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Effect of α-tocopherol and β-carotene supplementation on coronary heart disease during the 6-year post-trial follow-up in the ATBC study

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Aims To evaluate the 6-year post-trial effects of α-tocopherol and β-carotene supplementation on coronary heart disease (CHD) in the α-tocopherol, β-carotene cancer prevention (ATBC) study.
Methods and results 29 133 male smokers, aged 50–69 years were randomised to receive α-tocopherol 50 mg, or β-carotene 20 mg, or both, or placebo daily for 5–8 years. At the beginning of the post-trial follow-up, 23 144 men were still at risk for a first-ever major coronary event (MCE), and 1255 men with pre-trial history of myocardial infarction (MI) were at risk for MCE. Post-trial risk for MCE ($n = 2059$) was 0.95 (95% confidence interval 0.87–1.04) among α-tocopherol recipients compared with non-recipients, and 1.14 (1.04–1.24) among β-carotene recipients compared with non-recipients. The risk for non-fatal MI ($n = 993$) was 0.96 (0.85–1.09) and 1.16 (1.03–1.32), and for fatal CHD ($n = 1066$) 0.94 (0.83–1.06) and 1.11 (0.99–1.25), respectively. Among men with pre-trial MI no effects were observed in post-trial risk of MCE ($n = 257$).
Conclusion β-Carotene seemed to increase the post-trial risk of first-ever non-fatal MI but there is no plausible mechanism to support it. Our findings do not advocate the use of α-tocopherol or β-carotene supplements in prevention of CHD among male smokers.

Introduction

The possible protective effect of antioxidants on coronary heart disease (CHD) has been under intensive investigation during the last two decades. The major hypothesis behind this interest is the role of oxidised low-density lipoprotein (LDL)-cholesterol in atherogenesis and the in vitro evidence that antioxidants inhibit oxidative modification of LDL-cholesterol.[1] Oxidised LDL-cholesterol stimulates differentiation of monocytes into macrophages and accumulates in macrophages by a non-regulated scavenger receptor pathway. Oxidised LDL induces proliferation of smooth muscle cells, is chemotactic and cytotoxic, and impairs endothelial function.[2]

The most studied antioxidants are α-tocopherol (the main constituent of vitamin E) and β-carotene, both lipophilic compounds carried in lipoproteins. α-Tocopherol

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works as an efficient chain-breaking antioxidant, whereas β-carotene is suggested to act as a singlet oxygen quencher. β-Carotene may also regenerate the α-tocopheroxyl radical into α-tocopherol.[3] Observational studies indicate that high intake of dietary and also supplemental α-tocopherol and β-carotene are associated with decreased risk for CHD.[4–8] However, no primary preventive effect of α-tocopherol or β-carotene supplementation on CHD mortality or incidence of myocardial infarction (MI) has been observed in large controlled trials[9–12] and findings concerning secondary prevention of CHD have been contradictory.[13–17] Thus the possible beneficial role of antioxidants on CHD is still unanswered and results from ongoing trials are awaited.

No reports of extended follow-up concerning CHD have been published from previously completed antioxidant trials. We report herein the post-trial effects of α-tocopherol and β-carotene supplementation on major coronary events (MCE), i.e., non-fatal MI and fatal CHD, during a 6-year follow-up of the α-tocopherol, β-carotene cancer prevention (ATBC) study. Findings from the intervention period, the details of which have been previously reported,[10,15] are also presented herein to facilitate the interpretation of temporal changes in the endpoints.

