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Serum Tocopherol Levels and Vitamin E Intake are Associated with Lung Function in the Normative Aging Study

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Abstract

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Background and Aims—The results of studies assessing relationships between vitamin E intake and status and lung function are conflicting. This study aimed to evaluate the effect of vitamin E intake and serum levels of tocopherol isoforms on lung function in a cross-sectional sample of 580 men from the Normative Aging Study, a longitudinal aging study.

Methods—Regression models were used to look at associations of serum tocopherol isoform levels and vitamin E intake with lung function parameters after adjustment for confounders. Vitamin E intake was measured using a food frequency questionnaire and serum levels of γ, α, and δ-tocopherol levels were measured using high-performance liquid chromatography.

Results—After adjustment for potential confounders, serum γ-tocopherol had a significant inverse association with forced vital capacity (β=-0.10, p=0.05). Alpha and δ-tocopherol were not associated with any lung function parameter. After classifying COPD status according to Global Initiative for Obstructive Lung Disease (GOLD) stage criteria, serum levels of δ-tocopherol were lower in participants with more severe COPD (p=0.01). Serum levels of δ-tocopherol were also lower in participants with greater levels of smoking (p=0.02). Both vitamin E intake (β=0.03, p=0.02; β=0.03, p=0.01) and use of vitamin E supplements (β=0.05, p=0.03; β=0.06. p=0.02) were positively associated with FEV_1 and FVC, after adjusting for confounders. Subjects who took vitamin E supplements had significantly higher α-tocopherol levels (p<0.0001) and lower γ-tocopherol levels (p<0.0001) than non-users.

Conclusion—In this study, there is a positive association between dietary vitamin E intake and lung function, and evidence of an inverse relationship between serum levels of γ-tocopherol and lung function.

Keywords

lung function; vitamin E; tocopherols; inflammation; diet; COPD

Introduction

Nutrition and diet play an important role in the development and progression of many chronic diseases. Lung diseases have become a major public health concern in recent years; chronic obstructive pulmonary disease (COPD) is the major cause of respiratory morbidity and mortality, and results in an economic burden that is substantial and increasing. Therefore, interventions to promote lung health in populations without lung disease and to improve or maintain lung function in those with lung disease have become a public health priority.

Epidemiological and observational studies have demonstrated associations between both dietary vitamin E intake, serum vitamin E levels, and lung function.[1] Indeed, one study observed that increasing vitamin E intake was protective against COPD mortality.[2] Vitamin E has anti-oxidant properties whose primary function is as a chain-breaking anti-oxidant, preventing peroxidation of lipid molecules. Because oxidative stress and inflammation are features of many lung diseases, nutrients with anti-oxidant and anti-inflammatory properties could be a useful tool in prevention or treatment. However, studies of vitamin E in lung disease have had contradictory results.

Recently, interest has focused on the various tocopherol isoforms of vitamin E, including α-, γ, and δ-tocopherol. New evidence has demonstrated that different tocopherol isoforms may have opposing inflammatory mechanisms,[3] and therefore may possibly have differing actions with relation to lung function and disease. Many of the studies previously conducted exploring the relationship between vitamin E intakes or serum levels of vitamin E and lung function outcomes have not differentiated between the various tocopherol isoforms of vitamin E, which may in part offer an explanation for the conflicting results. Thus, the purpose of this analysis was to examine the association between both vitamin E intake and serum tocopherol levels with lung function measurements in a sample from a cohort of adult white men from the Veterans Administration Normative Aging Study (NAS). Our dataset included serum levels of α-, γ-, and δ-tocopherol, intake of dietary vitamin E and use of vitamin E supplements, and measures of lung function including Forced Expiratory Volume in 1 Second (FEV_1), Forced Vital Capacity (FVC), and FEV_1/FVC ratio. Additionally, there is no consensus regarding nutrient intakes vs. nutrient concentrations in the serum with regards to biomarkers of lung health. Therefore, we sought to determine if serum levels or dietary intake levels of vitamin E, or both, were associated with improved measures of lung function in this population.

