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The Effect of Vitamin E on Common Cold Incidence Is Modified by Age, Smoking and Residential Neighborhood

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ABSTRACT

Background: We have previously found a 28% reduction in common cold incidence with 50 mg/day vitamin E supplementation in a subgroup of the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study cohort: older city-dwelling men (≥65 years) who smoked only 5–14 cigarettes/day.

Objective: To carry out more detailed analyses to explore the modification of vitamin E effect by age, smoking, and residential neighborhood.

Methods: We examined the effect of vitamin E on common cold risk in subjects consisting of the placebo and vitamin E arms (n = 14,573) of the ATBC Study, which recruited males aged 50–69 years who smoked ≥5 cigarettes/day at the baseline. The ATBC Study was conducted in southwestern Finland in 1985–1993; the active follow-up lasted for 4.7 years (mean). We modeled common cold risk as a function of age-at-follow-up in the vitamin E arm compared with the placebo arm using linear splines in Poisson regression.

Results: In participants of 72 years or older at follow-up, the effect of vitamin E diverged. Among those smoking 5–14 cigarettes per day at baseline and living in cities, vitamin E reduced common cold risk (RR = 0.54; 95% CI 0.37–0.80), whereas among those smoking more and living away from cities, vitamin E increased common cold risk (RR = 1.58; 1.23–2.01).

Conclusions: Vitamin E may cause beneficial or harmful effects on health depending on various modifying factors. Accordingly, caution should be maintained in public health recommendations on vitamin E supplementation until its effects are better understood.

INTRODUCTION

Animal studies have found that vitamin E may affect susceptibility to and severity of diverse viral and bacterial respiratory infections (1-5). Although several studies found that vitamin E may have beneficial effects on various laboratory measures of the immune system in animals and humans (5,6), harmful effects on the immune system have also been reported (7,8). Two animal studies found positive effects on the immune system with moderate vitamin E doses, but adverse effects with large doses (9,10).

Only a few trials have examined the effect of vitamin E supplementation on clinical infectious disease outcomes, such as respiratory and urinary tract infections (5,11-15) and tuberculosis (16) in human subjects. On the whole, these trials found no unequivocal benefit from vitamin E and, paradoxically, one trial found an increase in the severity of acute respiratory illness with 200 mg per day of vitamin E (12). Three trials examined the effect of vitamin combinations containing vitamin E on respiratory infections; however, no specific conclusions of vitamin E can be drawn of these trials (17-19).

We previously found no overall effect on common cold risk with 50 mg per day of vitamin E in the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study (20). However, in a small subgroup of older city-dwelling men (≥65 years) who smoked only 5–14 cigarettes per day, vitamin E supplementation was associated with a statistically highly significant, but quantitatively modest, reduction in common cold incidence (RR = 0.72; 95% CI: 0.62–0.83) (20). Whether this observation resulted from a physiological effect or emerged by chance from a series of subgroup analyses remained an open question. Since the number of common cold episodes recorded in the ATBC Study was very high, we carried out more detailed analyses to explore the possibility that vitamin E effect is modified by age, smoking, and residential neighborhood.

PARTICIPANTS AND METHODS

Study Participants and Intervention Groups

The design and methods of the ATBC Study examining the effects of vitamin E (*dl*-*α*-tocopheryl acetate (AT), 50 mg/day) and *β*-carotene (BC, 20 mg/day) on the incidence of lung cancer and other cancers have already been described in detail (20,21). In brief, the trial participants were recruited in 1985–88 from the total male population aged 50–69 years living in southwestern Finland (n = 290,406). To be eligible, participants had to smoke ≥5 cigarettes per day at entry. The eligible participants (n = 29,133) were randomized to one of four intervention arms and administered placebo, AT, BC, or AT + BC. The planned intervention continued for 5 to 8 years (median 6.1 years) until April 30, 1993, with 3 follow-up visits annually, but because of deaths and drop-outs the active follow-up lasted for 4.7 years (mean). The trial was approved by the institutional review boards of the participating institutions; all participants gave written informed consent. At baseline, prior to randomization, the men completed a questionnaire on their medical and smoking histories and general background characteristics. In the current analysis we excluded participants who were administered *β*-carotene to avoid any problems caused by potential interaction between vitamin E and *β*-carotene, so that we restricted ourselves to the placebo and AT arms of the trial (n = 14,573; Table 1).

