

# Randomised vitamin E supplementation and risk of chronic lung disease in the Women's Health Study

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## ABSTRACT

**Background** The oxidant/antioxidant balance in lung tissue is hypothesised to contribute to the risk of chronic obstructive pulmonary disease (COPD). Observational studies consistently report higher antioxidant status associated with lower COPD risk, but few randomised studies have been reported.

**Methods** A post hoc analysis of 38 597 women without chronic lung disease at baseline was conducted in the Women's Health Study (WHS) to test the effect of vitamin E on the risk of incident chronic lung disease. The WHS is a randomised double-blind placebo-controlled factorial trial of vitamin E (600 IU every other day) and aspirin (100 mg every other day) in female health professionals aged  $\geq 45$  years. Using Cox proportional hazards models, the effect of randomised vitamin E assignment on self-reported physician-diagnosed chronic lung disease was evaluated.

**Results** During 10 years of follow-up (376 710 person-years), 760 first occurrences of chronic lung disease were reported in the vitamin E arm compared with 846 in the placebo arm (HR 0.90; 95% CI 0.81 to 0.99;  $p=0.029$ ). This 10% reduction in the risk of incident chronic lung disease was not modified by cigarette smoking, age, randomised aspirin assignment, multivitamin use or dietary vitamin E intake (minimum  $p$  for interaction=0.19). Current cigarette smoking was a strong predictor of chronic lung disease risk (HR 4.17; 95% CI 3.70 to 4.70; vs. never smokers).

**Conclusions** In this large randomised trial, assignment to 600 IU vitamin E led to a 10% reduction in the risk of chronic lung disease in women.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by progressive irreversible airflow limitation and comprises a significant public health burden, with increasing trends in incidence and prevalence.<sup>1</sup> The prevalence of COPD in the US adult population is 3–4% and, worldwide, the prevalence of COPD is about 10%.<sup>1–2</sup> COPD was the fifth leading cause of death in the USA in 2001 and is expected to become the third leading cause of death by 2020, largely due to population ageing and increasing cumulative exposure to cigarette smoke, the primary risk factor for COPD.<sup>1–3</sup>

Factors that may contribute to rising COPD incidence include obesity, dietary patterns, environmental and occupational exposures, and improved diagnostic and screening programmes.<sup>1–6</sup> Several lines of evidence support the hypothesis that diet plays a role in the aetiology of COPD.<sup>4–6</sup> Observational studies of diet or nutritional status

biomarkers and randomised trials of diet or nutritional supplements have investigated the relation between antioxidants (notably vitamin E) and lung outcomes. Observational studies investigating the association of dietary intake and pulmonary function consistently report that higher intake of nutrients with antioxidant properties is associated with better pulmonary outcomes, but causal inferences are limited by concerns about confounding and other biases.<sup>8–9</sup> Studies comparing patients with COPD with healthy individuals report lower plasma and peripheral skeletal muscle vitamin E ( $\alpha$ -tocopherol) concentrations in patients and a lower risk of death from respiratory disease with higher serum  $\alpha$ -tocopherol concentration, but whether nutrition contributed to the onset of COPD is less clear.<sup>10–12</sup>

Randomised trials of diet change or vitamin E supplements in clinical populations have reported mixed results. Patients with COPD who increased the intake of antioxidant-rich foods had improved pulmonary function over 3 years while those on usual diets experienced a continuous decline in lung function.<sup>13</sup> Studies of  $\alpha$ -tocopherol treatment in patients with COPD have reported mainly negative results, although conclusions are limited by an incomplete understanding of potential to benefit, the short duration of studies and case heterogeneity.<sup>14–16</sup> Very few large randomised studies of non-diseased individuals have been completed. In the Heart Protection Study (HPS), which included participants with coronary disease, other occlusive arterial disease or diabetes, a post hoc analysis found no effect of vitamin E supplements on the occurrence of respiratory-related death, on COPD/asthma hospitalisation rates or on pulmonary function measured by spirometry at the end of the study.<sup>17</sup> In the Alpha-Tocopherol and Beta-Carotene (ATBC) study, a study of male cigarette smokers, there was no effect of  $\alpha$ -tocopherol on the incidence of chronic bronchitis or COPD symptoms.<sup>16</sup>

Using data from the Women's Health Study (WHS), a large study of apparently healthy women aged  $\geq 45$  years, we tested the hypothesis that supplementation with 600 IU  $\alpha$ -tocopherol every other day decreases the rate of occurrence of chronic lung disease (CLD).

