 2 and 7 years of supplementation provided objective confirmation of compliance.[18]

A major difficulty in HRQoL studies is how to take into account morbid conditions and sickness. Participants who become ill during the follow-up are less likely to complete a HRQoL questionnaire later on, and some die. In the present cohort, the level of HRQoL at baseline is predictive of the occurrence of a major health event during follow-up. Moreover, the

Table 3 Mean initial HRQoL and change (final-initial) by belief about randomization (placebo or supplements) status, by sex

	Men									Women								
	No idea		Believe receiving supplements		Believe receiving placebo		*P*-value			No idea		Believe receiving supplements		Believe receiving placebo		*P*-value		
	Initial	Change	Initial	Change	Initial	Change	Time	Group*	Between#	Initial	Change	Initial	Change	Initial	Change	Time	Group*	Between#
SF36																		
Physical functioning	93.1	−1.0	93.3	0.0	92.3	−1.0	0.004	0.124	0.010	88.9	−0.3	89.7	−0.1	88.8	−1.0	0.022	0.246	0.033
Role-physical	88.5	−1.0	87.6	0.9	88.4	−1.7	0.274	0.219	0.849	81.5	0.8	84.2	0.0	80.9	−1.1	0.862	0.320	0.000
Bodily pain	76.5	−2.6	76.8	0.0	74.3	−3.3	0.000	0.004	0.000	70.9	−1.4	71.4	−0.2	69.2	−1.8	0.001	0.157	0.000
Mental health	71.6	1.4	71.5	2.2	69.9	1.4	0.000	0.431	0.006	64.9	1.6	66.1	2.0	63.4	1.4	0.000	0.623	0.000
Role-emotional	87.0	−0.2	86.1	0.7	85.3	1.1	0.376	0.582	0.524	79.4	1.0	80.4	1.3	78.1	1.3	0.038	0.967	0.082
Social functioning	83.7	0.7	83.2	1.9	81.9	1.0	0.002	0.387	0.036	77.0	2.0	78.5	3.1	76.2	0.8	0.000	0.042	0.000
Vitality	63.9	1.0	65.9	2.4	61.6	0.8	0.000	0.059	0.000	57.4	1.6	59.7	1.7	55.4	1.1	0.000	0.619	0.000
General health	72.5	−0.3	73.9	0.9	71.4	−1.2	0.387	0.007	0.000	72.4	−1.3	75.1	−1.0	71.4	-2.4	0.000	0.048	0.000
Physical summary scale	52.7	−0.8	52.8	0.0	52.3	−1.2	0.000	0.002	0.000	51.5	−0.5	52.2	−0.5	51.5	−1.1	0.000	0.043	0.000
Mental summary scale	49.0	0.8	49.3	1.0	48.1	1.0	0.000	0.804	0.011	45.7	1.1	46.3	1.3	44.9	1.0	0.000	0.666	0.000
GHQ12	71.3	1.6	72.0	1.4	69.9	1.7	0.000	0.897	0.000	67.3	1.5	68.8	1.3	66.8	0.8	0.000	0.424	0.000
Global Health (VAS)	75.9	−1.2	76.8	−0.2	73.8	−1.3	0.001	0.167	0.000	73.6	−0.8	75.9	0.1	72.6	−1.1	0.010	0.135	0.000
Transition question (%)									0.000!									0.000!
No change		62.6		54.4		58.2					58.1		48.7		55.3			
Better		12.5		28.2		8.7					16.4		32.8		11.1			
Worse		24.9		17.4		33.1					25.5		18.5		33.6			

* interaction time*group testing the null hypothesis of absence of difference in change between groups (within subject)
# test of the null hypothesis of absence of difference of initial and final mean between groups (between subjects)
! Pearson chi-square testing the null hypothesis of absence of a difference in distribution between groups