Outcome Definition and Smoking Status Evaluation during Follow-Up

At each follow-up visit to the local study center, 3 times per year with 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 infection" 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, since it is the subjective symptoms that 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 typical that self-diagnosis by the patient is usually correct (22). During 69,094 person-years of active follow-up covered by visits to the study centers, 55,770 common cold episodes were recorded.

At each follow-up visit, the participant was asked: "Have you been smoking since the previous visit?" with the following alternative responses provided: 1) no, 2) yes, but now I have quit, 3) yes, continuously (Table 1). In this study we used responses 1) and 3) when exploring the effect of smoking cessation before the follow-up visit.

Statistical Methods

Because we analyzed the modification of vitamin E effect by age, and the ATBC Study lasted for some 6 years, in the current analyses we used the age of participant at the follow-up visit. 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 risk ratio (RR) and the likelihood ratio-based 95% confidence interval (95% CI) were calculated using the SAS PROC GENMOD program (release 8.1, SAS Institute, Inc., Cary, NC). Linear spline-modeling (23) was carried out for the four groups defined by baseline smoking and residential neighborhood as follows.

First, using a base model containing the mean vitamin E-effect, and a linear trend to adjust for the average reduction in common cold incidence with age, we added ten linear splines to both trial arms at 2 year-intervals starting at 52 years of age-at-follow-up. Thereafter, linear spline terms for the vitamin E arm were added to the same knots, and the statistical significance of the vitamin E—age-at-follow-up interaction was calculated from the change in the –2 × Log(Likelihood) difference. This saturated model was simplified by dropping the knots that had the least effect on the vitamin E spline model, starting with those with the lowest Wald-test χ^2 value. The corresponding knots covering both arms were concurrently dropped out. The models were simplified until all remaining vitamin E arm knots gave a significant contribution to the spline model ($\chi^2 > 4$). Thus, the final model contained knots at the same years for both arms to provide the baseline, and for the vitamin E arm to provide the age-modification. Visually, the final models captured all the main features of the saturated models (graphs for saturated models not shown). The optimized models are described in Table 2 and the corresponding graphs in Fig. 1. Two-tailed *p*-values were used.

We tested the modifying effect of residential neighborhood on the vitamin E effect separately in participants who smoked 5–14 and those who smoked ≥15 cigarettes per day. Based on the appearance of the spline curves (Fig. 1), we restricted this analysis to participants aged ≥62 and ≥65 years at the follow-up visit, respectively, in the light and heavy smokers. First we added a linear trend to adjust for the average reduction in common cold incidence with age, the mean vitamin E-effect, mean effect of residential neighborhood, and a linear spline to the vitamin E arm at 62 or 65 years. To test the role of residential neighborhood, we further added the mean vitamin E effect and a linear spline to the vitamin E arm to the city-dwellers. The change in the –2 × Log(Likelihood) gives χ^2(2 df), which was used to calculate the *p*[2-tail]-value to test the role of residential neighborhood in the vitamin E spline-models.

As to supplementation, the analyses were carried out following the intention-to-treat principle. Compliance with supplementation was high: some 80% of participants took more than 95% of their prescribed capsules during their active participation in the trial; there were no differences in capsule consumption among the intervention groups (21). The outcome was, however, available only for those participants who continued with the trial and participated in the follow-up visits.

