

The effect of β -carotene on common cold incidence is modified by age and smoking: evidence against a uniform effect in a nutrient–disease relationship

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Background: Analyses in nutritional epidemiology usually assume that there is a uniform effect of a nutrient. The purpose of this study was to test whether the effect of β -carotene on common cold incidence is uniform over the population.

Methods: The Alpha-Tocopherol Beta-Carotene Study, which recruited male smokers aged 50–69 years, was conducted in Finland in 1985–1993. The active follow-up lasted for 4.7 years (mean). This analysis is restricted to the β -carotene and placebo arms ($n = 14,569$). The rate ratio (RR) of the common cold was modeled as a function of age at follow-up in the β -carotene arm compared with the placebo arm using Poisson regression.

Results: Separate regression models in four subgroups of participants were constructed on the basis of the age of smoking initiation (≤ 20 years versus ≥ 21 years) and baseline smoking level (5–14 versus ≥ 15 cigarettes/day). In three of the four subgroups, the effect of β -carotene was significantly modified by age. Among participants older than 70 years, the extent of smoking modified the effect so that β -carotene increased the incidence of colds in those who started smoking at an early age and smoked heavily: RR = 1.16 (95% confidence interval [CI]: 1.02–1.33), but decreased the incidence in those who started smoking at a later age and smoked less: RR = 0.76 (95% CI: 0.61–0.94).

Conclusions: The strong evidence of heterogeneity in the β -carotene effect on the incidence of colds challenges the validity of cohort studies on nutrients, because they are usually based on the assumption of a uniform effect of the nutrient over the studied population.

Keywords: antioxidants, dietary supplements, male, randomized controlled trial, respiratory infections

Trial registration: ClinicalTrials.gov NCT00342992.

Introduction

Randomized controlled trials are a much more reliable source for the evaluation of intervention effects than observational studies.¹ In observational studies, residual confounders may always remain, which may generate spurious differences between the groups compared.^{2–4} Because cohort studies are popular for analyzing associations between the level of dietary intake of nutrients and the incidence of diseases, the validity of cohort studies is a particularly important question in the field of nutrition.

In addition to the problem of residual confounding, another source of misleading results in cohort studies is the possible variation in the size of the effect between different population groups, ie, effect modification. If the size of the effect varies

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between population groups, it may be grossly misleading to calculate one overall estimate of effect and suppose that it is valid for all participants of the study population.

Our previous analyses of the data of the large-scale Alpha-Tocopherol Beta-Carotene (ATBC) Study found that the effect of vitamin E supplementation on common cold incidence was modified by the age at the follow-up visit, smoking, and residential neighborhood,⁵ while the effect on pneumonia was modified by age, smoking, age of smoking initiation, weight, and dietary vitamin C intake,^{6–8} and the effect on tuberculosis was modified by dietary vitamin C intake.⁹ Given the strong evidence that the effect of vitamin E supplementation varies between participant subgroups, it is apparent that one single estimate of effect calculated for the whole ATBC Study population is misleading in the case of these infections.

Several cohort studies have examined the association between dietary β -carotene intake and the incidence of respiratory tract infections.^{6,10–12} If the effect of β -carotene supplementation on respiratory infections depends on the characteristics of people in the same way as the effect of vitamin E supplementation does, the uniform effects reported in the cohort studies may be misleading.

We previously found that β -carotene supplementation had no overall effect on the incidence of pneumonia among the ATBC Study participants; however, the effect was significantly modified by the age of smoking initiation.⁶ β -Carotene supplementation had no overall effect on the incidence of the common cold,¹⁰ but significantly increased the incidence of colds in a small subgroup of participants who undertook heavy exercise during their leisure.¹³ The purpose of this study was to test whether the effect of β -carotene on common cold incidence is modified by age in four subgroups of the ATBC Study participants as defined by the age of smoking initiation and the level of smoking at the baseline of the trial. The modification of β -carotene effect by age was examined by spline modeling,¹⁴ so that the rate ratio (RR) of common cold episodes between the β -carotene and placebo arms was modeled by a series of connected line segments over the studied age range.

