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Alcohol Consumption and the Risk of Incident Pulmonary Embolism in U.S. Women and Men

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Abstract

Background: Moderate alcohol consumption has been variably associated with hemostatic and fibrinolytic factor levels, but the association between alcohol consumption and risk of incident pulmonary embolism (PE) remains uncertain.

Objective: To evaluate alcohol consumption amount and frequency in relation to PE risk.

Methods: Nurses' Health Study (NHS), NHS II, and Health Professionals Follow-Up Study participants free of venous thromboembolism (VTE) at baseline (n=217,442) reported alcohol consumption by type, quantity, and frequency, every 2–4 years. Incident PE cases were identified by self-report and confirmed for participants without cancer. In this cohort study, we used Cox proportional hazards models to estimate multivariable-adjusted hazard ratios (HRs) for PE associated with alcohol consumption amount and, separately, frequency. Secondary analyses evaluated alcohol type and heavy episodic drinking in relation to PE risk, and amount and frequency in relation to medical record-confirmed idiopathic PE and any self-reported VTE risk. Cohort-specific analyses were pooled using random-effects meta-analysis.

Results: During ≥20 years of follow-up, we identified 1,939 PE events. We found no strong evidence of an association between PE risk and alcohol consumption amount (pooled HR_{adj} for

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5.0–14.9 grams (g)/day vs. abstention = 0.97 [95%CI: 0.79, 1.20]) or frequency (pooled HR_{adj} for 5–7 drinking days per week vs. abstention = 1.04 [95%CI: 0.88, 1.23]). Secondary analyses of type, heavy episodic drinking, idiopathic PE, and VTE also yielded null findings.

Conclusions: Among three large prospective cohorts of U.S. men and women, we found no evidence of an association between the amount or frequency of alcohol consumption and PE risk.

Keywords

Diet; Epidemiology; Hemostasis; Pulmonary Embolism; Venous Thrombosis

Introduction

Venous thromboembolism (VTE), which includes both pulmonary embolism (PE) and deep vein thrombosis (DVT), occurs at an annual incidence rate of 1 to 2 events per 1,000 person-years.[1] Approximately 25 to 40% of PE events are idiopathic in nature,[1] with no known provoking factor such as recent surgery, trauma, or cancer, and for these PE events in particular, lifestyle characteristics may be important risk factors.

Alcohol consumption, which has a well-characterized non-linear U- or J-shaped relation with risk of arterial events like myocardial infarction, has demonstrated inconsistent associations with risk of PE and DVT in previous studies, with some studies reporting a lower VTE risk associated with greater alcohol consumption,[2–5] others reporting a U-shaped association,[6] and yet others reporting no association.[7–12] At the same time, moderate alcohol consumption has been associated with lower levels of fibrinogen, factor VII (FVII), and von Willebrand factor (vWF),[4, 13–15] differences which would be expected to influence VTE risk.

Importantly, the majority of studies of alcohol consumption and VTE risk to date have relied on only one baseline alcohol measurement,[2–4, 6, 10] without accounting for change over follow-up, or have not separated former drinkers from long-term abstainers, despite the likelihood that former drinkers are at disproportionately high risk.[16] In addition, few studies have evaluated the complex dimensions of alcohol consumption in relation to VTE risk, such as frequency and type of alcohol consumption, and engagement in heavy episodic drinking.

Thus, in three prospective cohorts of men and women in the United States, we evaluated the risk of incident PE associated with amount and frequency of alcohol consumption using updated measures of alcohol consumption and separating current former drinkers from abstainers. In these primary analyses, we hypothesized that light to moderate amounts of average alcohol consumption would be associated with a lower risk of incident PE than low or high amounts of average alcohol consumption (a U-shaped association) and that more frequent alcohol consumption would be associated with a lower risk of incident PE than less frequent alcohol consumption. Secondary analyses evaluated these exposures in relation to outcomes of secondary interest, risk of idiopathic PE and any VTE, and evaluated PE risk in relation to exposures of secondary interest, type of alcohol consumed and engagement in heavy episodic drinking.