Table 1. Baseline Characteristics of Participants, and the Age and Smoking Status at Follow-Up Visits, The ATBC Study 1985–1993; No β-Carotene Participants

Baseline characteristics	No. of participants
All participants	14,573 (100%)
Baseline age (years)	
50–54	5,275 (36%)
55–59	4,639 (32%)
60–64	3,183 (22%)
65–69	1,476 (10%)
Smoking (cigarettes/day)	
5–14	2,910 (20%)
15–	11,663 (80%)
Age of smoking initiation*	
<21 years	10,842 (74%)
≥21 years	3,727 (26%)
Residential neighborhood during the last 20 years*	
City (>50,000 inhab.)	6,233 (43%)
Town	3,093 (21%)
Village	2,092 (14%)
Countryside	3,153 (22%)

Follow-up visit variables	No. of visits
All visits	207,284 (100%)
Age at follow-up visit	
50–51	5,265
52–53	16,603 (8%)
54–55	25,517 (12%)
56–57	29,240 (14%)
58–59	28,127 (14%)
60–61	25,902 (12%)
62–63	22,588 (11%)
64–65	18,685 (9%)
66–67	14,513 (7%)
68–69	10,642 (5%)
70–71	6,485 (3%)
72–73	2,805 (1.5%)
74–77	912 (0.5%)
Smoking since the previous visit	
No	23,032 (11%)
Yes, but quit before current visit	5,817 (3%)
Yes, continuously	178,433 (86%)

* Data on residential neighborhood was missing from 2 participants, and on age at smoking initiation from 4 participants.

Table 2. Optimizing the Spline Models for the Age-Modification of Vitamin E Effect on Common Cold Incidence

Group	Saturated model*	Simple model*
≥15 cigarettes per day living away from cities	χ^2(10 df) = 40.9	χ^2(4 df) = 36.5 $p = 0.0000002$ knots at 52, 56, 58, 68 yrs
≥15 cigarettes per day living in a city	χ^2(10 df) = 17.3	χ^2(2 df) = 7.8 $p = 0.02$ knots at 64, 66 yrs
5–14 cigarettes per day living away from cities	χ^2(10 df) = 22.3	χ^2(1 df) = 18.9 $p = 0.00002$ knot at 56 yrs
5–14 cigarettes per day living in a city	χ^2(10 df) = 46.5	χ^2(2 df) = 38.7 $p = 0.000000004$ knots at 60, 62 yrs

* The χ^2 measures the improvement in the Poisson model when the knots indicated are added to the vitamin E arm in the simple model.
In the saturated model, 10 knots at 2-year intervals were added, starting at 52 years.

RESULTS

Table 1 shows the distributions for the baseline data for age, smoking level, age of smoking initiation, residential neighborhood, and follow-up data for age and smoking at the follow-up visits. On average, 0.27 common cold episodes were reported at each four-monthly follow-up visit, corresponding to an annual rate of 0.8 cold episodes.

There is no overall effect, with a narrow confidence interval, of vitamin E supplementation in the four groups defined by baseline smoking and residential neighborhood (Table 3). To examine the potential modification of vitamin E effect by age, we constructed linear spline models for the vitamin E effect as a function of age-at-follow-up separately for the four groups defined by baseline smoking and residential neighborhood. These groups show statistically highly significant modification of vitamin E effect by age-at-follow-up, except for city-dwellers smoking ≥15 cigarettes per day (Fig. 1, Table 2).