## METHODS

Additional details are given in the online supplement.

### Study design

The WHS, a randomised double-blind placebo-controlled two-by-two factorial trial, assessed the

risks and benefits of vitamin E supplements (600 IU every other day; Natural Source Vitamin E Association, Washington, DC, USA) and/or aspirin (100 mg every other day; Bayer AG, Leverkusen, Germany) in the primary prevention of cardiovascular disease and cancer. Full details of the study design are published elsewhere.<sup>18</sup> The study was registered with <http://clinicaltrials.gov/> (NCT00000479).

Eligibility criteria included age  $\geq 45$  years; healthcare professional; resident in the USA; no previous history of coronary heart disease, cerebrovascular disease, cancer (except non-melanoma skin cancer) or other major chronic illness; no more than weekly use of vitamins E, A or  $\beta$ -carotene supplements; no history of adverse aspirin effects; less than weekly use of aspirin or non-steroidal anti-inflammatory drugs or willingness to forgo; no use of anticoagulants or corticosteroids. A 3-month placebo-only run-in period identified likely long-term compliers. Of these, 39 876 women remained willing and eligible and were randomised into the WHS between April 1993 and January 1996.<sup>18</sup>

### Questionnaire data

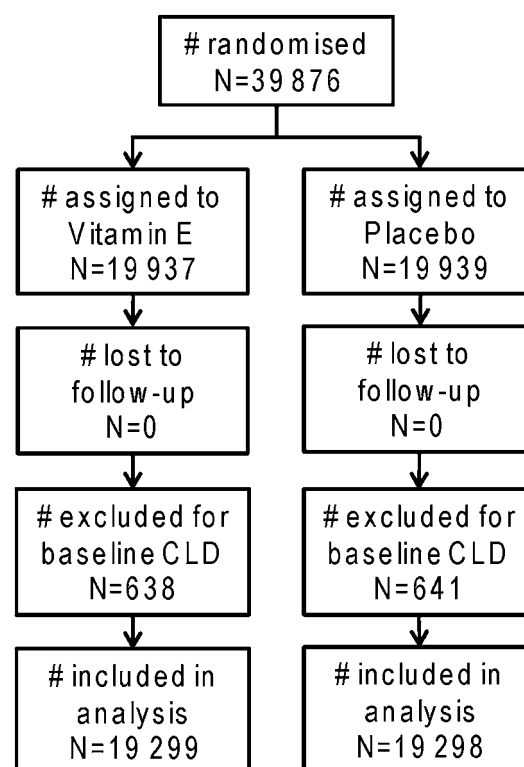
Mailed questionnaires collected baseline data on anthropometric, demographic, lifestyle and clinical characteristics. Follow-up questionnaires, completed twice during the first year and annually thereafter, assessed study supplement compliance, new disease occurrence and diagnosis date, personal characteristics and habits, non-study aspirin, vitamin and non-steroidal anti-inflammatory drug use and side effects. Compliance, defined as taking two-thirds of study supplements, was similar between the active and placebo groups (78.9% and 71.6% at 5 and 10 years, respectively).<sup>19</sup> Non-trial vitamin E supplement use  $\geq 4$  days/month was 10.0% and 10.9% at 5 and 10 years, respectively.<sup>19</sup>

### CLD ascertainment

CLD was not a prespecified trial end point. Occurrence of self-reported doctor-diagnosed CLD was ascertained on questionnaires beginning 12 months after study enrolment. A multipart question asked participants "Have you ever been diagnosed by a physician as having any of the following?". Choices included 'other chronic lung disease (eg, emphysema, chronic bronchitis, bronchiectasis)' as well as 'asthma'. For each diagnosis the date of the diagnosis was reported. Thereafter, annual questionnaires asked about diagnoses occurring since the previous questionnaire, including diagnosis date. Incident cases were ascertained to 31 March 2004 (scheduled trial end). Prevalent CLD was defined as CLD diagnosis prior to trial enrolment. Women with prevalent CLD were excluded from the analysis (figure 1).