Methods

Study Population

This study included participants of three large prospective ongoing American cohorts: the Nurses' Health Study (NHS), the NHS II, and the Health Professionals Follow-Up Study (HPFS).[17, 18] Enrollment of female nurses aged 30–55 years began in 1976 in NHS (n=121,700), enrollment of female nurses aged 24–42 years began in 1989 in NHS II (n=116,430), and enrollment of male health professionals aged 40–75 years began in 1986 in HPFS (n=51,529). Biennially, participants complete mailed questionnaires regarding medical history and lifestyle habits and every four years this questionnaire includes a food frequency questionnaire (FFQ). All participants provided written informed consent and study protocols were approved by the institutional review boards at the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

We defined baseline for this analysis as the year in which alcohol consumption was first reported: 1984 in NHS, 1991 in NHS II, and 1986 in HPFS and excluded persons who died or had a history of VTE prior to baseline, reported an implausible energy intake at baseline (<600 or >3500 kcal/day for women; <800 or >4200 kcal/day for men), had more than 70 blank items on the FFQ, were missing alcohol exposure data, or returned only the baseline questionnaire. We also excluded baseline and follow-up periods during which participants were pregnant. After exclusions, 74,841 NHS women, 93,444 NHS II women, and 49,157 HPFS men were eligible for analyses. During follow-up we censored individuals at death, warfarin use, loss to follow-up (approximately <15% in any given follow-up cycle)[17] or occurrence of the outcome of interest (i.e. PE in PE and idiopathic PE analyses; VTE in VTE analyses), and skipped an individual's contributing person time from that questionnaire cycle if alcohol exposure information was missing or reported energy intake was implausible.

Assessment of Alcohol Consumption

On an FFQ every four years, participants reported their usual average frequency of consumption in the prior year, by type (regular beer [1 glass/bottle/can], light beer [1 glass/bottle/can], red wine [4 oz. glass], white wine [4 oz. glass], and liquor [1 drink/shot]). Using standard ethanol equivalents of 12.8 grams ethanol/serving regular beer, 11.3 grams ethanol/serving light beer, 11.0 grams ethanol/glass of wine, and 14.0 grams ethanol per serving of liquor, we calculated the average amount of alcohol consumed in grams per day, by type and in total.[19] We categorized time-varying current alcohol consumption into: abstention (never reported consuming alcohol), former drinking (no alcohol consumption reported in current questionnaire cycle, but reported previously, or, no alcohol consumption reported in first questionnaire cycle but individual reported that alcohol consumption greatly decreased over the past 10 years), and current drinking of the average amount of 0.1–4.9 g/day (up to 1/3 drink per day), 5.0–14.9 g/day (1/3–1 drink/day), 15.0–29.9 g/day (approximately 1–2 drinks/day), and ≥30 g/day (greater than or equal to 2 drinks per day).

Participants separately reported how frequently they consumed alcohol by reporting the number of days per week they typically consumed alcohol (years asked in NHS: 1986, 1988,

1996, 2000, 2004; NHS II: 1991, 1995, 1999, 2003, 2007, 2011; HPFS: 1986, 1990, 1994, 1997, 2002, 2006, 2010). We classified persons who drank alcohol 0 days/week into abstainers and former drinkers and categorized drinking days/week into 1–2, 3–4, and 5–7 days/week. Participants also reported their engagement in heavy episodic drinking by reporting the largest number of drinks of beer, wine, and/or liquor they may have had in one day in a typical month during the past year (years asked in NHS: 1988, 1996, 2000, 2004; NHS II: 1989, which was carried forward to 1991, 2005, 2009; HPFS: 1988, 1992, 1996). We categorized responses into 0, 1–2, 3–5, and ≥6 drinks per day.

Ascertainment of Venous Thromboembolism

Participants were asked every two years whether a physician had diagnosed them with PE since the prior questionnaire. Participants who reported a PE were consented for medical records to confirm self-report, for the subset of participants without a previous confirmed cancer. In this analysis, we included PEs that were medical record confirmed (55.8% of included PE cases in NHS; 42.6% in NHS II; 53.3% in HPFS), PEs that were reconfirmed by the study participant but medical record review was refused or was unable to be completed (18.2% of included PE cases in NHS; 40.7% in NHS II; 7.3% in HPFS), and, PEs among persons with prior cancer, since these events were not sent for medical record review and potential confirmation (26.0% of PEs included in NHS; 16.7% in NHS II; 39.4% in HPFS). As a secondary outcome, we evaluated the risk of idiopathic PE, which were medical record confirmed and occurred without recent surgery, trauma, or cancer.

As an additional outcome of secondary interest, we evaluated the risk of incident VTE (first event of either PE or DVT), self-reported by the participant. In NHS, women reported DVT events by writing-in DVT as an “other major illness” occurring since the prior questionnaire. In NHS II and HPFS, participants were asked whether a physician had diagnosed them with DVT since the prior questionnaire. Reported DVT events were not reviewed for medical record confirmation; thus, due to these differences in outcome ascertainment of DVT and PE, our analysis of VTE was secondary.

Covariates and Other Measures

On biennial questionnaires, participants reported their demographic characteristics, lifestyle, and medical behaviors, including medication use (hormone therapy [HT], oral contraceptives [OCs], warfarin, and aspirin), all of which we updated over follow-up. Physical activity as measured in metabolic equivalent of tasks (METs) per week was calculated using questions about the average amount of time a participant spent per week doing a variety of physical activities. Cigarette smoking was categorized into never, former, 1–14 cigarettes/day, 15–24 cigarettes/day, ≥25 cigarettes/day.