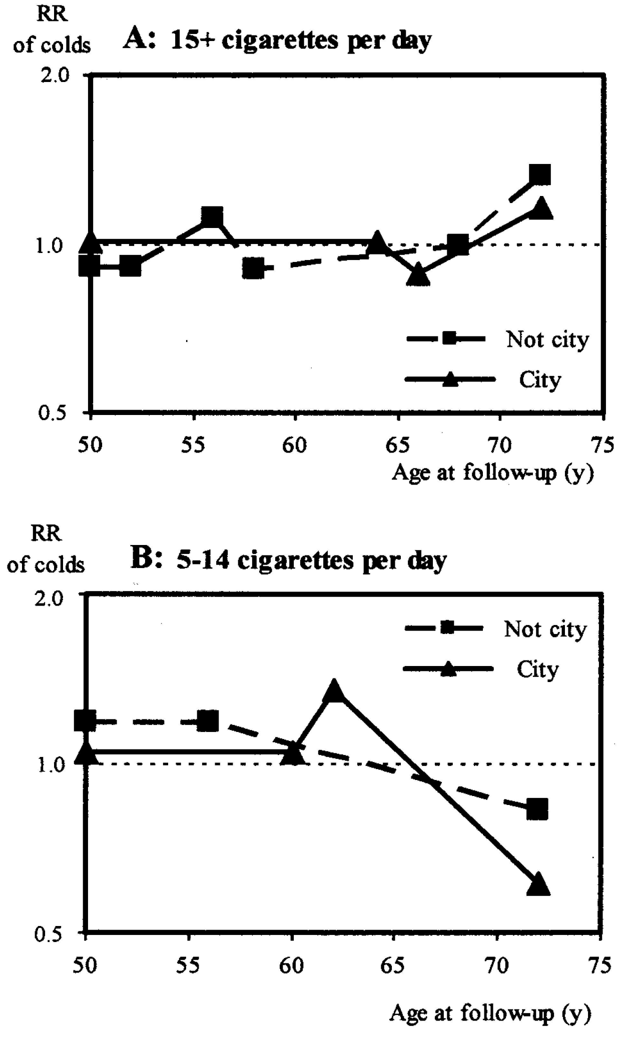

Fig. 1. The effect of vitamin E on the relative risk of common cold as a function of age at follow-up. Participants smoking more (A) and less (B) are further divided into subgroups by residential neighborhood. RR indicates the relative risk of colds between the vitamin E and placebo arms. See Table 2 for the description of the statistical models.
See Fig. 1. redrawn in 2014 at the end of this paper.

Among participants who smoked ≥15 cigarettes per day at baseline, the spline curve of vitamin E effect shows a trend towards harm for old participants (Fig. 1A). Among the heavy smokers living away from cities, there is a peak of increased risk at 56 years of age. Although there is no apparent biological rationale for such a sharp peak in the common cold risk, dropping out the knots at 52, 56, and 58 years would reduce the χ^2 value by 17.9 (3 df; $p = 0.0005$) so that these knots are retained in the spline model.

Among participants who smoked only 5–14 cigarettes per day at baseline, the spline curves suggest slight harm for young participants, but there is an age-dependent trend towards benefit in old participants (Fig. 1B). Among the city-dwellers who smoke less, there is a peak indicating harm at about 62 years of age. Although there is no apparent biological rationale for such a sharp peak here either, omitting the knot at 62 years reduces the χ^2 value by 16.3 (1 df; $p = 0.0001$); therefore both knots are retained in the spline model. The knot at 56 years in the participants smoking less, who live away from cities, remained after the stepwise reduction of the spline model, but there was no meaningful difference compared with spline models with a single knot located at 52, 54 or 58 years.

Because this work was motivated by the effect of vitamin E observed in the subgroup of ≥65 year old city-dwellers who smoked 5–14 cigarettes per day (20) and inclusion of that subgroup in the vitamin E spline model does not provide a test independent of the original finding, we examined whether age is a modifier outside of this small subgroup. When the participants aged ≥65 years at baseline were excluded from the spline model of the city-dwellers who smoked 5–14 cigarettes per day at baseline, the vitamin E spline model was still highly significant (χ^2[2 df] = 12.3, $p = 0.002$). The other three of the four subgroups test the age-modification of vitamin E effect independently of the original hypothesis-generating subgroup (Table 2).