### Statistical analysis

One thousand two hundred and seventy-nine women reported prevalent CLD (638 in vitamin E group; 641 in placebo group), leaving 38 597 participants available for analyses. All analyses followed the intention-to-treat principle. The cumulative incidence of CLD by study arm was assessed using Kaplan–Meier methods and log-rank tests to compare survival curves. Cox proportional hazards models estimated HRs. Further models considered whether the effect of vitamin E on incident CLD was modified by smoking status, age, body mass index, multivitamin use, alcohol intake, baseline asthma, history of cholesterol levels  $\geq 240$  mg/dl or randomised aspirin assignment. Effect modification was tested for statistical significance using likelihood ratio tests comparing models with and without interaction terms.



**Figure 1** Flow diagram of the vitamin E component of the Women's Health Study chronic lung disease (CLD) analysis.

Data management and analyses were completed using SAS (SAS Institute Inc).

### RESULTS

The baseline characteristics of the 38 597 participants, summarised in table 1, were balanced between the vitamin E and placebo arms. Thus, participants in both arms were similar in age, smoking, body mass index, multivitamin use, dietary intake of vitamin E, alcohol intake, history of asthma diagnosis and percentage with cholesterol  $\geq 240$  mg/dl (table 1). The mean age of study participants was 54.5 years, and women were followed on average for 9.8 years (376 710 person-years; 188 578 person-years in the vitamin E arm, 188 132 person-years in the placebo arm).

Participants reported 1606 new diagnoses of CLD, corresponding to a cumulative incidence of 4.2%. Participants in the vitamin E arm reported 760 incident CLD diagnoses (cumulative incidence 3.9%) compared with 846 diagnoses in the placebo arm (cumulative incidence 4.4%; figure 2), corresponding to a statistically significant 10% reduction in risk in participants randomised to receive vitamin E supplements (HR 0.90; 95% CI 0.81 to 0.99;  $p=0.029$ ). Comparing the cumulative CLD incidence by year of follow-up in the vitamin E and placebo groups (figure 3), the curves separate at about 1.5 years of study and continue to diverge until about 5 years of supplementation, maintaining a consistent separation thereafter. In contrast, the aspirin intervention had little or no association with risk of CLD (HR 0.98; 95% CI 0.89 to 1.08).

Cigarette smoking had a strong association with CLD incidence (current smoker vs never smoker: HR 4.17; 95% CI 3.70 to 4.70;  $p<0.0001$ ). In addition, other known COPD risk factors were positively associated with the CLD outcome: older age at randomisation (age  $\geq 65$  years vs  $<55$  years; HR 2.38; 95% CI 2.07 to 2.73;  $p<0.0001$ ), obesity (BMI  $\geq 30.0$  vs  $<25.0$ ; HR 1.60; 95% CI 1.41 to 1.81;  $p<0.0001$ ), asthma diagnosis prior to