Every two years, participants reported whether they had been diagnosed by a clinician with a variety of medical conditions, asked separately, including high blood pressure, elevated cholesterol, diabetes mellitus, myocardial infarction, angina pectoris, and cancer other than non-melanoma skin cancer. For each of these diseases, we determined whether the individual had prevalent disease in each questionnaire cycle by categorizing any past diagnosis as prevalent and updating during follow-up.

Statistical Analyses

Participants contributed person-time from the return of the 1984 questionnaire in NHS, the 1991 questionnaire in NHS II, and the 1986 questionnaire in HPFS to the first of date of PE diagnosis, start of warfarin use, death, last questionnaire return (date of last follow-up), or end of follow-up (June 1, 2012 in NHS; June 1, 2013 in NHS II; January 1, 2012 in HPFS). We used Cox proportional hazards models with time-varying covariates to estimate multivariable-adjusted hazard ratios (HRs) for PE associated with amount of alcohol consumed and, separately, frequency of alcohol consumption. Models were stratified by age in months and adjusted for possible confounders identified *a priori* (smoking [categorical], continuous body mass index [BMI] [calculated by dividing weight in kg by squared height in meters], race [white vs. non-white], aspirin use, continuous physical activity [as measured in METs per week], continuous caloric intake, and separate indicators for history of diabetes, hypertension, hypercholesterolemia, MI or angina, cancer other than non-melanoma skin cancer), and for factors known *a priori* to be strongly associated with PE risk, to improve precision of our estimates (HT use [in women only] and OC use [in NHS II only]). Missing exposure and covariate information was replaced with values from one questionnaire prior. If data remained missing after values were carried forward only one cycle, missing indicator variables were created and included in models as covariates.

We performed a test of linear trend by treating alcohol consumption amount and frequency as continuous variables and skipping person-time during which participants were former drinkers. We performed a test of quadratic trend in analyses of alcohol amount by squaring the continuous variables and including the squared (used to estimate the quadratic trend) and linear terms in one model. All analyses were conducted separately by cohort and meta-analyzed with random effects to estimate a pooled summary HR.

In secondary analyses, we evaluated amount of alcohol consumed, by type (beer, red wine, white wine, and liquor), and, the largest number of drinks consumed in one day in a typical month (i.e. heavy episodic drinking), in relation to PE risk. These secondary analyses excluded former drinkers. Additional secondary analyses evaluated alcohol consumption amount and frequency in relation to risk of idiopathic PE and self-reported VTE. Sensitivity analyses evaluated primary exposures of interest in relation to PE risk using (1) baseline values of alcohol consumption amount, and, (2) alcohol consumption amount lagged by 2-years.

We evaluated interaction between continuous quantity of alcohol consumed per drinking day and continuous frequency of alcohol consumption. Quantity of alcohol consumed per drinking day was calculated by dividing the amount of alcohol in grams consumed per week by the frequency of alcohol consumption; discordant values between the two alcohol questions regarding abstention were set to missing. We evaluated interaction on the multiplicative scale, by including an interaction term along with both main effects in a model. These analyses excluded person-time during which a participant was a former drinker. All analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

We identified 917 incident PE events during a mean follow-up of 23.2 years in NHS (1,739,210 total person-years), 540 PE events during 18.2 mean years follow-up in NHS II (1,691,134 total person-years), and 482 PE events during 19.2 mean years follow-up in HPFS (944,538 total person-years). In Table 1, we present age-standardized characteristics at baseline, by cohort and categories of alcohol consumption amount. At baseline, participants had a mean age of 50.5 years in NHS, 36.6 years in NHS II, and 54.3 years in HPFS.

We found no evidence of an association between amount of alcohol consumed and risk of incident PE in NHS, NHS II, or HPFS (Table 2). In the absence of between-study heterogeneity (Q-statistic p-values >0.05) we pooled cohort-specific estimates and observed a pooled HR_{adj} for 5.0–14.9 g/day alcohol consumption vs. abstention of 0.97 (95% CI: 0.79, 1.20; linear p-trend = 0.7; quadratic p-trend = 0.7). Compared to abstention, former drinking was associated with a greater risk of incident PE in NHS (HR=1.24; 95% CI: 1.01, 1.54) and NHS II (HR=1.38; 95% CI: 1.02, 1.88), but not in HPFS (HR=0.89; 95% CI: 0.60, 1.31). There was some suggestion of a U-shaped association between amount of alcohol consumed and idiopathic PE risk in HPFS (quadratic p-trend = 0.08), but there was no evidence of this trend in NHS, NHS II, or pooled analyses (Supplemental Table 1). In secondary analyses of VTE risk, the risk of incident VTE among NHS participants was inversely associated with alcohol consumption, but there was no evidence of the hypothesized U-shaped association (HR_{adj} for 5.0–14.9 g/day alcohol consumption vs. abstention = 0.87; 95% CI: 0.77, 1.00; linear p-trend = 0.02; quadratic p-trend = 0.3) (Supplemental Table 2). In NHS II, HPFS, and pooled analyses, there was no evidence of an association between amount of alcohol consumed and incident VTE risk. Sensitivity analyses that evaluated risk of PE associated with amount of alcohol consumed at baseline, found similar results to those in primary analyses, with all linear and quadratic p-values >0.3, suggesting no evidence of a linear or U-shaped association. Results of analyses using 2-year lagged exposures also yielded similar results, with all linear and quadratic p-trend values >0.4.

