Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking

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Abstract

Background: Antioxidants might protect against oxidative stress, which has been suggested as a cause of aging.

Methods: The ATBC Study recruited males aged 50-69 years who smoked at least 5 cigarettes per day at the baseline. The current study was restricted to participants who were followed up past the age of 65. Deaths were identified in the National Death Registry (1445 deaths). We constructed Kaplan-Meier survival curves for all participants, and for four subgroups defined by dietary vitamin C intake and level of smoking. We also constructed Cox regression models allowing a different vitamin E effect for low and high age ranges.

Results: Among all 10,837 participants, vitamin E had no effect on those who were 65 to 70 years old, but reduced mortality by 24% when participants were 71 or older. Among 2284 men with dietary vitamin C intakes above the median who smoked less than a pack of cigarettes per day, vitamin E extended life-span by two years at the upper limit of the follow-up age span. In this subgroup, the survival curves of vitamin E and no-vitamin E participants diverged at 71 years. In the other three subgroups covering 80% of the participants, vitamin E did not affect mortality.

Conclusions: This is the first study to strongly indicate that protection against oxidative stress can increase the life expectancy of some initially healthy population groups. Nevertheless, the lack of effect in 80% of this male cohort shows that vitamin E is no panacea for extending life expectancy.

Introduction

Half a century ago, Denham Harman proposed that endogenous free radicals might cause aging (1-3). There is evidence that the level of oxidative stress increases during aging (4,5), suggesting that its importance may be particularly great in the later phases of life. Yet, the role of oxidative stress in the aging of humans is not well understood.

A corollary of the oxidative stress theory is that antioxidants might increase life-span because they protect against oxidants. Administration of antioxidants and overexpression of antioxidative enzymes such as superoxide dismutase (SOD), catalase and glutathione reductase have in some cases increased the life-span of animals, but not uniformly. In *Drosophila*, overexpression of SOD increased life-span in strains in which it was initially short, but not in strains in which lifespan was initially long (6). Vitamin E administration (7) and overexpression of glutathione reductase (8) extended the life-span of *Drosphila* during hyperoxia, but not while the oxygen level was normal. Administration of low levels of vitamin C (7) and vitamin E (9) increased life-span of *Drosophila*, but high levels did not, indicating the importance of dosage. Finally, overexpression of SOD and catalase together extended the life-span of *Drosophila,* whereas each alone had only a minor effect (10). Heterogeneity in these findings seems to be particularly important since it indicates that antioxidant levels might be limiting factors under some conditions, although they are not a panacea for extending life-span universally.

Vitamin E supplementation increased life-span in some mice studies (11-13), but not in all (14,15); however, high levels of vitamin E reduced life-span (12,14). Furthermore, vitamin C administration and overexpression of catalase increased the life-span of mice in some studies (16-18), but vitamin C was ineffective in one study (19). These studies indicate that protection against oxidative stress may increase the life-span of mammals under some conditions.

Several large randomized trials of humans found that vitamin E supplementation does not reduce mortality (20-25). These negative findings have often been interpreted as evidence that vitamin E does not protect against oxidative stress in humans.

The Alpha-Tocopherol-Beta-Carotene (ATBC) Study was a large randomized trial which examined the effect of 50 mg/day of vitamin E on the risk of lung cancer in male smokers (25,26). In our previous analyses of the ATBC Study data, we found that age, smoking and dietary vitamin C intake significantly modified the vitamin E supplementation effect on the incidence of the common cold, pneumonia and tuberculosis (27-30). This heterogeneity motivated us to test whether the effect on mortality might also be heterogeneous. We found significant modification of the supplementation effect in that vitamin E decreased mortality by 41% among those who were 66 or older at baseline and consumed vitamin C at a level above the median (31).

A large trial can accurately estimate the overall effect of vitamin E on mortality. However, if vitamin E influences the life-span, it is possible that a benefit on the oldest participants might be camouflaged by the large middle-aged majority of study participants. In this study, we analyze the effect of vitamin E by the age of the participant at the follow-up. This allows us to accurately examine the age-dependency of vitamin E effect on the old ATBC Study participants. Since our focus is on the oldest participants, we restrict this analysis to the follow-up period when the participants were 65 and over.