Methods

The ATBC Study

The ATBC Study was a randomised, double-blind, placebo-controlled trial, the design and methods of which have been described in details elsewhere.[18] The primary aim was to test the effect of α-tocopherol and β-carotene supplementation on the incidence of lung cancer and the secondary aim to evaluate the effect on other cancers, all-cause mortality, and cardiovascular diseases. The trial cohort was screened by a postal survey from among a total population of 50- to 69-year-old men living in southwestern Finland ($n = 290\,406$). Men who were current smokers (smoked five or more cigarettes per day) and willing to participate in the study ($n = 42\,957$) were invited to undergo baseline examinations. Exclusion criteria were prior cancer, severe angina on exertion (Rose criteria, Grade 2),[19] any other serious disease limiting long-term participation, or use of vitamin E (over 20 mg per day), β-carotene (over 6 mg per day), or vitamin A (over 20 000 IU per day) supplements, or anticoagulants.[18] Enrolment took place from 1985 through 1988 during which a total of 29 133 men were randomised into one of four intervention regimens: 50 mg of dl-α-tocopheryl acetate, 20 mg of β-carotene, both, or placebo in one capsule per day. At baseline medical background information was collected, blood pressure was measured, a blood sample was drawn, and written informed consent was administered.

The intervention lasted for 5—8 years until April 30, 1993. Follow-up during the trial included three visits per year to the local study center. At every visit, men returned the pack with the remaining study capsules and received a new supply. Median capsule compliance was 99% during the active participation in all supplementation groups. At the end of the intervention phase, participants were informed by individual letter that the trial results and available other knowledge did not indicate that α-tocopherol and β-carotene should be used for prevention of cancer and cardiovascular disease.

The participants were followed up post-trial through national registers, and the present study includes the 6-year post-trial follow-up of MCEs from May 1, 1993 to April 30, 1999. Use of supplements were not monitored during the post-intervention follow-up since there was no active clinic-based follow-up.

The ATBC Study was approved by the institutional review boards of the National Public Health Institute, Finland, and the National Cancer Institute, USA.

Subjects

At trial baseline, 27 271 men reported no history of MI, and of these, 23 144 men were still at risk of first-ever MCE at the beginning of the post-trial follow-up, i.e., they had not suffered from MI during the intervention phase. Those men who had suffered from the first-ever MI during the intervention phase and were still alive at the beginning of the post-trial follow-up ($n = 1034$) were not included in the present study.

At trial baseline, 1862 men reported a history of MI diagnosed by a physician. Of them, 1255 men were alive at the beginning of the post-trial follow-up and had not experienced a recurrent non-fatal MI during the intervention phase.

Endpoints

The endpoints of the present study for those at risk of first-ever MCE in the beginning of the post-trial follow-up were primary non-fatal MI and death from CHD. For those who had reported a history of MI at the start of the trial, the post-trial endpoints were recurrent non-fatal MI and death from CHD. Only the first post-trial event was registered as an endpoint. Endpoints were identified through linkage with the national Hospital Discharge Register and the national Register of Causes of Death. Both registers use the codes of the International Classification of Diseases (ICD). The first MI during post-trial follow-up was sought in the Hospital Discharge Register records with ICD-9 codes 410 (used until 1996), or ICD-10 codes I21—I23. Non-fatal MI included all those cases that survived at least for 28 days from the onset of the attack. Fatal CHD events included all deaths due to the underlying causes of death 410—414 (ICD-9) or I20—I25 (ICD-10). In a validity study 94% of the diagnoses of the MCE in the registers were reviewed as a true MCE defined by strict criteria.[20]

Statistics

Analyses were based on the intention-to-treat principle and thus the post-trial follow-up also included the trial dropouts who were alive at the beginning of the post-trial follow-up. In all analyses censoring was assumed to be independent of the endpoint. In the analysis of MCEs censoring was defined as death or end of follow-up (April 30, 1999). For fatal CHD censoring was additionally defined as non-fatal MI. Rates per 1000 person-years during the 6-year post-trial period were calculated for MCEs, non-fatal MI, and fatal CHD for each of the four randomised treatment groups. The likelihood ratio test was used to test homogeneity of risk estimates between the supplementation groups. Calculations were also performed in the groups who either received α-tocopherol supplementation (α-tocopherol alone or α-tocopherol and β-carotene) or did not receive α-tocopherol supplementation (β-carotene alone or placebo), and similarly for the groups who either received β-carotene (β-carotene alone or α-tocopherol and β-carotene) or did not receive β-carotene supplementation (α-tocopherol alone or placebo). Relative risk (RR) estimates and their 95% confidence intervals

(95% CI) were obtained from Poisson regression models.[21] Effect modification by risk factor levels at the baseline of the trial on the post-intervention supplement effect was analysed by calculating RR estimates in the strata of each factor. The analyses were also performed adjusting for other trial baseline risk factors but the results were materially unaffected and therefore we report only the unadjusted risks. Likelihood ratio test was used to test homogeneity of post-trial effects in the strata of risk factors. Statistical tests were two-sided and a *p*-value of less than 0.05 was considered to indicate statistical significance.