Methods

Participants

The design and methods of the ATBC Study examining the effects of vitamin E (*dl*- α -tocopheryl acetate (AT), 50 mg/day (50 IU/day)) and β -carotene (BC, 20 mg/day) on the incidence of lung and other cancers have been described in detail.^{15,16} The ATBC Study is registered at ClinicalTrials.gov under

the identifier NCT00342992. In brief, the trial participants were recruited in 1985–1988 from the total male population aged 50–69 living in southwestern Finland. To be eligible, participants had to smoke ≥ 5 cigarettes per day at entry. The eligible participants ($n = 29,133$) were randomized into one of the four intervention arms and administered placebo, AT, BC, or AT + BC. The planned intervention continued for 5–8 years (median 6.1 years) until April 30, 1993, with three follow-up visits annually, but because of deaths and dropouts, the active follow-up lasted for 4.7 years (mean). The trial was approved by the institutional review boards of the participating institutions, and all participants gave their written informed consent. In this study, I excluded participants who were administered vitamin E to avoid problems caused by potential interaction between β -carotene and vitamin E.

At the baseline, prior to randomization, all the participants completed a questionnaire on their medical and smoking histories and general background characteristics. A detailed dietary history questionnaire was completed that provided data regarding their β -carotene and alcohol consumption.¹⁷ Weight was measured at the baseline. Data on the age of smoking initiation were missing for five participants, and they were also excluded, so I restricted this study to 14,564 participants (Table 1).

Table 1 Baseline characteristics of participants and the age distribution at the follow-up visits; the ATBC Study 1985–1993; the no-vitamin E participants

Baseline characteristics	No. of participants
All participants	14,564
Baseline age (years)	
50–54	5195
55–59	4700
60–64	3157
65–69	1512
Smoking (cigarettes/day)	
5–14	2959
≥ 15	11,605
Age of smoking initiation	
≤ 20 years	10,873
≥ 21 years	3691
Follow-up visits	No. of visits
All visits	206,170
Age at follow-up visit (years)	
50–54	33,202
55–59	70,648
60–64	58,577
65–69	33,295
70–72	6512
72–73	2996
74–75	873
76–77	67

Outcome definition

At each follow-up visit to the local study center, three times per year at 4-month intervals (Table 1), the participant was asked, 'Have you had a common cold since the previous visit, and if so, how many times?' The occurrence of 'other upper respiratory tract infections' and 'acute bronchitis' was also asked about. The number of colds reported at each follow-up visit was used as the outcome for this study. This outcome, self-reported colds, is based on subjective symptoms and not on any laboratory findings. However, because the subjective symptoms lead a person to seek medical attention and obtain sick leave, in this respect, the subjective outcome is most relevant for public health purposes. The manifestations of the common cold are so well known that self-diagnosis by the patient is usually correct.¹⁸ During 68,723 person-years of active follow-up covered by the 4-month visits to the study centers, 55,884 common cold episodes were recorded.

Statistical methods

Because the modification of β -carotene effect by age and the ATBC Study lasted for some 6 years, the baseline age was not used in the current analyses, but the age of the participant at the follow-up visit was used instead. This is the biological age at the point of time when the outcome for the preceding 4-month period is evaluated.

The number of common cold episodes was modeled using Poisson regression. The RR and the Wald 95% confidence interval (CI) were calculated using the SAS PROC GENMOD program (release 9.2; SAS Institute, Inc., Cary, NC). Linear spline-modeling^{5,14} was carried out for the four subgroups defined by the age of smoking initiation (≤ 20 or ≥ 21 years) and baseline smoking (5–14 or ≥ 15 cigarettes/day) as given below.