Methods

Participants
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 been described earlier (25,26). The ATBC Study is registered at ClinicalTrials.gov under the identifier NCT00342992.

In brief, male participants aged 50-69 years had to smoke ≥5 cigarettes per day at entry to be eligible, and those enrolled in the trial (N=29,133) were randomized to one of four intervention arms and administered placebo, AT, BC, or AT+BC, using a 2×2 factorial design. Compliance with supplementation was high: some 90% of the participants took more than 90% of their prescribed capsules during their active participation in the trial; there were no differences in capsule consumption among the intervention groups (25,26). Compared with the baseline levels, supplementation increased the serum level of α-tocopherol by 50% (25,26). The intervention continued until April 30, 1993. The trial was approved by the institutional review boards and all participants gave written informed consent. This study was restricted to the participants who contributed to follow-up time after the age of 65, which left 10837 men to this study. The lowest baseline age in this cohort was 56.7 years, and 1805 participants had baseline age below 60 years.

Baseline characteristics
Before randomization at the baseline, the men completed questionnaires on their medical and smoking histories and general background characteristics, and their weight was measured. A detailed dietary history questionnaire provided data regarding vitamin C and vitamin E consumption (32). Dietary data was not available for 806 of the 10837 participants.

Outcome and follow-up time
Deaths were identified in the National Death Registry as previously described (25). Follow-up time for each participant began from the age of 65 or the day of randomization (if it was over 65), and continued until death or the end of the trial (April 30, 1993). The median follow-up time of the participants in the present analysis was 3.4 years, and there was a total of 37,773 person years of observation.

Statistical models
We estimated the effect of vitamin E supplementation on mortality through Cox regression models. We calculated the risk ratio (RR) and the 95% confidence interval (CI) of the RR using PROC PHREG in SAS (release 8.2, SAS Institute, Inc., Cary, NC). We compared participants administered vitamin E (AT and AT+BC) with those not receiving vitamin E (the no-vitamin E participants; placebo and BC). As to supplementation, we carried out the analyses following the intention-to-treat principle. Because the deaths were identified in the National Death Registry which registers all deaths occurring in Finland, the loss-to-follow-up is insignificant.

To test whether the vitamin E supplementation effect is different at different age ranges, we first added a uniform vitamin E effect to the whole age range. Then we added separate vitamin E effects to early and late age regions (33). The improvement of the Cox model fit was thereafter calculated from the change in −2×log(likelihood) which follows the χ^2(1 df) distribution. Several cut off ages were tested, at 1-year intervals, around the region where the survival curves visually diverge in the figures. There were rather small differences between the models with the optimal cut point and models with cut point at the optimal ± 1 year. In Fig. 1, the cut point at 71 years led to χ^2(1 df)=5.06, at 72 years led to χ^2(1 df)=6.47 and at 73 years led to χ^2(1 df)=5.62 improvement in the Cox model fit. In Fig. 2A, the cut point at 69 years led to χ^2(1 df)=2.99, at 70 years led to χ^2(1 df)=6.13 and at 71 years led to χ^2(1 df)=6.04 improvement in the Cox model fit. Thus, the cut points at 72 and 70 years for Figs. 1 and 2A, respectively, lead to the best Cox models. However, the cut point at 71 years leads to essentially the same improvements in the Cox models as the optimal cut points, and to simplify our presentation in the Results, we selected the cut point at 71 years for both Fig. 1 and Fig. 2A.

Kaplan-Meier survival functions were constructed using STATA sts program (Release 9.1, Stata Corp, College Station, TX). Two-tailed *P*-values were used.

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Results

In all, 10837 men contributed to the follow-up after the age of 65 years and there were 1445 deaths during this period. There is no overall difference between the vitamin E and no-vitamin E groups when the entire survival curves are compared (Fig. 1; P=0.3 for the Cox model comparing the vitamin E and no-vitamin E groups). However, the survival curves for the vitamin E and no-vitamin E groups start to diverge at about 70 years. Therefore we tested whether the addition of separate vitamin E effects to the early and late follow-up age ranges would improve the Cox model fit (see Methods).