We found no evidence that frequency of alcohol consumption was associated with risk of incident PE in NHS, NHS II, HPFS, or pooled analyses (Table 3) (pooled HR_{adj} for 3–4 drinking days per week vs. abstention = 1.16; 95% CI: 0.97, 1.39; p-linear trend = 0.3). We also found no evidence of an interaction between the quantity of alcohol consumed per drinking day and frequency of alcohol consumption and PE risk (pooled p-interaction = 0.7). In secondary analyses, we found no evidence of an association of frequency on risk of idiopathic PE or any VTE (Supplemental Tables 3 and 4).

Secondary analyses suggested no evidence of an association between type of alcohol consumed (by amount) and incident PE risk (Table 4) (pooled HR_{adj} for: ≥5 g/day beer vs. 0 g/day beer = 0.92, 95% CI: 0.74, 1.14; ≥5 g/day red wine vs. 0 g/day red wine = 0.95, 95% CI: 0.74, 1.23; ≥5 g/day white wine vs. 0 g/day white wine = 1.02, 95% CI: 0.80, 1.30; ≥5 g/day liquor vs. 0 g/day liquor = 1.12, 95% CI: 0.95, 1.30). In our analyses of heavy episodic drinking, we found no evidence of an association between the largest number of

alcohol beverages consumed in one day in a typical month and the risk of incident PE (Table 5) (pooled p-linear trend = 0.9).

Discussion

Among three large prospective cohorts of U.S. men and women, we found no evidence of an association between amount or frequency of alcohol consumption and the risk of incident PE. Secondary analyses were modestly suggestive of a U-shaped association between amount of alcohol consumed per day and risk of idiopathic PE among men, but the quadratic trend did not reach statistical significance, and there was no association between alcohol frequency and idiopathic PE risk. In secondary analyses of VTE risk (either PE or DVT), which is a more encompassing but less specific outcome, there was no compelling evidence of an association with amount or frequency of alcohol consumed.

Our results are consistent with those of several studies that suggest no association between amount of alcohol consumed and incident VTE risk.[7–12] However, results generally have been inconsistent between studies, with some studies otherwise suggesting a linear decrease in risk associated with increasing amounts of alcohol consumption,[2–5] and others suggesting a U-shaped association.[6] Results may differ between studies in part due to differences in the treatment of former drinkers.[16] The majority of studies of VTE risk to-date have included former drinkers in with alcohol abstainers.[2–5, 7–9, 11, 12] However, including people who quit using alcohol because of underlying medical conditions or medication use (“sick quitters”)[16] in a reference category of non-drinkers may bias results, making alcohol consumption appear to be associated with a lower risk of VTE. In our study, we were able to reduce the influence of this bias by identifying former drinkers and separating them from alcohol abstainers.

It is reasonable to hypothesize that alcohol consumption may be associated with VTE risk, given differences in levels of hemostatic parameters[15] that have been associated with VTE risk. However, the proposed association between alcohol consumption and hemostatic parameters is complex and J or U-shaped,[14] with a hypothesis that light to moderate alcohol consumption may lower procoagulant factors such as fibrinogen, FVII, vWF, and plasma viscosity[14, 15] and may lower fibrinolytic parameters such as plasminogen activator inhibitor (PAI-1) activity and tissue plasminogen activator (tPA) antigen.[14, 20] In the Framingham Offspring Study, associations with procoagulant and fibrinolytic factors tended to be strongest for consumers of 7 to 21 drinks weekly,[14] a level of alcohol consumption higher than that of most NHS, NHS II, and HPFS participants. Although we observed no evidence of an association between alcohol consumption and PE risk among our cohorts of women and men with relatively low average amounts of alcohol consumption, studies with more heavy drinkers are needed to ascertain whether higher amounts of alcohol consumption may be associated with risk.