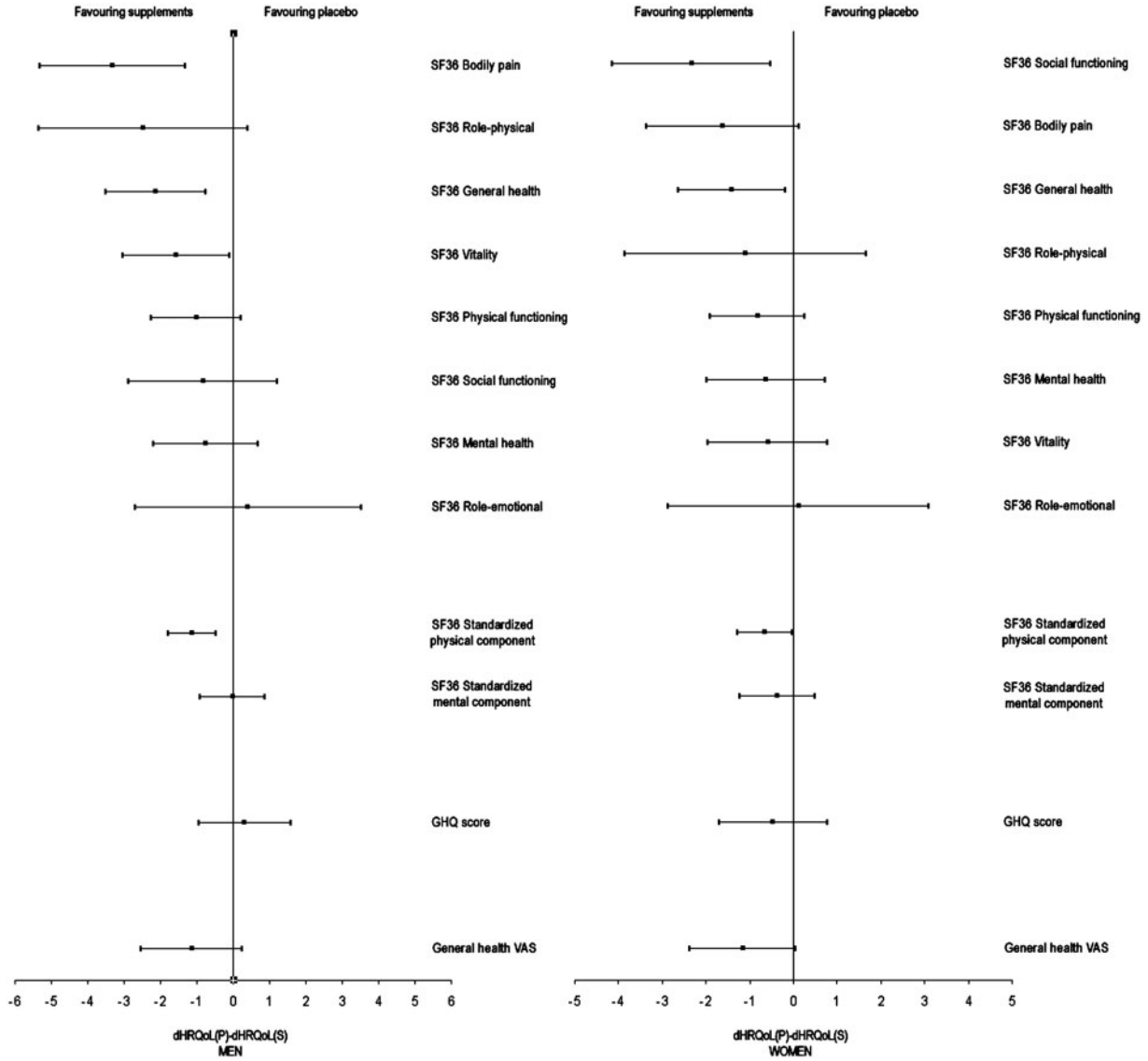

Figure 2 Differences in HRQoL change between participants who believed they received placebo and participants who believed they received vitamin and mineral supplementation, by instrument. In men/women dHRQoL(P) = final HRQoL − initial HRQoL among participants who believed they received placebo; dHRQoL(S) = final HRQoL − initial HRQoL among participants who believed they received supplements; squares represent HRQoL mean differences, vertical lines represent 95% lower and upper confidence limits

occurrence of cancer had a negative impact on HRQoL evolution.[26] As vitamin and mineral supplementation decreased the cancer incidence in men,[18] HRQoL scores would be related to supplementation. Re-running analyses without the participants who developed a major health event during the follow-up did not change the results. The weak occurrence of major health events among people who provided initial and final HRQoL measures and the only very small imbalance of health events occurrence between the two groups may explain the inability to detect an impact on HRQoL.

Modification of dietary intake (particularly if it increased antioxidant consumption in the placebo group) could lead to underestimation of the positive effect of supplementation in the supplement group. Limiting the main analysis to participants who did not have an opinion about group status (because they would be less likely to have altered their dietary intake) or adjusting and/or seeking for interaction for baseline levels of beta-carotene did not change the results.