The addition of separate vitamin E effects to the 65-70 years age range and for the ages over 71 significantly improves the statistical model (χ^2(1 df)=5.0, P=0.03). This model gives a risk ratio (RR) of 1.00 (95% CI: 0.89-1.13; 1113 deaths) for the 65-70 year age range, and RR=0.76 (0.61-0.95; 332 deaths) for ages over 71. A constant relative effect on mortality transforms into a continuously increasing difference in life-span by a higher age. At the end of the survival curves, the difference in the life-span between the vitamin E and no-vitamin E groups is about six months (Fig. 1).

Since we found previously that the effect of vitamin E on mortality was dependent on dietary vitamin C intake and the level of smoking (31), we constructed separate survival curves for the four groups defined by these variables (Fig. 2).

The benefit of vitamin E was restricted to men who had dietary vitamin C intake above the median (90 mg/day) and smoked less than a pack of cigarettes per day at the baseline of the trial (Fig. 2A). In this subgroup, the survival curves of the vitamin E and no-vitamin E participants start to diverge at the age of about 70 years. Adding separate vitamin E effects to Fig. 2A for the 65-70 year range and to the ages over 71 years significantly improves the Cox model fit (χ^2(1 df)=6.0, P=0.02). This model gives a RR of 0.91 (95% CI: 0.68-1.24; 169 deaths) for the 65-70 year age range, and RR=0.43 (0.25-0.74; 61 deaths) for ages over 71. Vitamin E supplementation increased life-span by about two years at the end of the survival curves in Fig 2A. The effect of vitamin E supplementation was not modified by β-carotene supplementation or dietary vitamin E intake (Table 1). We found previously that the age of smoking initiation modified the effect of vitamin E on pneumonia incidence (28), but it did not modify the effect on mortality in this subgroup (Table 1).

In the other three participant groups of Figs. 2B-D, defined by vitamin C intake and the level of smoking, there is no evidence that survival curves of the vitamin E and no-vitamin E participants diverge at about 70 years. Nevertheless, at the upper age range of each of these three figures, vitamin E participants lived slightly longer; however, the number of deaths at the upper age range is low (Fig. 2B-D).

Discussion

In this study, we found that vitamin E supplemented participants had overall approximately half-a-year longer life expectancy at the upper limit of the follow-up age. This benefit of vitamin E was restricted to participants who smoked less than a pack of cigarettes per day and had vitamin C intake over the median.

Since dietary vitamin C intake has a close correlation with the daily amount of fruit and vegetables, the calculated vitamin C intake might be a proxy for fruit and vegetable intake. However, in our previous analysis, other substances in fruit and vegetables did not explain the modification of the vitamin E effect on mortality (31). Furthermore, the synergism between vitamins E and C is well established. Vitamin E is the major lipid-soluble antioxidant that protects membranes against oxidative injury (34,35). In model systems, vitamin C reduces the oxidized form of vitamin E back to vitamin E (36-38), but the biological significance of this synergism is not well defined. Nevertheless, vitamin C administration prevented the concomitant decreases in tissue vitamin E levels and body-weight gain of weanling guinea pigs administered oxidized frying oil (39) indicating that both vitamins together may be essential to protect against some forms of oxidative stress. Furthermore, smoking increases the plasma α-tocopherol disappearance rate, which was normalized by vitamin C supplementation (40), and this physiological interaction between vitamins E and C and smoking gives a rationale for the relation between the extent of smoking, dietary vitamin C level and the effect of vitamin E supplementation in Fig. 2. The biochemical findings were interpreted as evidence that higher doses of vitamins E and C might be beneficial for smokers in particular (40), whereas in Fig. 2 the benefit of vitamin E was restricted to ATBC participants who smoked least.

The dependence of vitamin E supplementation effect on vitamin C intake level (Fig. 2) implies that studies focusing on a single antioxidant might suggest a misleading conclusion about the potential roles of antioxidants. Furthermore, if the benefit of vitamin E is conditional on high vitamin C intake, it seems possible that combined vitamin E and C supplementation might affect the life expectancy of men belonging to the subgroup of Fig. 2C.