We found only a modest suggestion of a U-shaped association between amount of alcohol consumed and risk of idiopathic PE in older men, although this association did not reach statistical significance (HPFS quadratic p-trend = 0.08), and was absent in the NHS and NHS II populations of women (quadratic p-trend = 0.3, 0.6, respectively). Several other

studies have evaluated alcohol consumption in relation to idiopathic PE risk.[6, 7, 12] However, evidence of a significant association with risk of idiopathic VTE was reported in only one of these studies, the Danish Diet, Cancer, and Health study, which reported evidence of a potentially U-shaped association with idiopathic VTE among drinkers that was present only among men and not among women; no formal test for trend was conducted.[6]

Few studies have evaluated drinking pattern in relation to VTE risk.[6, 10] In our study we found no association between frequency of alcohol consumption and incident PE risk, nor was there evidence of an interaction between quantity of alcohol consumed per drinking day and frequency of consumption, or an association between heavy episodic drinking and PE risk. According to the *2015–2020 Dietary Guidelines for Americans*, high-risk drinking is defined as the consumption of 4 or more drinks on any day or 8 or more drinks per week for women and 5 or more drinks on any day or 15 or more drinks per week for men.[21] Questions in our cohorts regarding heavy episodic drinking indicated that 3 or more drinks were consumed in any one day in a typical month during the past year by only 24% of NHS participants, 29% of NHS II participants, and 26% of HPFS participants (in the first year this question was asked: 1988, 1989, and 1988, respectively). This small proportion of participants engaging in heavy episodic drinking may limit our ability to evaluate this behavior in relation to PE risk. However, in the Tromsø study, there was also no significant association between binge drinking and VTE risk (HR_{adj}=1.17; 95% CI: 0.66–2.09; linear p-trend = 0.3).[10]

It is possible that differences in PE risk exist by beverage type, especially if a compound other than ethanol drives the proposed association between alcohol and PE risk. As above, previous studies of alcohol type have been inconsistent,[3, 6, 10] with studies suggesting a lower risk of VTE associated with less liquor consumption,[10] more liquor consumption,[3] more beer consumption,[3] as well as no association with beer[6, 10] or wine.[3, 6, 10] However, our study in conjunction with results from other cohorts[3, 6, 10] suggests no clear pattern of such an association between alcoholic beverage type and VTE risk.

As with all observational studies, the potential for residual confounding by lifestyle factors remains, although we were able to control for a number of factors using time-varying covariates updated over 20+ years of follow-up. Few participants (6% in NHS, 11% in NHS II, 12% in HPFS) reported drinking an average of two or more alcoholic drinks per day (≥30 g/day); thus, the range of alcohol intake in our three cohorts was relatively low. Therefore, our ability to assess heavy drinking and risk of PE was limited, as was our ability to evaluate secondary exposures of interest including amount of alcohol consumed by type, and heavy episodic drinking behavior. In addition, results of our study are likely most generalizable to populations similar to those of participants enrolled in the NHS, NHS II, and HPFS cohorts, and results may not be generalizable to populations of non-white race, or of differing socioeconomic categories.

Conclusions

In summary, among three large populations of women and men with relatively low average amounts of alcohol consumption, we found no evidence of an association between the

amount or frequency of alcohol consumption and the risk of PE. Future studies with larger numbers of heavy drinkers may help to elucidate this potential association more fully.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Essentials

- Moderate alcohol consumption's association with pulmonary embolism (PE) risk remains unclear.
- In three large U.S. cohorts, we evaluated the association of alcohol consumption with PE risk.
- We found no evidence of an association of alcohol consumption amount or frequency with PE risk.
- Secondary analyses of type and heavy episodic drinking also yielded null findings.

Table 1.

Age-standardized characteristics of the study population at baseline by categories of alcohol consumption.