**Table 1** Baseline characteristics of participants in the Women's Health Study by vitamin E randomisation

Characteristic	Vitamin E (N = 19 299)* N (%)‡	Placebo (N = 19 298)† N (%)‡
<b>Demographic/lifestyle</b>		
Age, years‡	54.5 (7.0)	54.6 (7.0)
<55	11714 (60.7)	11679 (60.5)
55–64	5654 (29.3)	5677 (29.4)
≥65	1931 (10.0)	1942 (10.1)
Cigarette smoking		
Current	2434 (12.6)	2491 (12.9)
Past	6937 (36.0)	6823 (35.4)
Never	9909 (51.4)	9968 (51.7)
Average duration, years‡ §	18.8 (12.5)	18.9 (12.6)
Body mass index, kg/m <sup>2</sup> ‡	26.0 (5.0)	26.0 (5.0)
<25.0	9598 (50.8)	9670 (51.1)
25.0–<30.0	5880 (31.1)	5837 (30.8)
≥30.0	3404 (18.0)	3411 (18.0)
<b>Nutrition</b>		
Multivitamin use		
Never	2521 (13.2)	2553 (13.4)
Past only	10927 (57.4)	10982 (57.7)
Current	5574 (29.3)	5499 (28.9)
Vitamin E intake, mg/day		
Diet only‡	6.6 (5.0)	6.6 (5.3)
Diet+supplements‡	63.2 (143.0)	62.6 (140.9)
Alcohol intake		
Rare/never	8743 (45.3)	8590 (44.5)
1–3/month	2531 (13.1)	2553 (13.2)
1–6/week	6048 (31.4)	6194 (32.1)
1+/day	1970 (10.2)	1959 (10.2)
<b>Medical conditions</b>		
Asthma diagnosis	1104 (5.7)	1105 (5.7)
Cholesterol ≥240 mg/dl	5615 (29.1)	5688 (29.5)
Study aspirin assignment	9638 (49.9)	9654 (50.0)

\*N total for each characteristic ranges from 18 882 to 19 299, given missing data in some variables.

†N total for each characteristic ranges from 18 918 to 19 298, given missing data in some variables.

‡Continuous variables are presented as mean (SD).

§Average smoking duration for current and past smokers only.

randomisation (HR 1.94; 95% CI 1.65 to 2.28;  $p < 0.0001$ ) and hypercholesterolaemia (HR 1.42; 95% CI 1.28 to 1.57;  $p < 0.0001$ ).

There was no statistical evidence that the effect of randomised vitamin E assignment on CLD risk was modified by age ( $p = 0.86$ ), smoking status ( $p = 0.96$ ), body mass index ( $p = 0.25$ ), multivitamin use ( $p = 0.67$ ), baseline asthma history ( $p = 0.89$ ), cholesterol  $\geq 240$  mg/dl ( $p = 0.84$ ) or by study aspirin assignment ( $p = 0.19$ ) (figure 3). Alcohol intake was borderline statistically significant ( $p = 0.054$ ) as a modifier of the effect of vitamin E on CLD, and women consuming one or more alcoholic drinks per day had the strongest vitamin E protective effect. In additional analyses there was no evidence of effect modification by race, exercise frequency, hypertension and baseline dietary intake of either vitamin E or C. For all models, controlling for randomised aspirin assignment did not alter the effect of vitamin E supplement assignment on CLD risk. An additional sensitivity analysis was conducted, censoring women who reported incident asthma from the CLD analysis; the association of vitamin E was similar with a 9% reduction in risk of CLD (HR 0.91; 95% CI 0.81 to 1.03).

## DISCUSSION

In this large randomised double-blind placebo-controlled trial in apparently healthy women, 600 IU vitamin E on alternate days

reduced the risk of self-reported newly diagnosed CLD by approximately 10%. There was no statistically significant difference in the magnitude of the effect of vitamin E by age, smoking status, randomised aspirin assignment, multivitamin use or asthma history, and the protective effect was slightly stronger in women consuming  $>1$  alcoholic drink/day. Randomised assignment to aspirin had no association with the risk of CLD.