Methods

Population

Study participants were from NAS, an ongoing longitudinal study of aging established in 1963. NAS is comprised of a cohort of 2,280 healthy male volunteers aged 21 to 80 years at study entry from the greater Boston, Massachusetts area. Participants were enrolled after an initial health screening determined that there were no pre-existing chronic medical conditions. Of 696 men who presented for at least one of their scheduled study visits between January, 2000 and November, 2007, 580 (83.3%) had stored plasma samples, information on diet, and lung function data available. Human subjects approval was granted by the Human Studies Subcommittee of the Department of Veterans Affairs Medical Center and the Institutional Review Board of the Brigham and Women's Hospital, and all participants provided written informed consent.

Measures

Plasma nutrient levels were measured at the Biomarker Research Laboratory at the Harvard School of Public Health. Concentrations of δ-tocopherol, γ-tocopherol, and α-tocopherol in plasma samples were measured using the method described by Hess et al[4] with some modifications. Plasma samples were mixed with ethanol containing rac-Tocopherol (Tocol) as an internal standard, extracted with hexane, evaporated to dryness under nitrogen, and reconstituted in ethanol, dioxane and acetonitrile. Samples were quantitated by high-performance liquid chromatography (HPLC) on a Restek Ultra C18 150mm × 4.6mm column, 3μm particle size encased in a Hitachi L-2350 column oven to prevent temperature fluctuations, and equipped with a trident guard cartridge system (Restek, Corp. Bellefonte, PA). A mixture of acetonitrile, tetrahydrofuran, methanol, and a 1% ammonium acetate solution (68:22:7:3) was used as mobile phase, flow rate 1.1 ml/min, using a Hitachi Elite LaChrom HPLC system comprised of an L-2130 pump in isocratic mode, an L-2455 Diode

Array Detector (monitoring at 300nm and 445nm), and a programmable AS-2200 auto-sampler with chilled sample tray. The system manager software (D-7000, Version 3.0) was used for peak integration and data acquisition (Hitachi, San Jose, CA). The minimum detection limits (MDLs) in plasma were (μg/L) 38.5 for δ-tocopherol, 102.5 for γ-tocopherol, and 184.0 for α-tocopherol. Every run included two replicates each of a two-level plasma pool sample set. For external quality control, the laboratory participates in the standardization program for carotenoid analysis from the National Institute of Standards and Technology U.S.A.

A semi-quantitative Willett food frequency questionnaire (FFQ) was used to assess diet. To calculate vitamin E intake, the Harvard nutrient-composition database, which contains food composition values from the US Department of Agriculture, was used. Spirometry was performed on all participants as previously described[5] and acceptability of spirograms was judged according to American Thoracic Society standards.[6] Lung function was also expressed as a percent of predicted using the spirometric reference values from the third National Health and Nutrition Examination Survey.[7] COPD was classified according to Global Initiative for Obstructive Lung Disease (GOLD) stage criteria.[8]

Statistical Analysis

Descriptive statistics were calculated for all participants. The Spearman correlation coefficient was used to look at associations between lung function measures (FEV_1, FVC, and FEV_1/FVC ratio) and serum levels of tocopherol, and intake level of vitamin E. Variables significant in univariate analysis were included in a multivariate regression model that adjusted for the possible confounders of age, height, Body Mass Index (BMI), serum cholesterol, energy intake, and smoking. Covariates in the multivariate models were chosen for their clinical relevance and associations in univariate models. Smoking status was incorporated into all models and was categorized into three levels: never, current, and former. Non-parametric methods were used for vitamin E intake analysis, and log transformed serum levels and intake levels of tocopherols and vitamin E were used in the univariate and multiple regression models. The Wilcoxon rank sum test and Kruskal-Wallis test were used to compare median vitamin E levels between groups (e.g. GOLD stage and smoking status). Fisher's exact tests were used to compare categorical data. A p-value of 0.05 was considered statistically significant. SAS version 9.3 (SAS Institute, Cary NC) was used for all analysis.