NHS (n=74,841) at 1984 Baseline						
	Abstainers(n=17,196)	**Former Drinkers(n=6,260)**	**0.1–4.9 g/day(n=24,966)**	**5.0–14.9 g/day(n=16,128)**	**15.0–29.9 g/day(n=6,064)**	**≥30 g/day(n=4,227)**
Age, years, mean (SD)	50.7 (7.3)	50.8 (7.4)	49.9 (7.3)	50.4 (7.1)	50.9 (6.9)	51.6 (6.8)
Current smokers, %	17	25	22	27	29	46
Prevalent Diagnosis						
Hypertension, %	24	26	21	19	20	27
Diabetes, %	5	6	3	1	1	1
Hyperlipidemia, %	10	10	9	7	7	9
MI or angina, %	4	4	3	2	2	3
Cancer, %	5	5	5	5	5	6
BMI, kg/m^2, mean (SD)	25.9 (5.3)	25.9 (5.3)	25.1 (4.7)	24.0 (3.8)	23.7 (3.6)	24.0 (3.9)
White race/ethnicity, %	93	93	94	95	96	95
Physical activity, METs/week, mean (SD)	11.6 (17.8)	13.5 (22.6)	14.4 (21.9)	15.6 (22.5)	16.8 (23.1)	14.0 (19.4)
NHS II (n=93,444) at 1991 Baseline						
	Abstainers(n=12,461)	**Former Drinkers(n=27,401)**	**0.1–4.9 g/day(n=36,194)**	**5.0–14.9 g/day(n=13,876)**	**15.0–29.9 g/day(n=2,497)**	**≥30 g/day(n=1,015)**
Age, years, mean (SD)	36.8 (4.5)	36.6 (4.6)	36.4 (4.7)	36.6 (4.7)	37.4 (4.6)	38.0 (4.3)
Current smokers, %	4	12	13	17	23	38
Prevalent Diagnosis						
Hypertension, %	7	8	6	5	7	7
Diabetes, %	1	1	1	0	0	1
Hyperlipidemia, %	14	16	14	13	12	13
MI or angina, %	1	1	1	1	0	0
Cancer, %	1	1	1	2	2	3
BMI, kg/m^2, mean (SD)	25.1 (5.8)	25.6 (5.9)	24.3 (5.0)	23.3 (4.0)	23.3 (3.8)	23.6 (4.3)
White race/ethnicity, %	91	96	97	98	98	98

NHS II (n=93,444) at 1991 Baseline

	Abstainers(n=12,461)	Former Drinkers(n=27,401)	0.1–4.9 g/day(n=36,194)	5.0–14.9 g/day(n=13,876)	15.0–29.9 g/day(n=2,497)	≥30 g/day(n=1,015)
Physical activity, METs/week, mean (SD)	17.1 (23.3)	19.1 (26.4)	21.7 (27.4)	24.7 (30.9)	24.8 (28.8)	23.2 (29.3)

HPFS (n=49,157) at 1986 Baseline

	Abstainers(n=5,044)	Former Drinkers(n=6,626)	0.1–4.9 g/day(n=11,862)	5.0–14.9 g/day(n=13,345)	15.0–29.9 g/day(n=6,456)	≥30 g/day(n=5,824)
Age, years, mean (SD)	53.2 (9.6)	55.6 (10.2)	53.5 (10.0)	53.9 (9.7)	53.9 (9.5)	55.6 (9.6)
Current smokers, %	5	9	8	9	10	21
Prevalent Diagnosis						
Hypertension, %	20	24	21	21	23	27
Diabetes, %	4	7	3	2	2	2
Hyperlipidemia, %	10	13	13	13	12	13
MI or angina, %	6	8	7	6	6	6
Cancer, %	3	4	4	4	4	4
BMI, kg/m^2, mean (SD)	25.0 (5.0)	25.1 (5.3)	25.0 (5.1)	24.8 (5.0)	24.8 (4.8)	25.0 (5.0)
White race/ethnicity, %	94	93	95	96	97	97
Physical activity, METs/week, mean (SD)	15.7 (23.1)	17.4 (24.9)	17.7 (24.3)	20.1 (27.2)	21.2 (29.5)	18.8 (26.0)

Abbreviations: BMI = body mass index; g = grams; HPFS = Health Professionals Follow-up Study; kg = kilograms; m = meter; MET = metabolic equivalent of task; MI = myocardial infarction; NHS = Nurses' Health Study; SD = standard deviation.

Table 2.

Amount of alcohol consumption and the risk of incident pulmonary embolism.

	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*,‡	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI
	NHS N=74,841; 917 events			NHS II N=93,123; 540 events			HPFS N=49,157; 482 events			Pooled Analysis§ N=217,121; 1939 events		
Abstainers	314	1.00	reference	54	1.00	reference	44	1.00	reference	412	1.00	reference
Former Drinkers	126	1.24	(1.01, 1.54)	193	1.38	(1.02, 1.88)	73	0.89	(0.60, 1.31)	392	1.19	(0.96, 1.47)
0.1–4.9 g/day	251	1.06	(0.89, 1.26)	173	1.14	(0.83, 1.56)	99	0.89	(0.62, 1.28)	523	1.05	(0.91, 1.20)
5.0–14.9 g/day	137	0.96	(0.78, 1.18)	89	1.23	(0.86, 1.74)	104	0.79	(0.55, 1.13)	330	0.97	(0.79, 1.20)
15.0–29.9 g/day	53	0.96	(0.71, 1.30)	22	1.09	(0.65, 1.81)	90	1.05	(0.72, 1.53)	165	1.01	(0.82, 1.25)
≥30.0 g/day	36	0.96	(0.67, 1.37)	9	0.96	(0.47, 1.97)	72	1.12	(0.75, 1.66)	117	1.02	(0.79, 1.31)
Linear P-Trend†		0.6			0.7			0.4			0.7	
Quadratic P-Trend†		0.5			0.8			0.4			0.7	