First, a base model was constructed containing the mean β -carotene effect and a linear trend to adjust for the average

reduction in common cold incidence with age. Then nine linear splines were added to both trial arms at 2-year intervals, starting at 54 years of age at follow-up. Thereafter, linear spline terms were added for the β -carotene arm to the same knots. This saturated model was simplified by dropping the knots that had the least effect on the β -carotene spline model, starting with those with the lowest Wald test χ^2 value. Concurrently, the corresponding knots covering both arms were dropped out. The models were simplified until all remaining β -carotene arm knots made a significant contribution to the spline model (Wald test $\chi^2 > 4$). The final model thus contained knots at the same years for both arms to provide the baseline and for the β -carotene arm to provide the age modification of the β -carotene effect. If none of the knots were significant in the Wald test, the effect of β -carotene was reduced to a uniform effect that is constant over the studied age range. The statistical significance of the interaction between β -carotene effect and age at follow-up was calculated from the change in the $-2 \times \log(\text{likelihood})$ difference when comparing the final model and the model without knots in the β -carotene arm. The change in the $-2 \times \log(\text{likelihood})$ gives the χ^2 value with the degrees of freedom defined by the number of knots in the final model.

To test the statistical significance of interaction between β -carotene supplementation and potential modifying factors in Tables 2–5, ie, heterogeneity, supplementation and the modifying factor were first added to the regression model. Thereafter, the interaction terms of β -carotene supplementation and the modifying factor were added to the model. The statistical significance of the interaction from the change in $-2 \times \log(\text{likelihood})$ was calculated, which gives the χ^2 value with degrees of freedom defined by the number of interaction terms in the model.

As to supplementation, the analyses were carried out following the intention-to-treat principle. Compliance with

Table 2 The effect of β -carotene on common cold incidence; the ATBC Study 1985–1993: participants aged 50–59 years at the follow-up visit

Age of smoking initiation (years)	Cigarettes/day	No. of participants	No. of visits	Intervention colds/visit		RR	95% CI
				β -carotene	Placebo		
≥ 21	5–14	574	6130	0.292	0.269	1.08	0.98, 1.19
≥ 21	≥ 15	1783	20,554	0.311	0.304	1.02	0.97, 1.08
≤ 20	5–14	1036	10,929	0.315	0.273	1.15	1.08, 1.24
≤ 20	≥ 15	5939	66,237	0.295	0.293	1.00	0.98, 1.04

Notes: Each participant visited the study center three times per year for evaluation of whether he had had common cold episodes after the preceding visit. Adding a uniform β -carotene effect onto all of the 103,850 visits at the follow-up age of 50–59 years yields RR = 1.030 (95% CI: 1.007, 1.053). Adding an individual β -carotene effect, shown in this table, to each of the four subgroups improves the Poisson model by χ^2 (3 df) = 14.2, corresponding to $P = 0.003$. There is a significant interaction between baseline smoking and the effect of β -carotene ($P = 0.0004$) but not between the age of smoking initiation and the effect of β -carotene ($P = 0.6$). There is no second-order interaction between the age of smoking initiation and baseline smoking with the effect of β -carotene ($P = 0.2$).

Table 3 The effect of β -carotene on common cold incidence; the ATBC Study 1985–1993: participants aged ≥ 70 years at the follow-up visit

Age of smoking initiation (years)	Cigarettes/day	No. of participants	No. of visits	Intervention colds/visit		RR	95% CI
				β -carotene	Placebo		
≥ 21	5–14	178	1515	0.205	0.269	0.76	0.61, 0.94
≥ 21	≥ 15	325	2619	0.216	0.204	1.06	0.90, 1.26
≤ 20	5–14	256	1960	0.236	0.235	1.00	0.83, 1.21
≤ 20	≥ 15	640	4354	0.218	0.187	1.16	1.02, 1.33

Notes: Each participant visited the study center three times per year for evaluation of whether he had had common cold episodes after the preceding visit. Adding a uniform β -carotene effect onto all of the 10,448 visits at the follow-up age of ≥ 70 years yields RR = 1.03 (95% CI: 0.95, 1.13). Adding an individual β -carotene effect, shown in this table, to each of the four subgroups improves the Poisson model by χ^2 (3 df) = 11.6, corresponding to $P = 0.009$. There is a significant interaction between baseline smoking and the effect of β -carotene ($P = 0.007$), and between the age of smoking initiation and the effect of β -carotene ($P = 0.035$). There is no second-order interaction between the age of smoking initiation and baseline smoking with the effect of β -carotene ($P = 0.5$).

supplementation was high: about 80% of participants took more than 95% of their prescribed capsules during their active participation in the trial, and there were no differences in capsule consumption between the intervention arms.^{15,16} The outcome was available only for those participants who continued with the trial and participated in the follow-up visits. Two-tailed P values were used.