Among the oldest participants, the effect of vitamin E on common cold incidence substantially diverges in the light and heavy smokers, but the role of residential neighborhood is less evident (Fig. 1). Therefore we tested whether including the residential neighborhood significantly improves the vitamin E spline models at the upper age range. Among participants who smoked 5–14 cigarettes per day there was strong evidence that the age at visit of 62 years or more modifies the vitamin E effect differently in city-dwellers and those who live away from cities ($p = 0.018$). In contrast, for those who smoked ≥15 cigarettes per day there was weaker evidence that the age at visit of 65 years or more modifies the vitamin E effect differently in the residential neighborhood groups ($p = 0.042$).

Based on the appearance of the spline curves, certain age-ranges were selected for explicit calculation of the effect estimate of vitamin E supplementation and its confidence interval (Fig. 1, Table 3). Vitamin E supplementation for participants smoking less was associated with a significant increase in the risk of colds at 50–56 years in those who live away from cities, and at 61–63 years in the city-dwellers. For city-dwellers who smoke less, vitamin E supplementation caused a substantial reduction in the risk of colds for participants aged 69 years or more, but the benefit was smaller among participants living away from cities. Among the heavy smokers, vitamin E supplementation significantly increased the risk of colds among the oldest participants (Table 3).

It is noteworthy that among the ≥72 year old participants the greatest benefit was seen in city-dwellers smoking 5–14 cigarettes per day, whereas the greatest harm was seen in the mirror image, i.e., participants living outside cities and smoking ≥15 cigarettes per day (Fig. 1, Table 3). The confidence intervals for the vitamin E effect on these two groups are strikingly different. It is also noteworthy that in both of these groups there is a peak of harm at 62 and 54 years respectively, whereas the remaining two groups do not show comparable peaks for the younger participants.

The preceding analysis is based on defining the subgroups by smoking level at baseline. To explore whether other measures of cigarette smoke exposure would further modify the effect of vitamin E, we analyzed the risk of colds in participants aged ≥72 years by combining the residential neighborhood groups, but keeping the baseline low and heavy smoking groups separate. Among the old participants who smoked heavily at baseline, the vitamin E effect is significantly modified by the age of smoking initiation (Table 4). In these heavy smokers, there was no definite evidence of harm from vitamin E in those who quit smoking before the visit, but the number of quitters is low. Among participants who smoked less at baseline, age of smoking initiation did not modify the vitamin E effect, and smoking cessation did not lead to a greater vitamin E benefit (Table 4).

Table 3. The Effect of Vitamin E Supplementation on the Risk of the Common Cold in Selected Age-Groups by Baseline Smoking and Residential Neighborhood

	≥15 cigarettes per day		**5–14 cigarettes per day**	
	Town, village, or countryside	**City**	**Town, village, or countryside**	**City**
Number of participants:	6,587	5,074	1,751	1,159
All visits (207,270 visits)				
RR	0.98	1.00	1.02	1.02
95% CI	0.95–1.01	0.97–1.03	0.97–1.08	0.96–1.08
Age at visit				
50–56 yrs (62,054 visits)				
RR	1.01	0.98	1.20	1.07
95% CI	0.96–1.05	0.93–1.03	1.08–1.32	0.96–1.20
61–63 yrs (35,182 visits)				
RR	0.93	1.02	0.97	1.30
95% CI	0.87–0.99	0.95–1.10	0.86–1.09	1.13–1.50
69–71 yrs (11,321 visits)				
RR	1.11	1.04	0.80	0.68
95% CI	0.98–1.27	0.90–1.19	0.67–0.96	0.54–0.84
72–77 yrs (3,717 visits)				
RR	1.58	1.35	0.90	0.54
95% CI	1.23–2.01	1.03–1.76	0.63–1.28	0.37–0.80

Table 4. Modification of Vitamin E Effect on Common Cold Risk by Age at Smoking Initiation and by Recent Smoking among Participants Aged 72 Years or More at the Follow-Up Visit