*Analyses are stratified by age (in months) and adjusted for smoking (never, former, 1–14 cigarettes/day, 15–24 cigarettes/day, ≥25 cigarettes/day, missing), BMI (continuous and indicator for missing), prevalent diabetes, prevalent hypertension, prevalent hypercholesterolemia, prevalent MI/angina, prevalent cancer, race (white vs. non-white), aspirin use (including missing indicator), physical activity (continuous and indicator for missing), caloric intake (continuous), HT use (including missing indicator; in women only), and OC use (including missing indicator; in NHS II only).

†P-trends estimated by skipping person-time for former drinkers.

‡NHS II n is smaller in Table 2 than in Table 1 because person-time for pregnant women is skipped during follow-up.

§NHS, NHS II, and HPFS cohorts were meta-analyzed to estimate a pooled summary HR. All p-values for between study heterogeneity >0.05.

Abbreviations: adj = adjusted; CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study; PE = pulmonary embolism.

Table 3.

Frequency of alcohol consumption and the risk of incident pulmonary embolism.

	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*,†	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI
	NHS N=58,096; 726 events			NHS IIN=91,993; 489 events			HPFSN=49,058; 442 events			Pooled Analysis§ N=199,147; 1,657 events		
Abstainers	292	1.00	reference	125	1.00	reference	72	1.00	reference	489	1.00	reference
Former Drinkers	65	1.27	(0.96, 1.67)	153	1.30	(1.01, 1.63)	57	0.91	(0.64, 1.30)	275	1.18	(0.97, 1.43)
1–2 Drinking Days/Week	195	1.19	(0.98, 1.43)	135	1.08	(0.85, 1.38)	104	0.87	(0.64, 1.19)	434	1.08	(0.91, 1.26)
3–4 Drinking Days/Week	65	1.22	(0.92, 1.61)	45	1.21	(0.86, 1.71)	62	1.02	(0.72, 1.45)	172	1.16	(0.97, 1.39)
5–7 Drinking Days/Week	109	1.08	(0.86, 1.36)	31	0.99	(0.67, 1.48)	147	1.01	(0.75, 1.36)	287	1.04	(0.88, 1.23)
Linear P-Trend‡		0.4			0.7			0.6			0.3	

*Analyses are stratified by age (in months) and adjusted for smoking (never, former, 1–14 cigarettes/day, 15–24 cigarettes/day, ≥25 cigarettes/day, missing), BMI (continuous and indicator for missing), prevalent diabetes, prevalent hypertension, prevalent hypercholesterolemia, prevalent MI/angina, prevalent cancer, race (white vs. non-white), aspirin use (including missing indicator), physical activity (continuous and indicator for missing), caloric intake (continuous), HT use (including missing indicator; in women only), and OC use (including missing indicator; in NHS II only).

†To achieve model convergence, this model was stratified by ordinal continuous age groups rather than age in months and adjusted for current versus never/past smoking rather than smoking status and amount.

‡Linear p-trend estimated by skipping person-time for former drinkers.

§NHS, NHS II, and HPFS cohorts were meta-analyzed to estimate a pooled summary HR. All p-values for between study heterogeneity >0.05.

Abbreviations: adj = adjusted; CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study; PE = pulmonary embolism.

Table 4.

Amount of alcohol consumed, by type, and the risk of incident pulmonary embolism.

	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI
	NHS N=74,500; 791 events			**NHS II N=81,106; 347 events**			**HPFS N=45,156; 409 events**			**Pooled Analysis‡ N=200,762; 1547 events**		
Beer												
0 g/day†	660	1.00	reference	215	1.00	reference	154	1.00	reference	1029	1.00	reference
0.1−4.9 g/day	112	1.06	(0.89, 1.31)	109	0.92	(0.72, 1.17)	171	0.99	(0.78, 1.25)	392	0.99	(0.87, 1.13)
≥5.0 g/day	19	0.85	(0.53, 1.34)	23	0.89	(0.57, 1.39)	84	0.96	(0.72, 1.28)	126	0.92	(0.74, 1.14)
Linear P-trend†		0.4			0.5			0.4			0.9	
Quadratic P-trend†		0.4			0.7			0.6			0.4	
Red Wine												
0 g/day†	569	1.00	reference	197	1.00	reference	176	1.00	reference	942	1.00	reference
0.1−4.9 g/day	189	0.93	(0.77, 1.12)	140	0.98	(0.77, 1.25)	193	0.94	(0.74, 1.20)	522	0.95	(0.83, 1.07)
≥5.0 g/day	33	1.16	(0.81, 1.66)	10	0.71	(0.37, 1.37)	40	0.85	(0.59, 1.24)	83	0.95	(0.74, 1.23)
Linear P-trend†		0.6			0.8			0.5			0.8	
Quadratic P-trend†		0.8			0.09			0.7			0.4	
White Wine												
0 g/day†	470	1.00	reference	136	1.00	reference	175	1.00	reference	781	1.00	reference
0.1−4.9 g/day	284	1.07	(0.90, 1.27)	194	1.16	(0.91, 1.47)	208	0.96	(0.76, 1.21)	686	1.06	(0.94, 1.20)
≥5.0 g/day	37	0.86	(0.61, 1.22)	17	1.18	(0.70, 1.98)	26	1.19	(0.77, 1.84)	80	1.02	(0.80, 1.30)
Linear P-trend†		0.3			0.7			0.8			0.7	
Quadratic P-trend†		0.7			0.1			0.3			0.4	