Two previous randomised trials investigated vitamin E supplementation in relation to lung outcomes and both reported no effect of intervention.<sup>16 17</sup> In the HPS, 20 536 adults aged 40–80 years with prevalent coronary artery disease were randomised to a combined intervention of 600 IU vitamin E, 250 mg vitamin C and 20 mg  $\beta$ -carotene or placebo daily for 5 years.<sup>17</sup> The HPS differed from the WHS in important ways. The HPS enrolled participants with clinically diagnosed coronary artery disease, occlusive arterial disease or diabetes and 75% of the participants were men<sup>17</sup> while the WHS comprised women without a history of cardiovascular disease. Study duration (5 years in the HPS vs 10 years in the WHS) and supplement formulation (combined supplement in the HPS vs vitamin E alone in the WHS) also differed. Finally, the outcomes in the HPS (pulmonary function measured by spirometry, death due to respiratory illness and COPD or asthma-related hospitalisations) differed from the WHS which investigated the incidence of a CLD diagnosis.<sup>17</sup>

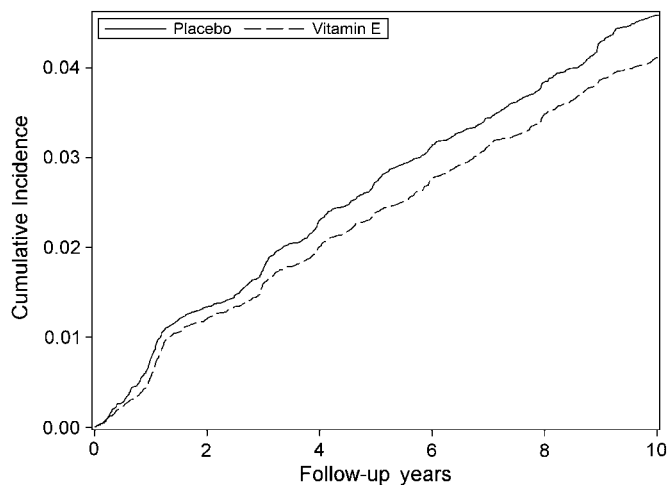
In the ATBC study, 29 133 male cigarette smokers aged 50–69 years were randomised to receive 50 mg vitamin E and/or 20 mg  $\beta$ -carotene or placebo daily for 4 years.<sup>16</sup> The ATBC differed substantially from the WHS in the supplement studied, trial duration and the population studied.<sup>16</sup> The ATBC reported no effect of vitamin E on COPD-related symptoms, a substantially different end point from the incidence of CLD diagnosis.

The strengths of the WHS include the large number of participants, the large number of self-reported doctor-diagnosed CLD outcomes, high adherence rate and high follow-up rate. CLD is associated with ageing, so the minimum age required for study enrolment (45 years) yielded a population at risk for incident CLD.

Several limitations deserve mention. While the size of this trial was adequate to detect a statistically significant small to moderate effect of vitamin E supplementation on incident CLD, the trial was not specifically designed to test the studied hypothesis. Thus, outcome ascertainment was based solely on self-reported doctor diagnosis, a concern that is partly mitigated by the fact that participants were female health professionals. A validation study of self-reported COPD outcomes in female nurses found that 78% of self-reported cases of COPD were confirmed by medical record review, which suggests that self-report of lung disease by the female health professionals comprising the WHS is likely to have excellent validity.<sup>20</sup> While the question about outcome occurrence included bronchiectasis, the low incidence of bronchiectasis in this age range leads to the reasonable assumption that most occurrences reported refer to COPD. Current cigarette smoking was a strong predictor of CLD in these data, providing evidence of face validity for the outcome ascertainment. Finally, if the outcome is misclassified (either by undercounting cases or by including false positives), the misclassification is likely to affect both arms of the trial equally and the HR may therefore be an underestimate of the true effect size.