Results

Table 1 shows the distributions for the baseline data for age, level of smoking, and age of smoking initiation and follow-up data for age at the follow-up visits. On an average, 0.27 common cold episodes were reported at each 4-month follow-up visit, corresponding to an annual rate of 0.8 cold episodes. With a particularly narrow CI, β -carotene had no overall

effect on the incidence of colds in the whole participant population: RR = 1.009 (95% CI: 0.993, 1.026).

To test the potential modification of β -carotene effect by age, I constructed linear spline models for the β -carotene effect as a function of the age at follow-up separately for the four subgroups defined by the baseline smoking level and the age of smoking initiation (Figures 1 and 2). Three subgroups show statistically highly significant modification of β -carotene effect by age, whereas the subgroup of participants who initiated smoking at ≥ 21 years and smoked ≥ 15 cigarettes per day at baseline does not show modification of β -carotene effect by age.

Based on the appearance of the spline curves, two age ranges were selected for calculating the estimates of the β -carotene supplementation effect and for testing the

Table 4 The effect of β -carotene on common cold incidence; ATBC Study participants aged ≥ 70 years: the age of smoking initiation ≥ 21 years and smoking 5–14 cigarettes per day at baseline

Subgroup	No. of visits	RR of colds	95% CI	Interaction P
All	1515	0.76	0.61, 0.94	
Dietary β -carotene (mg/day)*				
<2.0	731	0.89	0.64, 1.23	0.5
≥ 2.0	710	0.77	0.58, 1.03	
Weight (kg)				
<60	125	0.42	0.21, 0.81	0.015
60–84	1003	0.97	0.74, 1.26	
≥ 85	387	0.57	0.37, 0.88	
Alcohol (mL/day)*				
0	223	0.77	0.42, 1.37	0.9
>0–9.9	877	0.76	0.58, 0.99	
≥ 10	341	0.85	0.54, 1.34	

Notes: *Restricted to participants with data available on the variable. β -Carotene intake level is cut close to the median.

Table 5 The effect of β -carotene on common cold incidence; ATBC Study participants aged ≥ 70 years: the age of smoking initiation ≤ 20 years and smoking ≥ 15 cigarettes per day at baseline

Subgroup	No. of visits	RR of colds	95% CI	Interaction P
All	4354	1.16	1.02, 1.33	
Dietary β -carotene (mg/day)*				
<1.6	2035	1.39	1.14, 1.71	0.015
≥ 1.6	2054	1.00	0.82, 1.20	
Weight (kg)				
<60	400	1.05	0.67, 1.66	0.4
60–84	2940	1.12	0.95, 1.31	
≥ 85	1014	1.38	1.04, 1.85	
Alcohol (mL/day)*				
0	743	1.88	1.31, 2.69	0.010
>0–9.9	1724	1.13	0.91, 1.40	
≥ 10	1622	1.00	0.82, 1.23	

Notes: *Restricted to participants with data available on the variable. β -Carotene intake level is cut close to the median.