To estimate the calendar time-specific rates, we calculated smoothed rate estimates using a generalised additive model.[22] We first divided calendar time into monthly intervals with the exception that we combined calendar time until April 1986 for the first interval because the risk sets were small at this earliest phase of the recruitment period that started in 1985. The monthly observations that were nearest to the target were used to define a neighborhood where a weighted linear curve was used to estimate the rate at the target point. The weights for the monthly observations around the target point were calculated from a tri-cube kernel centred at the target point.

Results

Subject characteristics

At the beginning of the post-trial follow-up, the median age of the 23,144 men at risk for first-ever MCE was 63 years (range 55—77 years). Their coronary risk characteristics at the start of the trial in 1985-1988 were similar across the four intervention groups (Table 1). Likewise the median age of the 1255 men with pre-trial history of AMI was 65 years and their characteristics at trial baseline were similar across the four intervention groups (data not shown).

Major coronary event

Altogether 2059 first-ever MCEs occurred during the post-trial period. Of these, 993 were non-fatal MIs and 1066 fatal CHD events. The rate of MCE per 1000 person years varied significantly between the supplementation groups being lowest among those who had received α-tocopherol alone (15.16) and highest among those who had received β-carotene alone (18.14) (Table 2). When we compared those who had received α-tocopherol with those who had not received it, the relative risk for MCE was 0.95 (95% CI 0.87—1.04), and among those who had received β-carotene compared with those who had not received it, the relative risk was 1.14 (95% CI 1.04—1.24). The estimated smoothed rates of MCE per 1000 person years from trial randomisation to the end of post-trial follow-up in the four treatment groups are shown in Fig. 1.

Among men with pre-trial MI, 257 MCEs occurred, 107 recurrent non-fatal MIs and 150 fatal CHD events. No significant effect of any supplementation on MCE was observed during the post-trial follow-up (Table 3).

Non-fatal myocardial infarction

The post-trial rates of first-ever non-fatal MI varied non-significantly from 7.23 to 8.73 per 1000 person-years between the intervention groups (Table 2). The relative risks for non-fatal MI were 0.96 (95% CI 0.85—1.09) in those who had received α-tocopherol compared with those who had not received it, and 1.16 (95% CI 1.03—1.32) in those who had received β-carotene compared with those who had not received it. Fig. 2 shows the estimated smoothed rates in the four supplementation groups.

Among men with pre-trial MI no difference in risk of recurrent non-fatal MI was observed during the post-trial follow-up (Table 3).

Fatal coronary heart disease

The post-trial rates of fatal CHD events varied non-significantly from 7.93 to 9.41 per 1000 person-years between the intervention groups (Table 2). Among those who had received α-tocopherol the relative risk was 0.94 (95% CI 0.83—1.06) compared with those who had not received it; among those who had received β-carotene risk was 1.11 (95% CI 0.99—1.25) compared with those who had not received it. The estimated smoothed rates of the four supplementation groups are shown in Fig. 3.