Our findings are also important for the interpretation of the large randomized trials on vitamin E which have mostly found no benefit from supplementation (20-25). The large-scale vitamin E trials test the theory that cancers and cardiovascular diseases are caused by oxidative mechanisms. However, the average effect on mortality in a group of people with a wide age range does not measure the effect on life-span. For example, although there is no overall difference between the survival curves of the vitamin E and no-vitamin E groups in Fig. 1, the groups diverge at 71 years. The number of deaths in the 65 to 70 year age range (n = 1113) is substantially greater than in the ages over 71 years (n = 332). If these two age ranges are analyzed together, ignoring age as a potential modifier of the vitamin E effect, the early follow-up period is weighted much more in standard analyses, camouflaging the beneficial effect at the older age. Given the evidence that the severity of oxidative stress increases with age (4,5), it would seem more appropriate to analyze large antioxidant trials by biological age as in Figs. 1 and 2, and not by the time after randomization which has been customary (21-25).

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In conclusion, our findings among the older ATBC participants support the previous reports indicating that protective measures against oxidative stress may increase the life expectancy of mammals under some conditions (11-13,16-18). Although the two-year increase in life-span in the subgroup of participants who had high vitamin C intake and smoked less is substantial (Fig. 2A), only 20% of the study participants belong to this subgroup. The lack of benefit in the other participants, consisting of 80% of this male cohort, shows that vitamin E is no panacea for extending life expectancy. Given the heterogeneity in the effect, the findings should not be generalized without caution. Nevertheless, our findings warrant further study on the possible effect of vitamin E on old people.

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Table 1: Effect of vitamin E on mortality among ATBC Study participants aged ≥71 years at follow up; men who had dietary vitamin C intake ≥90 mg/day and smoked 5-19 cigarettes/day.

Subgroup	No. of men *	No. of Deaths		RR (95% CI) †
		vit E	no-vit E	
All participants	647	19	42	0.43 (0.25-0.74)
β-Carotene supplementation				
No	338	12	20	0.55 (0.27-1.13)
Yes	309	7	22	0.31 (0.13-0.72)
Dietary vitamin E (mg/day) ‡				
<11.5	321	8	20	0.36 (0.15-0.80)
≥11.5	326	11	22	0.50 (0.24-1.04)
Age of smoking initiation ‡				
≤20	387	11	26	0.35 (0.17-0.71)
≥21	259	8	16	0.57 (0.24-1.32)

* In these subgroups, the vitamin E and no-vitamin E groups were of equal size within 14% accuracy.

† Cox proportional hazards model comparing participants who received vitamin E with those who did not. RR, risk ratio for death, CI, confidence interval.