	Risk of colds in the vitamin E arm RR; 95% CI	**Test of interaction** *p*
Baseline smoking ≥15 cigarettes per day		
All in the subgroup (2,513 visits)	1.42; 1.18–1.70	
Age at smoking initiation		
<21 years (1,482 visits)	1.68; 1.34–2.12	0.02
≥21 years (1,031 visits)	1.09; 0.82–1.45	
Smoking at follow-up		
Continued (1,992 visits)	1.48; 1.21–1.80	0.10
Quit (444 visits)	0.96; 0.59–1.55	
Baseline smoking 5–14 cigarettes per day		
All in the subgroup (1,204 visits)	0.71; 0.54–0.91	
Age at smoking initiation		
<21 years (578 visits)	0.67; 0.45–0.98	0.6
≥21 years (626 visits)	0.75; 0.53–1.06	
Smoking at follow-up		
Continued (788 visits)	0.62; 0.45–0.87	0.12
Quit (368 visits)	0.98; 0.61–1.55	

DISCUSSION

In a previous paper we reported a 28% reduction in common cold incidence with vitamin E supplementation in older city-dwelling men who smoked only 5–14 cigarettes per day (20). The present work was carried out to analyze whether the three characteristics specifying the small subgroup, i.e., age, smoking, and residential neighborhood, would cause a more general modification of the vitamin E effect. The current spline model analyses over age-at-follow-up seem to show that the reduction of common cold incidence with vitamin E in the previously identified small subgroup (20) is explained by its physiological effects rather than by a chance occurrence emerging from a series of subgroup analyses.

Age and smoking are plausible modifying factors for the effect of vitamin E on common cold incidence, but a biological rationale for the role of residential neighborhood as a modifying factor is not as apparent. Possibly higher level of air pollution or much more frequent use of public transport with concomitant exposure to infectious agents could explain the observed difference between cities and smaller communities.

Recently, a small trial with 617 elderly participants in long-term care facilities found a slightly lower incidence of colds among participants administered 200 mg per day of vitamin E (RR = 0.83; 95% CI: 0.68–1.01) (13). Another small trial with 652 elderly noninstitutionalized people found a slightly higher incidence of respiratory infection among participants administered 200 mg per day of vitamin E (RR = 1.12; 0.88–1.25), and a statistically significant increase in symptom severity, fever and restriction in activity (12). Although such divergence may result from the small size of the trials, it might also result from biological heterogeneity, as we found both increases and decreases in common cold risk with 50 mg per day of vitamin E supplementation in our current study, depending on the characteristics of the subgroup.

We found quite sharp peaks of increase in common cold risk at 54 and 62 years with vitamin E supplementation in two of our four subgroups (Fig. 1), both highly unlikely to be due to chance, although there is no apparent biological rationale for such peaks. Possibly the peaks may be related to social factors such as retirement, which in Finland occurs usually at about 58 to 60 years; however, retirement does not occur as such a sharp peak as seen in the spline models.

The modification of the vitamin E effect on the common cold risk by age, smoking, and residential neighborhood may be of more general interest as regards the physiological effects of antioxidants. There is evidence indicating that free radical production may be important in the emergence of various chronic diseases such as cancer and cardiovascular diseases (24,25) as well as in the pathogenesis of certain viral and bacterial diseases (26–28). It is sometimes assumed that antioxidants, including vitamin E, might have a consistent unidirectional broad-spectrum benefit on the human system by protecting it against the free radicals (24,25). Our finding that vitamin E supplementation significantly increases or decreases common cold risk depending on the three variables in question is inconsistent with the notion of uniform benefits from antioxidant supplementation.