Among men with pre-trial MI, the fatal CHD events were evenly distributed in the four supplementation

Table 1 Subject characteristics at the beginning of the trial in subjects still at risk for first-ever major coronary event at the beginning of the post-trial follow-up

Characteristics	Placebo	α-Tocopherol	α-Tocopherol and β-carotene	β-Carotene
No. of subjects	5841	5794	5741	5768
Age (years)[a]	56 (53—61)	57 (53—61)	57 (53—61)	57 (53—61)
Years of smoking (years)	36 (30—40)	36 (30—41)	35 (30—40)	36 (30—41)
No. of cigarettes/day	20 (15—25)	20 (15—25)	20 (15—25)	20 (15—25)
Serum total cholesterol (mmol/L)	6.13 (5.43—6.90)	6.13 (5.42—6.91)	6.16 (5.44—6.97)	6.13 (5.46—6.89)
Serum HDL-cholesterol[b] (mmol/L)	1.13 (0.97—1.34)	1.13 (0.96—1.34)	1.12 (0.96—1.34)	1.13 (0.97—1.35)
Blood pressure systolic (mmHg)	140 (128—152)	140 (128—152)	140 (128—154)	140 (128—152)
Blood pressure diastolic (mmHg)	88 (80—94)	88 (80—94)	88 (80—94)	88 (80—94)
Body mass index (kg/m^2)	25.9 (23.6—28.5)	25.9 (23.7—28.4)	26.0 (23.7—28.5)	25.9 (23.7—28.4)

[a] Median with interquartile range (25—75th percentiles) in parentheses.
[b] HDL = high-density cholesterol.

Table 2 Incidence and relative risk of coronary heart disease endpoints among subjects at risk for first-ever major coronary event by regimen

Endpoint	Trial[a]					Post-trial				
	Placebo	α-Tocopherol	α-Tocopherol and β-carotene	β-Carotene	*p*-Value	Placebo	α-Tocopherol	α-Tocopherol and β-carotene	β-Carotene	*p*-Value
No. at risk	6849	6820	6781	6821		5841	5794	5741	5768	
MCE										
No. of incident cases	534	520	511	548		504	472	528	555	
Rate/1000 person-years	13.59	13.33	13.16	14.04		16.08	15.16	17.35	18.14	
Relative risk	1.00	0.98	0.97	1.03	0.75	1.00	0.94	1.08	1.13	0.02
95% CI		0.87–1.11	0.86–1.10	0.92–1.17			0.83–1.07	0.95–1.22	1.00–1.28	
Non-fatal MI										
No. of incident cases	296	309	289	314		240	225	261	267	
Rate/1000 person-years	7.54	7.92	7.44	8.05		7.66	7.23	8.57	8.73	
Relative risk	1.00	1.05	0.99	1.07	0.73	1.00	0.94	1.12	1.14	0.11
95% CI		0.90–1.24	0.84–1.17	0.91–1.26			0.78–1.14	0.94–1.34	0.95–1.36	
Fatal CHD										
No. of incident cases	238	211	222	234		264	247	267	288	
Rate/1000 person-years	6.06	5.41	5.72	6.00		8.42	7.93	8.77	9.41	
Relative risk	1.00	0.89	0.94	0.99	0.61	1.00	0.94	1.04	1.12	0.25
95% CI		0.74–1.08	0.78–1.14	0.82–1.19			0.79–1.12	0.87–1.24	0.94–1.33	

Abbreviations: MCE, major coronary event; MI, myocardial infarction; CHD, coronary heart disease; CI, confidence interval.

[a] Published earlier in detail.[10]

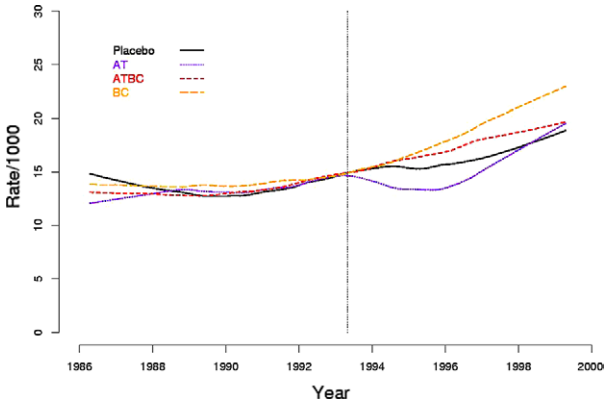

Fig. 1 Smoothed calendar time-specific rates of major coronary events by regimen. The vertical line refers to the start of the post-trial follow-up. Abbreviations: AT, α-tocopherol; ATBC, α-tocopherol and β-carotene; BC, β-carotene supplementation.

groups showing no differences in post-trial risks (Table 3).