Results

Baseline characteristics of the partcipants are displayed in Table 1. A small number of subjects met the classification for COPD using GOLD criteria; of 580 subjects with lung function measurements recorded, 20% (115) were defined as having COPD based on GOLD categories. A significant portion of the population reported some former or current smoking, with only 29.5% of subjects reporting never smoking.

Serum nutrients

In the univariate analysis, a statistically significant inverse association was seen between γ-tocopherol and FEV_1(r=-0.12, p=0.003) as well as FVC (r= -0.10, p=0.01). Alpha and δ-tocopherol were not associated with any lung function parameter. After adjustment for age, height, BMI, smoking status, and serum cholesterol levels, serum γ-tocopherol maintained a significant inverse association with FVC (β=-0.10, p=0.05). Including α- and γ- tocopherols in the same regression model with γ-tocopherol did not significantly alter the results. When a ratio of serum α-tocopherol/γ- tocopherol was created, no association between this ratio and FVC or FEV_1/FVC ratio was seen. However, in the univariate analysis there was a marginally statistically significant association between alpha/gamma tocopherol ratio and FEV_1 (r=0.07, p=0.07). Results of regression models are shown in Table 2.

Because the tocopherols have been reported to have opposing actions on lung function, we perfomed an analysis to determine if the associations of one tocopherol with lung function differed if the concentration of the opposing tocopherol was low, as proposed by Cook-Mills et at.[9] For this analysis, subjects were divided into above or below the median for levels of both α- or γ-tocopherol, and then the association with lung function of the opposing tocopherol were evaluated. Using this approach, there was no association between serum α-tocopherol and measures of lung function in subjects with serum γ-tocopherol that was either above or below median values. A similar analysis using quartiles in place of medians also did not yield statistically significant results. When the analysis was conducted using subjects above and below the median for serum α-tocopherol levels, γ-tocopherol retained a significant inverse association with lung function measures, which reached statistical significance in the group with higher α-tocopherol levels (Table 3).

When levels of serum tocopherols were analyzed according to GOLD classification, serum δ-tocopherol levels decreased with increasing GOLD stage (p=0.01, Figure 1). Alpha and γ-tocopherol were not significantly different by GOLD stage, although the directions of their associations with GOLD stage were the reverse of that for γ-tocopherol. Additionally, when subjects were stratified by smoking status, there were significant differences in serum levels of δ-tocopherol between smoking groups (p=0.02), with lowest levels of δ-tocopherol in current smokers (Figure 2). Interactions between smoking status and δ-tocopherol were evaluated on the outcomes, however no significant interactions were found.

Nutrient Intake

In the univariate analysis, vitamin E intake was positively associated with FEV_1 and FVC (r=0.10, p=0.01, and r=0.12, p=0.007, respectively) (Table 2). After adjustment for age, height, BMI, energy intake and smoking status, vitamin E intake retained a positive association with both FEV_1 and FVC (β=0.03, p=0.02; β=0.03, p=0.01, respectively). Intake of vitamin E was highly correlated with the sum of the serum tocopherol levels (r=0.49, p<0.0001) and positively correlated with α- and δ-tocopherol (r=0.56, p<0.001,r=0.10, p=0.02, respectively). Intake of vitamin E showed an inverse relationship with γ-tocopherol (r=-0.58, p<0.001).

The use of vitamin E supplements was associated with an increase in FEV_1 (2.8 vs. 2.6 L for users and non-users, respectively, p=0.03) and FVC (3.7 vs. 3.5 L for users and non-users, respectively, p=0.02) (Table 2). This relationship was maintained after adjustment for confounders (β=0.05, p=0.03; β=0.06. p=0.02 for FEV_1 and FVC, respectively). When vitamin E intake from supplements was excluded from total vitamin E intake, the relationships between vitamin E intake and measures of lung function were no longer significant. Serum levels of both α-tocopherol and γ-tocopherol were significantly different between subjects who took vitamin E supplements and those who did not, with significantly higher α-tocopherol levels (20,236.0 vs. 13,237.0 ug/L, p<0.0001) and lower γ-tocopherol levels (953.2 vs. 2342.0 ug/L, p<0.0001) for those using vitamin E supplements compared to those who did not (Figure 3).