‡ The cut-off level for dietary vitamin E intake is at the median. Information on the age of smoking initiation was missing for 1 participant.
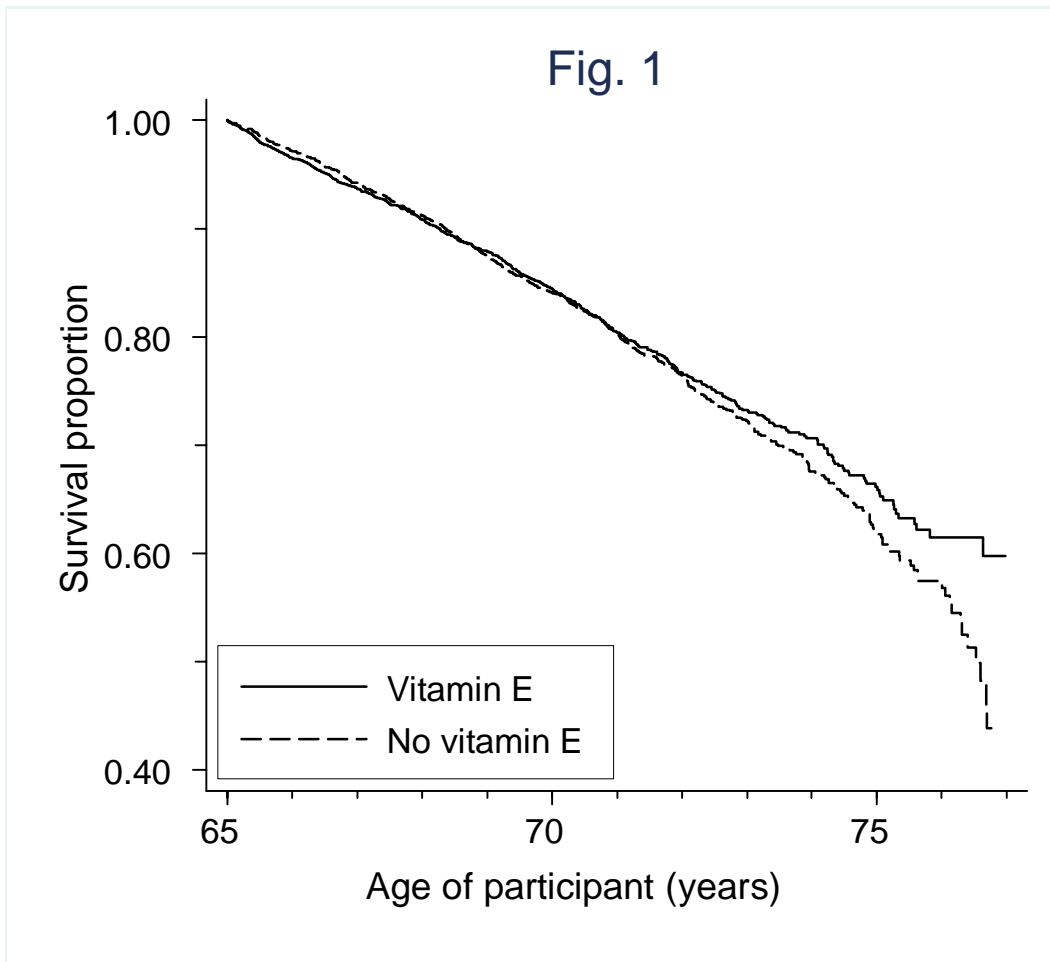
Figure 1

Effect of vitamin E supplementation on the life-span of ATBC Study participants.