Effect modification

Body mass index measured at the beginning of the trial significantly modified the post-trial effect of β-carotene supplementation on first-ever non-fatal MI ($p = 0.048$); β-carotene increased the risk of non-fatal MI in the highest tertile of body mass index but not in the lowest tertile (Table 4). A similar pattern was also observed for MCE, but the differences in post-trial effects between the BMI tertiles did not reach statistical significance. Body mass index did not modify the post-trial effect of α-tocopherol. Other risk factors measured at the beginning of the trial including smoking years, number of cigarettes smoked per day, serum cholesterol levels or blood pressure did not modify the post-trial supplementation effects. Since the supplementations had no post-trial effects in men with pre-trial MI, no effect modification analyses were performed in this group.

Discussion

α-Tocopherol supplementation had no significant post-trial effect on first-ever MCEs during the 6-year follow-up, a result similar to that observed during the trial period.[10] In contrast, β-carotene supplementation increased the post-trial risk of MCE and non-fatal MI by 14% and 16%, respectively. Post-trial risk for fatal CHD increased by 11%, but did not reach statistical significance. These findings of β-carotene were unexpected since no increased risk was observed during the trial period when the corresponding relative risks were 1% for MCE, 0% for non-fatal MI and 2% for fatal CHD.[10]

We also looked at the late effects of α-tocopherol and β-carotene on MCEs in men with pre-trial MI. α-Tocopherol supplementation had no significant effect on MCEs in these men either during or after the intervention. During the intervention the risk of fatal CHD was significantly increased by 44% among those who received β-carotene compared with those who did not,[15] whereas β-carotene had no post-trial effect on fatal CHD or non-fatal recurrent MI.

Observational studies have indicated that diets rich in vitamin E and the use of α-tocopherol supplements are associated with decreased risk for CHD.[4–7] Large controlled trials in humans have not confirmed these findings, and instead they have revealed inconsistent results. In the randomised but unblinded GISSI-Prevenzione trial of 11,000 patients surviving recent MI a daily dose of 300 mg of α-tocopherol for 3.5 years showed no effect on fatal or non-fatal cardiovascular events.[14] In another open trial, i.e., the Primary Prevention Project, no effect of 300 mg of α-tocopherol daily on fatal or non-fatal cardiovascular disease was found among over 4000 subjects at high risk for cardiovascular disease.[23] In the double-blind Heart Outcomes Prevention Evaluation (HOPE) Study, the effect of 400 IU of α-tocopherol daily was evaluated among nearly 10 000 participants with cardiovascular risk factors and no effect on MI or cardiovascular death was observed during 4.5 years of follow-up.[13] In the latest double-blind study, the Heart Protection Study (HPS), an antioxidant cocktail including 600 mg of α-tocopherol, 250 mg of vitamin C and 20 mg of β-carotene was supplemented for five years without any benefit on major coronary events among over 20 000 high-risk subjects.[17] In contrast, the Cambridge Heart Antioxidant Study among 2000 patients with angiographically proven coronary atherosclerosis found a significant decrease in risk for non-fatal MI (RR 0.23, 95% CI 0.11—0.47), but this surprisingly high risk-reduction was not reflected in cardiovascular mortality (RR 1.18, 95% CI 0.62—2.27).[16]

It has been suggested that the finding of no benefit of α-tocopherol in the ATBC Study might be due to the low dose employed and the fact that all subjects were smokers. However, although HOPE, GISSI and HPS trials used a high dose of vitamin E and the proportion of smokers was smaller, they still did not show a benefit. Furthermore, a recent meta-analysis taking into account 6 trials with 77 000 subjects found no effect of vitamin E on risk for cardiovascular death or non-fatal MI.[24] There are several large trials currently ongoing testing the effect of α-tocopherol, mostly in combination with other antioxidants, on both primary and secondary prevention of CHD.[25–28] These trials will hopefully give us greater insight into the relation between antioxidant vitamins and CHD.