Discussion

Our findings of positive associations between dietary vitamin E intake and lung function, and the evidence of an inverse relationship between serum levels of γ-tocopherol and lung function contribute to the evidence supporting the fact that vitamin E plays a role in lung health, as well as the emerging evidence regarding possible opposing actions of serum tocopherols on lung function.

We found an inverse association between serum levels of γ-tocopherol and lung function. Many previous trials evaluating the relationship between serum vitamin E levels and pulmonary function show mixed results, however most have measured only serum α-tocopherol, or failed to distinguish between tocopherols isoforms. Our finding of a negative effect of γ-tocopherol on lung function is supported in a recently published study by Marchese et al,[10] which found increased serum concentrations of γ-tocopherol were associated with lower measures of lung function, while increased serum concentrations of α-tocopherol were associated with higher measures of lung function.[10] These effects were more evident when the concentration of opposing tocopherols were lower, causing the least amount of competing effects.

A possible mechanism for these findings may be explained by recent evidence that documents differential regulation of inflammation by varying vitamin E isoforms.[11] while γ-tocopherol has been shown to elevate inflammation through endothelial cell signal regulation inleukocyte recruitment.[12] In contrast, γ-tocopherol has also been shown to reduce airway neutrophil recruitment and inhaled endotoxin challenge.[13] In spite of possible anti-inflammatory effects of α-tocopherol, we did not find a protective effect on lung function with increasing serum levels of α-tocopherol; however γ-tocopherol isoforms at as little as 10% of the concentration of α-tocopherol have been shown to ablate the anti-inflammatory benefit of α-tocopherol.[12] The concentrations of γ-tocopherol exceeded 10% of the concentrations of α-tocopherol in our population, and in non-vitamin E supplement users approached 18%. Therefore, it is possible that the relatively high levels of γ-tocopherol obscured any positive effects of α-tocopherol.

We also document decreased levels of δ-tocopherol in smokers, as well as in more advanced stages of COPD. Much less is known about the association of δ-tocopherol with clinical

outcomes, as α- and γ-tocopherol are the most frequently studied. Although not statistically significant, serum levels of γ-tocopherol were much higher in subjects with COPD GOLD stage 4, which may support a role for different tocopherol isoforms in lung disease. Levels of δ-tocopherol were significantly lower in participants with greater levels of smoking. However, α-tocopherol and γ-tocopherol did not show a statistically significant difference in smokers vs. non-smokers. Why one of the tocopherol isoforms was affected by smoking status in our study while others were not is unclear.

Vitamin E intake was also associated with meaures of lung function in our study. Associations between vitamin E intake and pulmonary health have been found in other studies,[1,2,14,15], however these findings have not been consistent.[16-19] It is possible that differing outcomes of trials evaluating the effect of vitamin E intake or serum levels of vitamin E on lung function may be due to the lack of differentiation between various isoforms of vitamin E in the diet. In one study to do so, Dow et al. reported a positive association between α-tocopherol intake and FEV_1 in elderly subjects in the United Kingdom.[20] Gamma-tocopherol is the major form of vitamin E in the American diet,[21] and is more than twice as abundant in food as α-tocopherol. Serum levels of tocopherols have been shown to reflect intake in the diet,[22] and concentrations of tocopherols in lung tissue have been shown to be well correlated with serum levels.[23] As a Westernized diet is high in γ-tocopherol, primarily from vegetable and soy oils, our results raise interesting questions about the ratio of vitamin E isomers and lung function in the American diet. Levels of γ-tocopherol are lower and α-tocopherol are higher in other oils, including sunflower, safflower, and olive oil. One interesting finding in our study was that while an association between vitamin E intake and lung function was present, we did not find an association between serum α-tocopherol levels and lung function. One possible explanation may be that nutrient databases do not distinguish between the different tocopherol versions in food. Therefore, total vitamin E intake could potentially include other vitamin E isforms, and it is possible that these isoforms, or a combination of isoforms, are responsible for the effect.