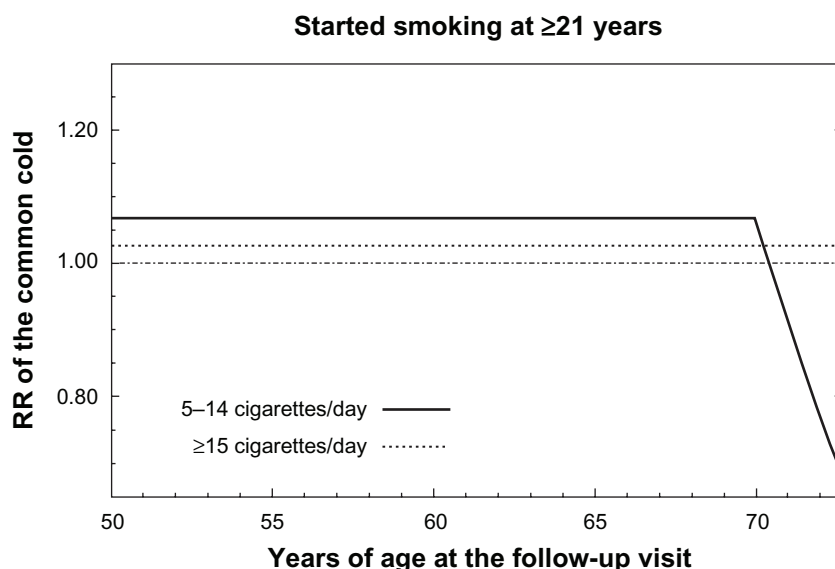


Figure 1 RR of the common cold incidence in the β -carotene arm compared with the placebo arm. The ATBC Study 1985–1993: participants who started smoking at ≥ 21 years. Adding one knot to the spline curve of the participants who smoked 5–14 cigarettes per day at baseline improves the spline model by χ^2 (1 df) = 11.9, corresponding to $P = 0.0006$. In the participants who smoked ≥ 15 cigarettes per day at baseline, no knot made a significant contribution to the form of the spline curve, which is located horizontally at $RR = 1.03$. The placebo arm level is indicated by the broken line at $RR = 1.00$.

modification of β -carotene effect by smoking. Among the 50- 59-year-old participants, β -carotene increases the incidence of colds in those who smoked 5–14 cigarettes per day, whereas it has no effect on those who smoked ≥ 15 cigarettes per day (Table 2). In this group, baseline smoking significantly modifies the effect of β -carotene, but the age of smoking initiation does not (Table 2). There is statistically significant heterogeneity in the effect of β -carotene in the four subgroups among the 50- 59-year-old participants.

Among the ≥ 70 -year-old participants, the effect of β -carotene diverges (Table 3). In this group, both baseline smoking and the age of smoking initiation significantly modify the effect of β -carotene, but the two measures of smoking exposure do not have interaction (Table 3). The greatest benefit of β -carotene is seen among those who initiated smoking at ≥ 21 years and smoked 5–14 cigarettes per day, whereas the greatest harm is seen in the reverse, ie, in those who started smoking at ≤ 20 years and smoked ≥ 15 cigarettes per day.

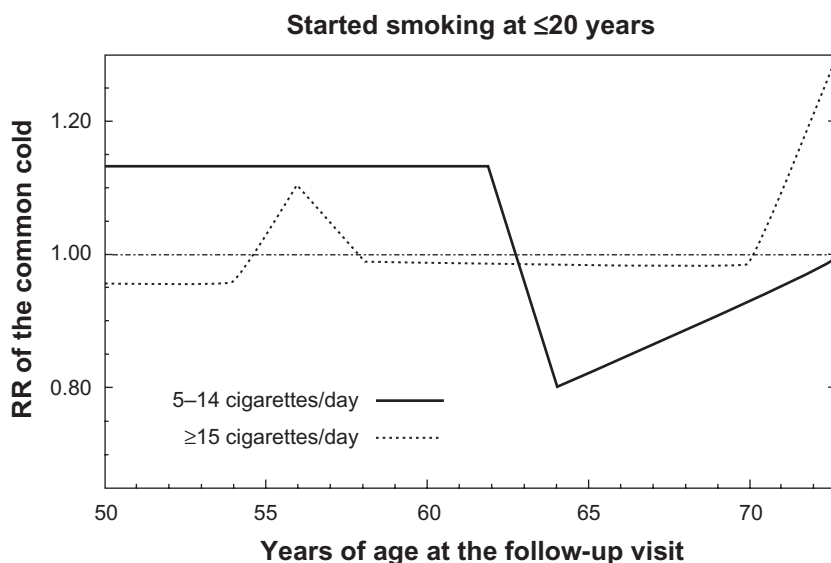


Figure 2 RR of the common cold incidence in the β -carotene arm compared with the placebo arm. The ATBC Study 1985–1993: participants who started smoking at ≤ 20 years. Adding two knots to the spline curve of the participants who smoked 5–14 cigarettes per day at the baseline improves the regression model by χ^2 (2 df) = 30.1, corresponding to $P = 0.0000003$. Adding four knots to the participants who smoked ≥ 15 cigarettes per day at baseline improves the regression model by χ^2 (4 df) = 18.8, corresponding to $P = 0.0009$. The placebo arm level is indicated by the broken line at $RR = 1.00$.