	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI
	NHS N=74,500; 791 events			**NHS II N=81,106; 347 events**			**HPFS N=45,156; 409 events**			**Pooled Analysis‡ N=200,762; 1547 events**		
Liquor												
0 g/day†	576	1.00	reference	208	1.00	reference	171	1.00	reference	955	1.00	reference
0.1–4.9 g/day	118	1.06	(0.85, 1.30)	115	1.42	(1.12, 1.80)	96	0.99	(0.76, 1.29)	329	1.14	(0.93, 1.42)
≥5.0 g/day	97	1.10	(0.87, 1.37)	24	1.28	(0.83, 1.98)	142	1.09	(0.86, 1.39)	263	1.12	(0.95, 1.30)
Linear P-trend†		0.9			0.2			0.6			0.5	
Quadratic P-trend†		0.5			0.3			0.8			0.9	

*Analyses are stratified by age (in months) and adjusted for smoking (never, former, 1–14 cigarettes/day, 15–24 cigarettes/day, ≥25 cigarettes/day, missing), BMI (continuous and indicator for missing), prevalent diabetes, prevalent hypertension, prevalent hypercholesterolemia, prevalent MI/angina, prevalent cancer, race (white vs. non-white), aspirin use (including missing indicator), physical activity (continuous and indicator for missing), caloric intake (continuous), HT use (including missing indicator; in women only), and OC use (including missing indicator; in NHS II only), and consumption amount of all types of alcohol other than the type of interest (continuous g/day).

†Person-time for current former drinkers of any alcohol skipped in all analyses presented in Table 4.

‡NHS, NHS II, and HPFS cohorts were meta-analyzed to estimate a pooled summary HR. All p-values for between study heterogeneity >0.05.

Abbreviations: adj = adjusted; CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study; PE = pulmonary embolism.

Table 5.

Largest number of alcoholic beverages consumed in one day in a typical month and the risk of incident pulmonary embolism.

	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI	N Cases	HR_{adj}*	95% CI
	NHS N=65,596; 672 events			NHS II N=89,719; 339 events			HPFS N=34,649; 309 events			Pooled Analysis‡ N=189,964; 1320 events		
0 drinks†	250	1.00	reference	80	1.00	reference	59	1.00	reference	389	1.00	reference
1–2 drinks	325	1.09	(0.91, 1.29)	170	1.30	(0.98, 1.70)	153	1.11	(0.81, 1.51)	648	1.14	(1.00, 1.30)
3–5 drinks	85	0.97	(0.75, 1.26)	79	1.29	(0.92, 1.80)	80	1.37	(0.96, 1.95)	244	1.16	(0.93, 1.45)
≥6 drinks	12	1.15	(0.64, 2.07)	10	0.64	(0.32, 1.25)	17	1.03	(0.58, 1.82)	39	0.94	(0.66, 1.33)
Linear p-trend†		0.8			0.5			0.9			0.9	

*Analyses are stratified by age (in months) and adjusted for smoking (never, former, 1–14 cigarettes/day, 15–24 cigarettes/day, ≥25 cigarettes/day, missing), BMI (continuous and indicator for missing), prevalent diabetes, prevalent hypertension, prevalent hypercholesterolemia, prevalent MI/angina, prevalent cancer, race (white vs. non-white), aspirin use (including missing indicator), physical activity (continuous and indicator for missing), caloric intake (continuous), HT use (including missing indicator; in women only), and OC use (including missing indicator; in NHS II only).

†Person-time for current former drinkers skipped for all analyses presented in Table 5.

‡NHS, NHS II, and HPFS cohorts were meta-analyzed to estimate a pooled summary HR. All p-values for between study heterogeneity >0.05.

Abbreviations: adj = adjusted; CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study; PE = pulmonary embolism.