## Outcome definition

The complexity of airway disease phenotypes raises substantial concern about misdiagnosis of COPD and asthma, particularly



**Figure 2** Cumulative incidence of chronic lung disease during the randomised component of the Women's Health Study.

in women.<sup>21</sup> To address the possibility that women reporting a new asthma diagnosis actually had COPD, a sensitivity analysis was conducted. When women reporting incident asthma were excluded from the analysis, vitamin E was associated with a 9% reduction in the risk of CLD (HR 0.91; 95% CI 0.81 to 1.03), similar to the findings in the full study group. There was little or no effect of vitamin E supplementation on incident self-reported doctor-diagnosed asthma (HR 0.99; 95% CI 0.90 to 1.08;  $p=0.83$ ). Kurth *et al*<sup>22</sup> investigated the effect of randomised aspirin assignment on the risk of incident adult-onset

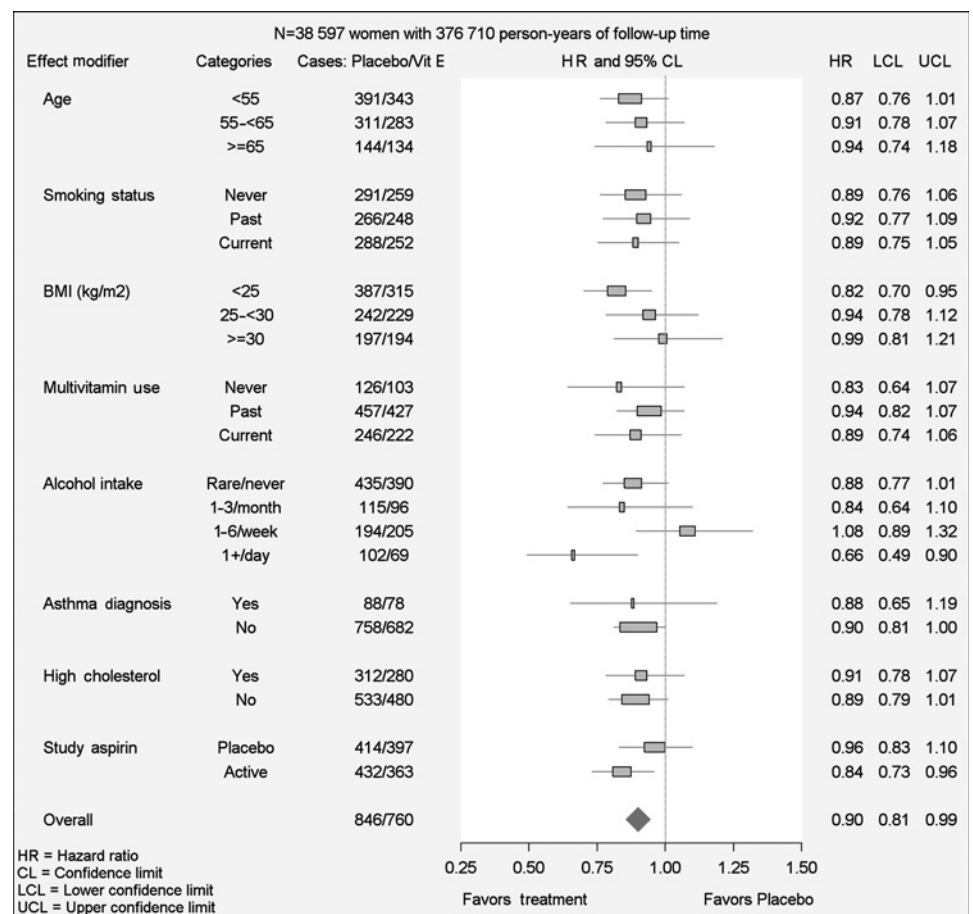
asthma in the WHS; women in the aspirin arm had a 10% lower risk of incident asthma than those in the placebo arm. When women developing COPD over follow-up were censored from the analysis, the findings were similar. The effect of aspirin on incident asthma and the lack of effect of aspirin on incident CLD supports the notion of differentiation in the self-reported diagnoses.