The CI for the β -carotene effect on these two subgroups is strikingly different (Table 3). In Tables 4 and 5, further possible modifications were explored in the subgroups of ≥ 70 -year-old participants who had the greatest benefit and the greatest harm from β -carotene supplementation.

Among the ≥ 70 -year-old participants who started smoking at ≥ 21 years and smoked 5–14 cigarettes per day, dietary β -carotene intake did not modify the effect of supplementation (Table 4). The benefit of β -carotene supplementation was restricted to the low- and heavy-weight participants, whereas it had no effect on those with medium body weight. Alcohol intake did not modify the β -carotene effect.

Among the ≥ 70 -year-old participants who had started smoking at ≤ 20 years and smoked ≥ 15 cigarettes per day, the interaction between dietary and supplement β -carotene was significant, the harm from the supplement being restricted to those who had low dietary β -carotene intake (Table 5). Weight did not significantly modify the effect of β -carotene, although the harm was more apparent in the heaviest participants. Alcohol intake modified the β -carotene effect, so that this effect was restricted to those who did not consume alcohol at all.

Discussion

In the ATBC Study, β -carotene supplementation had no overall effect on common cold incidence.¹⁰ However, the current study refutes the notion that the effect of β -carotene supplementation on common cold incidence is uniform over the whole ATBC Study population. In three of four subgroups defined by the exposure to cigarette smoking, the effect of β -carotene supplementation was significantly modified by age. Furthermore, β -carotene significantly reduced the incidence of colds among older participants who were least exposed to smoking, whereas among older participants who were most heavily exposed to smoking, β -carotene significantly increased the incidence of colds. The strong evidence indicating that the β -carotene effect on common cold incidence varies between population groups has important implications.

It has been pointed out that observational studies on vitamins, ie, case control and cohort studies, are often unreliable because diet is strongly associated with numerous lifestyle factors which cannot be fully adjusted for in statistical models.^{3,4} The ATBC Study was initiated because observational studies found reduced lung cancer risk in people who had a high dietary intake of β -carotene. However, the ATBC and CARET studies found, paradoxically, that β -carotene supplementation increased the incidence of lung cancer,

thereby refuting the conclusions based on the observational studies.^{15,19} Similarly, meta-analyses of vitamin E trials^{20,21} refuted the cohort studies suggesting that increased vitamin E intake would reduce the risk of cardiovascular diseases in large population groups.^{22,23}

The variation in β -carotene supplementation effect between different population groups found in this study provides further evidence against the validity of observational studies in nutrition. Confounders are typically adjusted for statistically in observational studies, allowing calculation of a uniform effect across the population. However, the significant modification of the β -carotene effect by age and smoking means that the effect of β -carotene should be studied separately in groups defined by age and appropriate measures of cigarette smoke exposure, rather than calculating a uniform effect adjusting for those variables as if they were confounders. The marked heterogeneity in the β -carotene effect on common cold incidence in the ATBC Study is thus a further refutation of the studies calculating correlations between the levels of dietary substances and the incidence of diseases. Large randomized trials such as the ATBC Study can give accurate estimates for subgroups, as shown by the current study and our earlier subgroup analyses of vitamin E supplementation effects.^{5–9,13,24} However, similar subgroup analyses in observational studies are much more challenging or impossible because of the close associations between dietary variables with each other and with numerous other lifestyle factors.^{3,4}

A number of cohort studies have reported on the association between dietary β -carotene intake and the incidence of respiratory tract infections suggesting that the relationship is uniform over the study population.^{6,10–12} The current findings on the randomized groups of the ATBC Study refute the notion of uniformity, implying that the results of the cohort studies can be unreliable.