β-Carotene trials have not provided evidence of favourable effects on CHD, although the opposite was expected based on the observational studies.[5,8,29] In the Physicians' Health Study, no effect on cardiovascular mortality or risk for MI was observed among over 22 000 male physicians randomised to receive 50 mg of β-carotene or placebo every other day for 12 years.[11] In nearly 40 000 US women randomised to receive 50 mg of β-carotene, or 600 IU of α-tocopherol, or 100 mg of aspirin, or placebo every other day no early effect of β-carotene was observed on cardiovascular endpoints.[30] In these two studies, only 11% and 13% of the participants, respectively,

Table 3 Incidence and relative risk of coronary heart disease endpoints among subjects with pre-trial MI by regimen

Endpoint	Trial					Post-trial				
	Placebo	α-Tocopherol	α-Tocopherol and β-carotene	β-Carotene	*p*-Value	Placebo	α-Tocopherol	α-Tocopherol and β-carotene	β-Carotene	*p*-Value
No. at risk	438	466	497	461		306	329	322	298	
MCE										
No. of incident cases	93	94	123	113		67	60	68	62	
Rate/1000 person-years	41.24	38.92	49.02	48.74		45.25	38.32	44.13	43.20	
Relative risk	1.00	0.94	1.19	1.18	0.23	1.00	0.85	0.98	0.95	0.79
95% CI		0.70—1.26	0.90—1.56	0.89—1.56			0.59—1.21	0.69—1.38	0.67—1.36	
Non-fatal MI										
No. of incident cases	54	40	58	40		29	22	30	26	
Rate/1000 person-years	23.94	16.56	23.12	17.25		19.59	14.05	19.47	18.12	
Relative risk	1.00	0.69	0.97	0.72	0.16	1.00	0.72	0.99	0.93	0.61
95% CI		0.46—1.05	0.66—1.41	0.47—1.09			0.41—1.26	0.59—1.67	0.54—1.59	
Fatal CHD										
No. of incident cases	39	54	65	73		38	38	38	36	
Rate/1000 person-years	17.29	22.36	25.91	31.49		25.66	24.27	24.66	25.08	
Relative risk	1.00	1.29	1.50	1.82	0.02	1.00	0.95	0.96	0.98	1.00
95% CI		0.85—1.97	1.00—2.25	1.22—2.71			0.60—1.50	0.61—1.52	0.61—1.56	

Abbreviations: MCE, major coronary event; MI, myocardial infarction; CHD, coronary heart disease; CI, confidence interval.

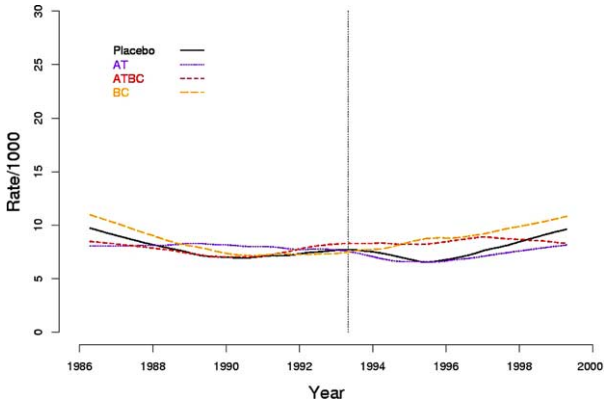

Fig. 2 Smoothed calendar time-specific rates of non-fatal myocardial infarction by regimen. The vertical line refers to the start of the post-trial follow-up. Abbreviations: AT, α-tocopherol; ATBC, α-tocopherol and β-carotene; BC, β-carotene supplementation.