There were 1445 deaths among 10,837 men who contributed to the 37,773 person-years of observation after the age of 65 years. Kaplan-Meier survival curves for the vitamin E and no-vitamin E groups are shown. Each step indicates 1 death. The curves have been cut off at 77 years because the number of participants declined abruptly thereafter.
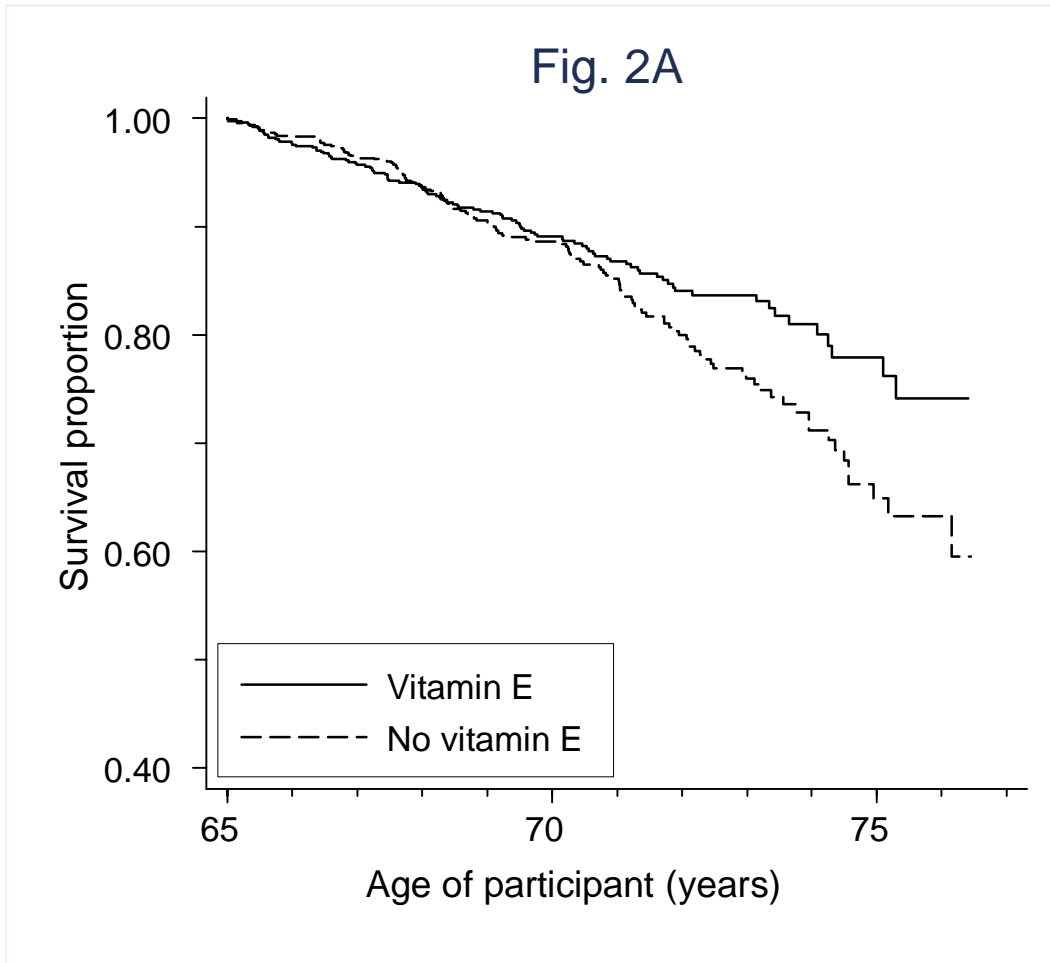
Figure 2

Effect of vitamin E supplementation on life-span in four subgroups according to dietary vitamin C intake and level of smoking.