Another source of data for assessing the role of β -carotene on infections is available from the multivitamin supplement trials with elderly people.^{25–27} If there is no effect on infections in a multivitamin trial, it seems justified to conclude that each vitamin of the supplement lacks an effect. The trials with multivitamin supplements containing 1.2–16 mg/day of β -carotene did not show a reduction in the number of respiratory infections,^{25–27} implying that the increase in the level of β -carotene intake had no effect. Although the negative findings in the multivitamin trials discourage multivitamin supplementation for the purpose of reducing infections among the elderly, the conclusions are limited by the small size of the trials. A great proportion of the participants in

the multivitamin trials were under 70, and the trials were small, with a maximum of 1024 infection episodes recorded by Graat et al.²⁶ In the ATBC Study, β -carotene had no effect on participants somewhat older than 60, whereas it had significantly divergent effects on those more than 70. Figures 1 and 2 are based on 55,905 common cold episodes, which provide statistical power to carry out analyses of age dependency in the four subgroups. Thus, it may be justified to examine the effect of β -carotene on less smoking and nonsmoking males who are older than 70 years (Figure 2), even though the average effect in the ATBC Study was null and the β -carotene containing multivitamin supplements had no effects.^{25–27}

A further implication of the current study is that it provides a strong argument against the opinion that subgroup analyses of controlled trials should be strongly discouraged because they can lead to false positive findings due to the multiple comparison problem.²⁸ Biology is complex, and it seems unlikely that the belief in a uniform effect is usually justified. Given the long-term commitment of participants and the resources invested, it might even be considered as a duty of the researchers to analyze the large trial databases as extensively as possible rather than simply calculating an overall effect. Subgroup findings should obviously be considered cautiously, and the interpretation of *P* values must be related to the number of subgroup analyses being carried out. Nevertheless, the current subgroup findings of the ATBC Study suggest that further studies of β -carotene in males older than 70 years may be justified, although the overall estimate of $RR = 1.009$ indicates that no further studies would be worthwhile.

Exploratory subgroup analyses of the two groups of the old participants who showed the greatest harm and the greatest benefit from β -carotene supplementation were carried out (Tables 4 and 5). Since a fixed β -carotene dose was used in the ATBC Study, the dose–response of β -carotene supplementation cannot be examined directly. Nevertheless, it can be explored indirectly by examining the variation in β -carotene effect by body weight. Previously, it was found that vitamin E supplementation increased the incidence of pneumonia among low-weight ATBC participants, but not among middle-weight participants, consistent with the dose–response assumption.⁷ However, vitamin E also increased the incidence of pneumonia in the heaviest participants, which lacks a similar simple rationalization.⁷ Among the old ATBC Study participants who started smoking at a later age and smoked less at the baseline, the effect of β -carotene on common cold incidence was similarly restricted to the low

and high ends of the body-weight scale (Table 4). Weight did not modify β -carotene effect among the heavy smokers who initiated smoking at an early age (Table 5).

Dietary β -carotene intake might influence the effect of β -carotene supplementation. There was a significant interaction between dietary and supplement β -carotene among heavy smokers who started smoking at an early age (Table 5); however, this modification might be caused by other substances in vegetables as well and does not imply specificity to β -carotene.

Previously, the increased risk of lung cancer with β -carotene supplementation was restricted to participants who had a high intake of alcohol.²⁹ In this study, alcohol intake modified the effect of β -carotene on common cold incidence among heavy smokers who started smoking at an early age, so that the harm was restricted to teetotalers (Table 5).

The purpose of this study was to test whether the effect of β -carotene supplementation on common cold incidence is uniform among the ATBC Study population. The numerical estimates calculated for the subgroups are much less essential than the strong evidence of heterogeneity. Although the primary focus of this study was on age and smoking as variables potentially modifying the effect of β -carotene supplementation, Tables 4 and 5 indicate that many more variables may modify the supplementation effect. When the effect of β -carotene supplementation depends on individual characteristics, the estimates of effect obtained in one study cannot be confidently generalized to other population groups.

Conclusions

The main finding of this study is that β -carotene supplementation may increase, decrease, or have no effect on the incidence of common cold among male smokers depending on age and the level of smoking exposure. It is premature to draw any practical conclusions from the current subgroup findings, but the strong evidence of heterogeneity in the β -carotene supplementation effect challenges the validity of observational studies in nutrition, because they are usually based on the assumption of a uniform effect over the study population.

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