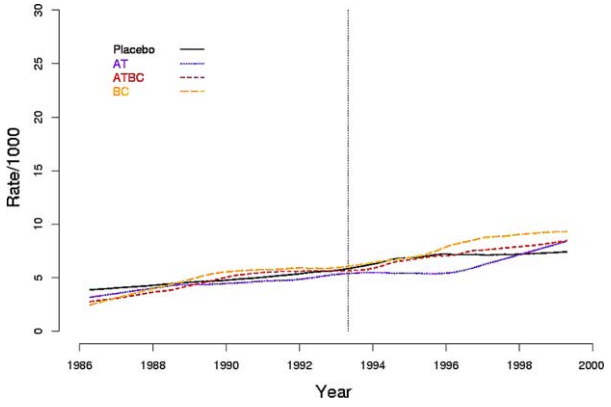

Fig. 3 Smoothed calendar time-specific rates of fatal coronary heart disease by regimen. The vertical line refers to the start of the post-trial follow-up. Abbreviations: AT, α-tocopherol; ATBC, α-tocopherol and β-carotene; BC, β-carotene supplementation.

were smokers. In the Beta-Carotene and Retinol Efficacy Trial (CARET), the effect of the combination of 30 mg of β-carotene and 25 000 IU of vitamin A supplementation on lung cancer and cardiovascular diseases was assessed among 18 000 current or former smokers or workers exposed to asbestos. A suggestion of increased risk for cardiovascular mortality (RR 1.26, 95% CI 0.99-1.61) was observed among those who received combination supplementation compared with those who received placebo group after an average follow-up of 4 years.[12] In a meta-analysis of 6 randomised trials the risk of cardiovascular death with β-carotene treatment was slightly increased (odds ratio 1.10, 95% CI 1.03–1.7).[24]

It is unclear why β-carotene, a compound that was considered non-toxic, seems to be harmful, especially in smokers. The increased incidences of lung cancer observed in the ATBC Study and in CARET have been speculated to be due to an interaction between smoking and high dose of β-carotene.[31] Whether or not a similar interaction could also explain the excess of MCEs, is speculation. Another clue comes from the endarterectomy studies, which have shown that β-carotene is preferably incorporated into atherosclerotic plaques rather than into the normal arterial wall.[32,33] This may promote the progression of existing atheromas that rupture more easily.

The increased post-trial risk of first-ever non-fatal MI among subjects initially supplemented with β-carotene is perplexing, as no such risk was observed during the trial itself. The difference was accentuated among subjects with trial baseline body mass index over 27.6 kg/m^2. The fatter men probably had larger stores of β-carotene in their adipose tissue and longer-lasting release of β-carotene to circulation after discontinuation of the supplementation. It could be speculated that adipose tissue metabolises β-carotene to atherogenic or thrombogenic derivatives, with increased mobilisation after the inhibitory influence of the supplementation ends. There is, however, to our knowledge, no data available to support such a mechanism. Therefore, chance is the most plausible explanation for the observations. The likelihood of a chance finding is further supported by the fact that, despite of aging, the rates of non-fatal MI and fatal CHD decreased in the α-tocopherol alone and placebo groups during the first years after the completion of the trial as shown in Figs. 2 and 3.

In conclusion, our findings regarding the late effects of α-tocopherol and β-carotene in male smokers indicate against the use of these supplements in prevention of CHD.

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Table 4 Post-trial risk of coronary heart disease endpoints among recipients of β-carotene compared with non-recipients by the tertiles of trial baseline body mass index

Endpoint	BMI (kg/m^2)			
	<24.5	24.5–27.6	>27.6	*p*-Value[a]
Major coronary event	1.03 (0.88–1.22)[b]	1.09 (0.93–1.27)	1.27 (1.10–1.46)	0.14
Non-fatal MI	0.92 (0.72–1.17)	1.20 (0.96–1.50)	1.35 (1.10–1.65)	0.048
Fatal CHD	1.15 (0.92–1.45)	0.99 (0.80–1.23)	1.19 (0.98–1.45)	0.41

Abbreviation: BMI, body-mass index; MI, acute myocardial infarction; CHD, coronary heart disease.
[a] *p*-Value refers to test of homogeneity.
[b] Values are expressed as relative risk (95% confidence interval).

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