Adherence was important and difficult for a long follow-up period of 7.5 years, especially as adherence would be affected by the health status of participants. People who felt good would be more likely to adhere to the treatment regimen, whereas those who felt otherwise might stop taking the capsules or

self-medicate with real supplements or foods. If such selection bias occurred, participants were more compliant and consequently felt better than participants lost to follow-up, and the positive impact of supplementation on HRQoL, if it exists, should have been increased in the supplement group. Thus, in the absence of a difference between the supplement and the placebo groups, the interpretation of the results is not altered.

It is widely believed that vitamins and minerals help maintain good health and provide a sense of well-being.[16] A huge number of web-sites convey the same message; a request inputting the two key words 'well-being' and 'vitamin' in a search engine yields more than 1 500 000 sites. This contrasts with the limited number of scientific publications available. The few published randomized trials have included sick[27,28] or recovering participants[29] and those with a particularly deficient diet.[30,31] Study populations are generally very small, and the HRQoL instruments used have not always been established as valid. Barringer *et al.*[32] found no effect of daily multivitamin and mineral supplementation for 1 year on HRQoL as measured by the SF-12 questionnaire. Results of large prevention trials using a validated HRQoL instrument, with a design comparable to that used here, are not yet available: only baseline HRQoL and/or primary outcomes results of PCPT[33–36] and SELECT[37,38] have been published. Thus, no meta-analysis is possible at the present time. With these results, SU.VI.MAX contributes hugely to the debate on contradictory claims between observational epidemiological studies and randomized trials.[39]

Strengths and limitations

Methodological and nutritional questions arise. The instruments used were exclusively generic, as they had to be in a primary prevention trial involving initially healthy participants. The particular questionnaires were selected for their ability to detect change and because they were documented to be of sufficient validity.[40] In accord with the present findings, the SF36 mental health dimension and the GHQ-12 global score have previously been reported to exhibit similar psychometric performance.[41] The SF36 tended to exhibit low changes, probably because the dimensions of the SF36 explore contextual states and thus it is able to better detect changes over time than instruments including permanent characteristics or traits less susceptible to change over time. General and global health states do not appear to be highly relevant in this type of long-term assessment, as physical and mental scores evolve in opposite directions.

The numerous claims of a positive effect of vitamins on health and well-being, and the fact that some participants probably participated because of such a belief, make it important to assess this factor—particularly given the long duration of the supplementation. The data contribute to a comprehensive interpretation of the negative results of the main analysis.

How and where a questionnaire is completed may affect the results. A home-setting and self-administration (as used here for both examinations) are reported to introduce less bias and to be more cost-effective.[42] It has been suggested that assessing HRQoL after randomization may introduce a selection bias favouring participants with better overall and mental health scores.[43] It was, however, practically impossible to introduce HRQoL instruments prior to randomization. A comparison of participants who completed and returned questionnaires with those who did not confirmed that such a bias existed, but the design of the trial ensured that the groups remained comparable.

As the effect of supplementation on HRQoL was not the main objective of the trial, the question arises of whether the statistical power was sufficient to detect any such changes. As stated in the methods section, the detectable differences were lower than those commonly defined as a clinically important change.

Overall, this trial meets the general requirements proposed for HRQoL assessment in controlled trials, particularly with regard to the relevance of the instruments, the duration of follow-up, the number of participants included, control for confounding factors and blinding.[42,44]

Conclusions

The present trial suggests that long-term antioxidant vitamin and mineral supplementation does not improve well-being and HRQoL. Notwithstanding a possible beneficial effect mediated by the prevention of major morbid events, this result, combined with the observation that physical HRQoL dimension scores are positively correlated with serum concentrations of beta-carotene, vitamin C and selenium, underlines the importance of avoiding such deficiencies through a healthy diet. There is no proof that supplementation with these vitamins and minerals is beneficial in participants whose dietary intakes are already sufficient. The perception that supplementation improves general well-being is not supported by this trial. A reverse causal pathway may even be advocated (healthier participants may have been more likely to believe they were in the supplement group). The major implication for public health of the present findings is that a lifelong diet rich enough in vitamins and minerals may be preferable to supplementation that is likely not to be efficacious and has the potential to be harmful.[7]

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KEY MESSAGES

- Vitamin supplementation is an important public health issue because of the widely held belief that it helps maintain good health and provides a sense of well-being.
- We demonstrate that long-term supplementation with antioxidant vitamins and minerals has no effect on quality of life.
- In the context of recent findings showing no effect (indeed a negative effect) of antioxidant supplements on mortality, our results strengthen the evidence that this type of intervention has no beneficial impact on health.

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