### Proposed mechanisms

Previous studies have documented the presence of vitamin E in the lung compartment and the mechanisms of delivery of vitamin E to alveolar type II cells in the lung.<sup>23</sup> Vitamin E transport to the type II cells is hypothesised to occur via high-density lipoproteins because type II cells have no physical contact with plasma and interact only with interstitial fluid lipoproteins, which are predominantly HDL lipoproteins.<sup>23</sup> Thus, the concentration of HDL cholesterol in the plasma and in the interstitial fluid predicts the amount of vitamin E available to the lung compartment to combat oxidative stress. Previous studies have reported that HDL cholesterol and apolipoprotein A-I levels are positively associated with forced expiratory volume in 1 s, even after adjusting for serum antioxidant concentrations, a finding that may reflect the delivery of vitamin E to lung tissues.<sup>24</sup> Thus, a higher HDL cholesterol level is hypothesised to deliver a greater effective dose of vitamin E to the lung compartment.

Given that HDL cholesterol levels are 20–25% higher in women than in men of all age groups, differences in the biologically effective dose of vitamin E may contribute to the difference in findings between women in the WHS and the

**Figure 3** Effect modification of the vitamin E/chronic lung disease effect in the Women's Health Study. BMI, body mass index.





predominantly male participants in the HPS and ATBC.<sup>25</sup> Sex-related differences in the effect of vitamin E supplementation on all-cause mortality have been reported, with stronger protective effects of low-dose vitamin E supplementation evident in study populations comprised of  $\geq 75\%$  women.<sup>26</sup>

Alcohol intake is proposed to reduce the risk of cardiovascular disease by raising HDL cholesterol levels, and a threshold of  $\geq 1$  alcoholic drink per day is associated with both higher HDL cholesterol levels and attenuation of the risk of cardiovascular disease.<sup>27–28</sup> Given the important role of HDL cholesterol in transporting vitamin E to the lung, exploratory analyses considered alcohol intake as a modifier of the effect of vitamin E on CLD. Among variables considered as possible effect modifiers, alcohol intake was marginally statistically significant ( $p=0.054$ ), and the preventive effect of vitamin E on CLD was greatest in women consuming the highest level of alcohol ( $\geq 1$  drink/day). These preliminary findings are consistent with the hypothesis that delivery of vitamin E to lung tissue may vary by plasma levels of HDL cholesterol.

Under our hypothesis, the effect of antioxidant supplementation was expected to be stronger in participants with a higher oxidative burden—for example, current cigarette smokers. Contrary to expectation, there was no evidence of effect modification by smoking. If supplementation with vitamin E acts through other systemic mechanisms—for example by improving immune system function—then a general effect of vitamin E would be supported.<sup>29</sup>

### Efficacy and safety considerations

There has been substantial discussion of the efficacy and safety of vitamin E supplementation in the scientific literature.<sup>30</sup> Potential harmful effects include an increased risk of all-cause mortality, susceptibility to bleeding and haemorrhagic stroke.<sup>31–33</sup> The meta-analysis linking high-dose vitamin E supplementation to increased risk of mortality, however, has been criticised for its methodology and a recent paper suggested that vitamin E has beneficial effects on the risk of ischaemic stroke.<sup>33–35</sup> Thus, the design of future vitamin E supplementation trials must carefully consider information about risks and benefits, and recommendations may need to be tailored to specific populations.

### CONCLUSION

The WHS comprised female health professionals aged  $>45$  years, the majority of whom were of European descent. Healthy women taking 600 IU vitamin E supplements every other day were 10% less likely to report a new CLD diagnosis during the study period. Any decisions about use of vitamin E as a preventive must consider information about vitamin E-associated risks and bioavailability.<sup>22–26–30–32–34</sup> Given that there are few prevention strategies for emphysema and chronic bronchitis, further study of vitamin E in relation to COPD is of public health interest.

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**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the Brigham and Women's Hospital and Cornell University (for analyses in this study of previously collected data). The Women's Health Study was approved by the institutional review board of Brigham and Women's Hospital and monitored by an external data and safety monitoring board.

**Contributors** Conception and design of Women's Health Study: JEB, JMG; conception of research question: PAC, AHA; analysis and interpretation: AHA, PAC, TK; writing and editing: AHA, PAC, TK, JEB, JMG.

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