In the current work we had available a very large number of outcomes (55,770 episodes of the common cold) which rendered it possible to analyze the age-dependence of the vitamin E effect in the four subgroups accurately. With severe diseases such as cancers or cardiovascular diseases, the statistical power is usually too small to permit analyses similar to the current spline models. Still, it is possible that comparable effect-modification occurs in the case of more serious diseases, even though directly extrapolating the particular modifying factors observed in this work to any other diseases is not justified. In a previous analysis of the ATBC Study cohort, we found that the effect of vitamin E on the risk of pneumonia was modified by the age of smoking initiation so that vitamin E reduced pneumonia risk in participants who began smoking at a later age, whereas vitamin E slightly increased the risk among participants who began smoking at an early age (14) (see also Table 4). Thus, our findings for pneumonia risk also suggest substantial heterogeneity between population groups in the effects of vitamin E supplementation.

A recent meta-analysis focusing on the potential harm of vitamin E supplementation found that, starting from approximately 150 mg/day of vitamin E, there was increased mortality among people supplemented with vitamin E (29). However, it is possible that there is biological heterogeneity between population groups, so that people's characteristics may determine whether vitamin E supplementation caused net benefit or harm. In our current study, the vitamin E dose was 50 mg/day, which is substantially less than the estimated threshold level in the above-mentioned meta-analysis (29); however, our current analyses on common cold incidence and our previous analyses on pneumonia incidence make it seem probable that some population groups are harmed at levels of 50 mg/day, even though the same low dose seems beneficial for other population groups (14,15). Thus, it may be unjustifiable to assume that there is a single threshold level for harmful effects that is valid for the entire population. Another recent review on vitamin E safety concluded that supplements appear harmless for most adults in amounts up to 1 g/day (30), whereas our subgroup analyses indicate harmful effects on restricted population groups at doses as low as 50 mg/day (Tables 3 and 4).

The definition of a common cold episode in our study was based on self-diagnosis, which is usually reliable (22). Although subjective perception of what is classified as a cold varies between participants, such inaccuracy in outcome assessment does not lead to consistent differences between our double-blinded study arms; rather, the inaccuracy renders the differences smaller than they may actually be. Our implicit assumption in this work was that the effect of vitamin E is based on its reported effects on the immune system (5,6), but even if the mechanism of the effect of vitamin E would be on other factors that determine whether a person has subjective symptoms of the common cold, the conclusions of our double-blind trial are not affected. Furthermore, even though a proportion of the self-reported colds may be caused by non-infectious etiology, this does not affect the validity of our observation that this common set of symptoms seems to be affected differently with vitamin E in different subgroups of people.

The modification of the vitamin E effect on common cold risk also bears on the heterogeneity of findings in common cold trials examining vitamin C, the major water-soluble antioxidant, which interacts with lipid-soluble vitamin E (5,31,32). The largest vitamin C trials found no effect on the risk of the common cold; however, low dietary vitamin C intake and acute physical stress were proposed as modifying factors that may explain statistically significant reduction in common cold risk with vitamin C supplementation in several small trials (5,33,34). Thus, it seems possible that these two closely related antioxidants, vitamin E and vitamin C, may affect common cold risk in restricted groups of people, even though there seems to be no overall effect in the general Western population.

The main finding of our study is that vitamin E supplementation may cause benefit or harm to health depending on several modifying factors. It is premature to draw any practical conclusions from our study except that general caution should be maintained in public health recommendations on vitamin E supplementation until the effects of this vitamin are better understood. The possibility that vitamin E may reduce the risk of the ubiquitous common cold infection by half in some groups of elderly people would seem to warrant further study to define more precisely the population groups that might benefit from supplementation.