We report that use of vitamin E supplementation was associated with improved lung function, and dietary intake of vitamin E in our study was found to be associated with lung function until vitamin E from supplementation, which would presumably be primarily α-tocopherol, was excluded. These results are consistent with a recent report from the Women's Health Study that reported a 10% reduction in the risk of chronic lung disease with supplementation of 600 IU of vitamin E every other day.[24] Some evidence exists supporting the role of α-tocopherol supplementation in decreasing inflammation and oxidative stress in subjects with lung disease. A randomized trial of 800 IU/day vitamin E supplementation as α-tocopherol in subjects with existing COPD reported increased levels of endogenous antioxidants in the vitamin E supplemented group.[25] There was no improvement in clinical parameters in the subjects; however the 8-week length of the trial may not have allowed adequate time for changes in these measures. This is consistent with results repored by Daga et al., who provided vitamin E supplementation (presumably α-tocopherol) for 12 weeks to subjects with COPD and demonstrated improved measures of lipid perioxidation in the serum of subjects receiving of vitamin E supplementation, There was no improvement in lung function measures in the latter study,[26] however, there was no significant increase in the serum α-tocopherol levels of the subjects receiving vitamin E supplementation, which

may have limited clinical effects of supplementation. Another study by Hoskins et al that provided vitamin E supplementation in the form of α-tocopherol demonstrated increased plasma α-tocopherol, decreased γ-tocopherol, and improvemen in airway responsiveness to a methacholine challenge in asathmatic subjects.[27] We add pertinent data to these findings; in our study we demonstrate higher α-tocopherol and lower γ-tocopherol levels in the serum of those using vitamin E supplements, and a resulting association with measures of lung function.[27] However, the effects of vitamin E supplementation have been shown to be different in different populations,[28] and the results of recent trials evaluating vitamin E supplementation and cancer risk indicate that vitamin E supplementation should be initiated with caution.[29] Supplementation with one tocopherol, which is usually α-tocopherol, has been shown to decrease serum levels of other tocopherols, including γ- and δ-tocopherol.[30] More research is needed to elucidate the roles of various tocopherols in health and disease, as well as ideal serum levels and ratios for optimal health.

This study does have several weaknesses. Our data is cross sectional, and cannot be used for any temporal or casual evaluation of the effect of vitamin E on lung function. The overall effect sizes demonstrated are small. It is possible that other compounds, not well studied, that occur in conjunction with vitamin E could be responsible for our findings. It may be possible that subjects with higher intakes of vitamin E lead overall healthier lifestyles. However, a major strength of our study is that subjects had both serum and intake levels of tocopherols and vitamin E available. Also, serum levels of vitamin E isoforms were not combined, as they are in many other studies, allowing for further elucidation of these relationships.

Conclusion

This study demonstrates that both vitamin E intake and serum levels of vitamin E tocopherols may impact measures of lung function. Given the importance of inflammation and oxidant stress in lung function, a direct effect of nutrients that have anti-oxidant and anti-inflammatory properties is readily plausible. Future studies to elucidate the role of vitamin E in the development and progression of lung disease are warranted.

Acknowledgments

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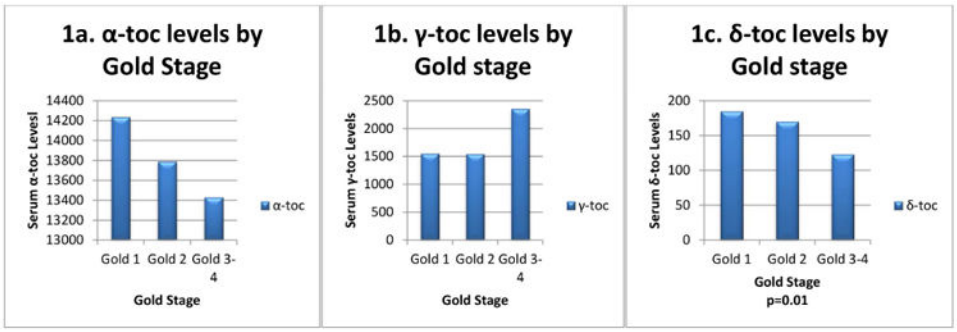

Figure 1.