A) 2284 participants with ≥90 mg/day vitamin C and 5-19 cigarettes per day, B) 2400 participants with ≥90 mg/day vitamin C and ≥20 cigarettes per day, C) 2245 participants with <90 mg/day vitamin C and 5-19 cigarettes per day, D) 3102 participants with <90 mg/day vitamin C and ≥20 cigarettes per day. Vitamin C intake level was not available for 806 men, who are missing from these figures. Kaplan-Meier survival curves for the vitamin E and no-vitamin E groups are shown. Each step indicates 1 death. The curves have been cut off at 76.5 years because the number of participants declined abruptly thereafter.
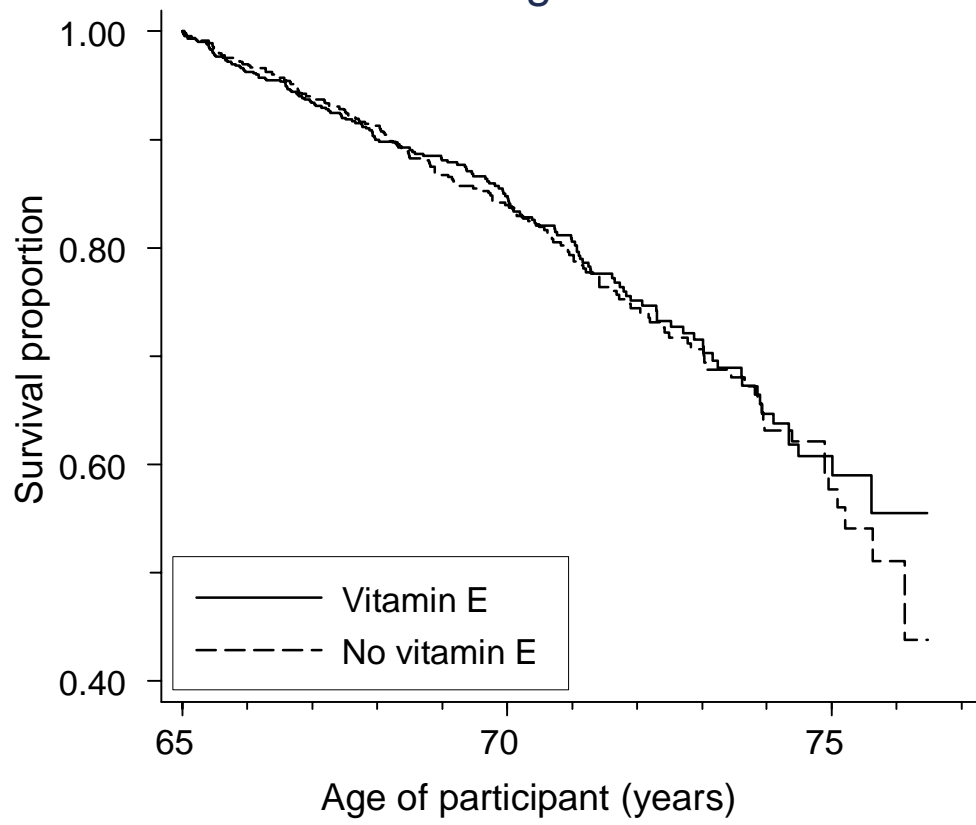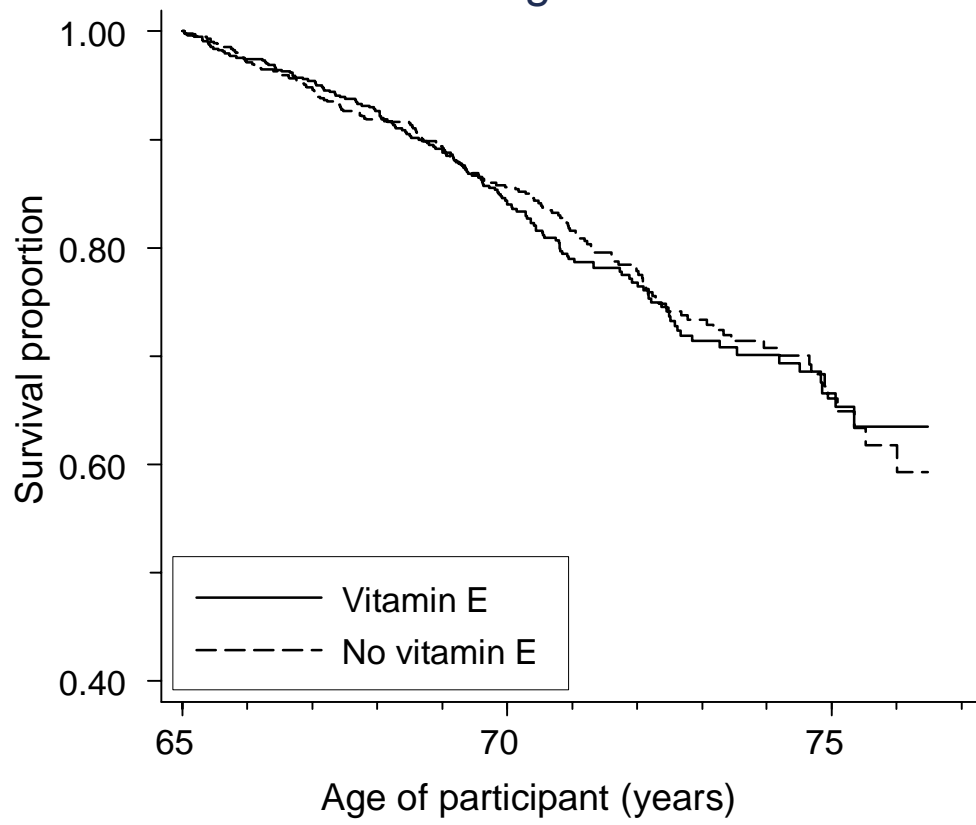
Fig. 2B

Fig. 2C

Y-axis: Survival proportion

X-axis: Age of participant (years)

Legend:
— Vitamin E
---- No vitamin E

Fig. 2D