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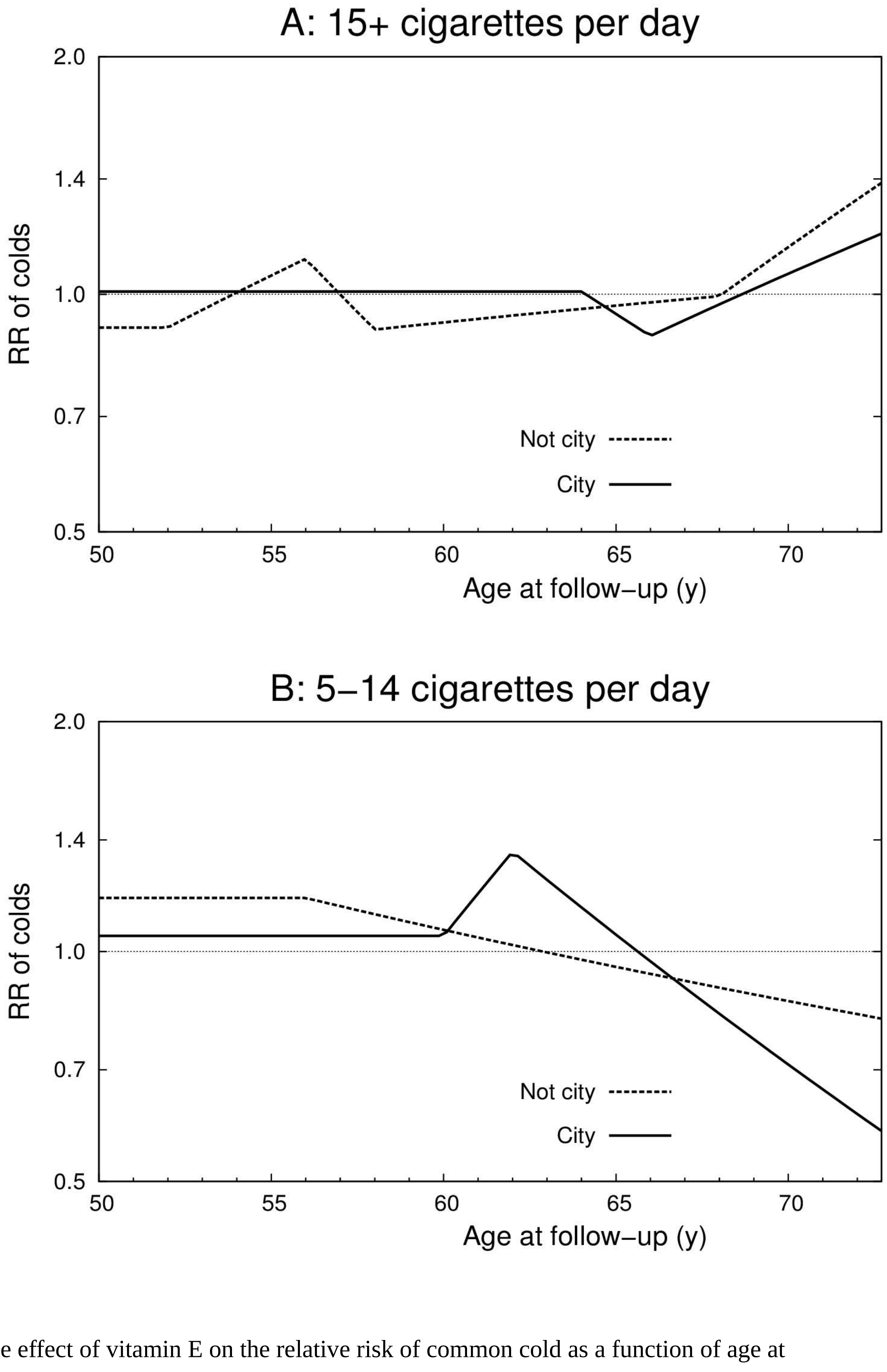
A: 15+ cigarettes per day

B: 5–14 cigarettes per day

Fig. 1. The effect of vitamin E on the relative risk of common cold as a function of age at follow-up. Participants smoking more (A) and less (B) are further divided into subgroups by residential neighborhood. RR indicates the relative risk of colds between the vitamin E and placebo arms. See Table 2 for the description of the statistical models. These versions were redrawn in 2014.