Median serum Levels of tocopherol levels by Gold Stage. Panels 1a and 1b: Serum α-tocopherol decreased and serum γ-tocopherol increased as Gold stage increased, although these relationships were not statistically significant. Panel 1c: Serum δ-tocopherol levels showed a statistically significant decrease as GOLD stage increased (p=0.01 using Kruskall Wallis test; a non-parametric alternative to ANOVA).

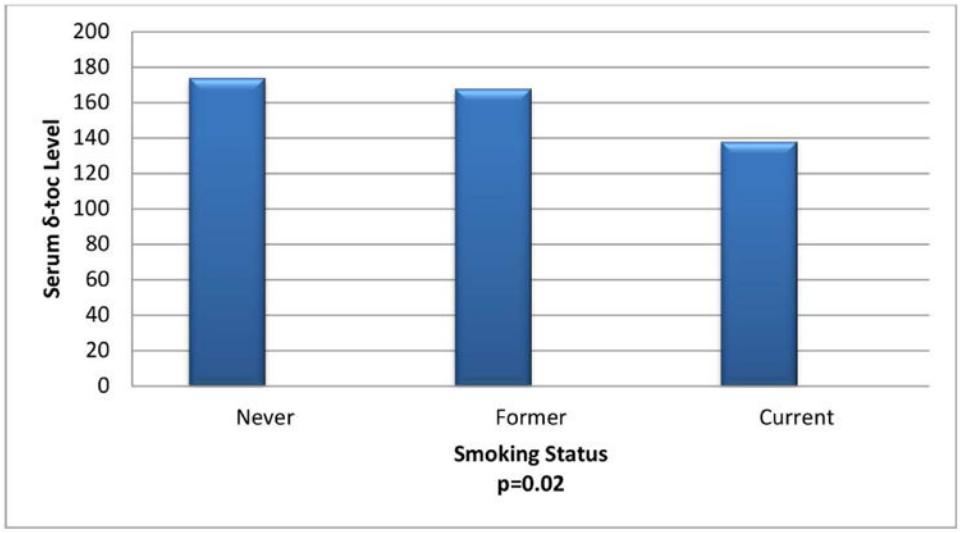

Figure 2.

Serum tocopherols were analyzed according to the methods. Median serum Levels of δ-tocopherol were significantly different between different categories of smoking (p=0.02).

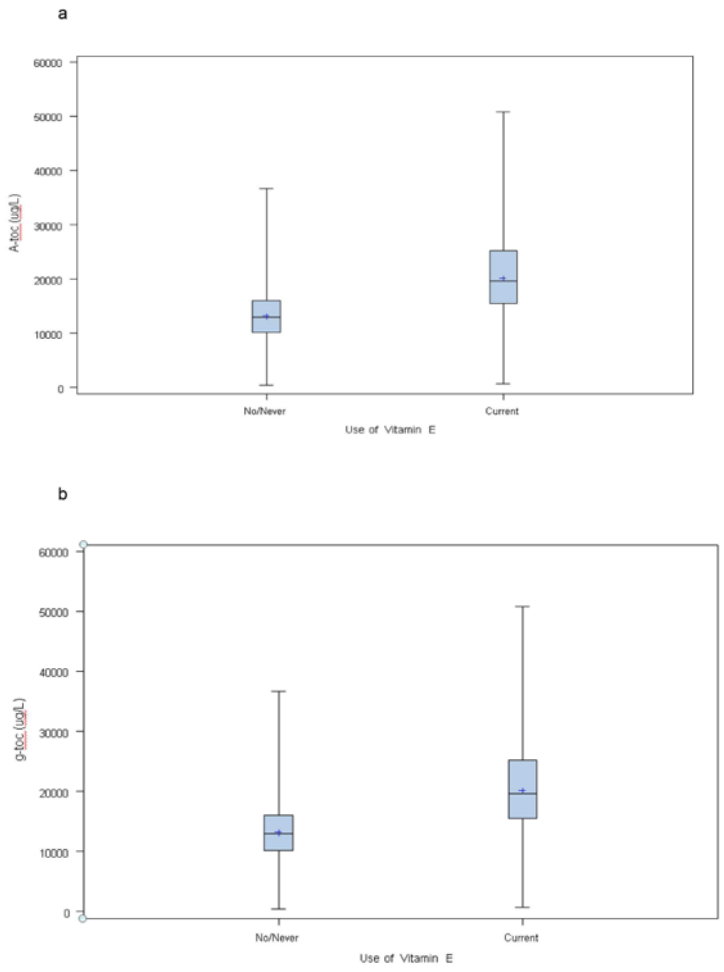

Figure 3.

Mean serum α-and γ-tocopherol levels in subjects in vitamin E users and non-users. Serum levels of α- and γ-tocopherol were measured as described in the methods. Serum levels of α-tocopherol were higher (p=0.001) and serum levels of γ-tocopherol were lower (p=0.001) in vitamin E supplement users when compared to non-users.

Table 1
Baseline characteristics of white male subjects from the Normative Aging Study

	Study subjects	
	N	**Mean (SD)**
Age, yr	580	73.6 (6.7)
BMI	563	28.3 (4.0)
FEV1 (L)	580	2.7 (0.6)
FEV1, %pred	574	94.0 (20.7)
FVC (L)	580	3.6 (0.7)
FVC, %pred	574	90.5 (15.6)
FEV1/FVC ratio	580	74.81 (8.3)
Serum α-tocopherol (ug/L)	580	16,146.87 (7830.3)
Serum δ-tocopherol (ug/L)	580	190.76 (225.3)
Serum γ-tocopherol (ug/L)	580	1776.62 (1330.5)
Vitamin E Intake (mg/day)	531	197.35 (237.3)
	N	%
Smoking Status (Current/former/never)	25/377/171	4.3/65.8/29.9
Taking Vitamin E supplement (Y/N)	219/320	40.6/59.4
COPD GOLD Stage 1	51	
COPD GOLD Stage 2	51	
COPD GOLD Stage 3/4	13	

Definition of abbreviations: COPD=chronic obstructive pulmonary disease, GOLD=Global Initiative for Chronic Obstructive Lung Disease, %pred=%predicted.

Table 2

Relationship of Multivariate Regression Analysis of Vitamin E Measures with Lung Function Outcomes

Variable	FEV_1		FVC	
	β	p	β	p
α-tocopherol	-	-	-	-
δ-tocopherol	-	-	-	-
γ-tocopherol	-0.06 *a*	0.2	-0.10 *a*	0.05
Vitamin E intake	0.03*b*	0.02	0.03*b*	0.01
Use of vitamin E supplements	0.05	0.03	0.06	0.02

a γ-tocopherol model adjusted for age, height, BMI, smoking status, and serum cholesterol α- tocopherol, and δ-tocopherol

b Vitamin E intake model adjusted for age, height, BMI, smoking status, energy intake, and serum cholesterol

Table 3

Analysis of Lung Function and Serum Tocopherols Divided by Median Values

3a: Association of α-Tocopherols and Lung Function in Groups Above or Below the Median of γ-Tocopherol						
	FEV_1		**FVC**		**Ratio**	
	r	**p**	**r**	**p**	**r**	**p**
γ-tocopherol < 1494.1*	0.03	0.64	0.02	0.72	0.06	0.24
γ-tocopherol > 1494.1*	-0.007	0.89	-0.008	0.89	-0.03	0.60
*Median value for serum γ-tocopherol levels = 1494.1						

3b: Association of γ-Tocopherols and Lung Function in Groups Above or Below the Median of α-Tocopherol						
	FEV_1		**FVC**		**Ratio**	
	r	**p**	**r**	**p**	**r**	**p**
α-tocopherol < 14,832.9*	-0.10	0.08	-0.09	0.11	-0.001	0.97
α -tocopherol > 14,832.9*	-0.12	0.03	-0.10	0.07	-0.04	0.47

*Median value for serum α-tocopherol levels = 14,832.9