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Prospective study of ABO blood type and the risk of pulmonary embolism in two large cohort studies

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Summary

Prior studies have suggested an association of ABO blood type and the risk of venous thromboembolism; however, most studies were retrospective and lacked important covariates or validated endpoints. Moreover, risk estimates varied widely across studies. Therefore, we prospectively examined the association of blood type and the risk of incident pulmonary embolism (PE) in two large cohort studies, the Nurses' Health Study and Health Professionals Follow-up Study. During 1,010,378 person-years of follow-up among 77,025 women and 30,105 men, 499 participants developed PE. Compared to those with O-blood type, participants with non-O blood type had multivariable-adjusted hazard ratios (HR) of 1.86 (95% CI, 1.35–2.57) for idiopathic PE, 1.29 (95% CI, 1.03–1.62) for non-idiopathic PE, and 1.46 (95% CI, 1.22–1.76) for any PE. Hazard ratios were similar for participants with blood types A, B, and AB. Age-adjusted absolute rates of idiopathic PE over 10 years of follow-up differed by blood type: 0.11% for O, 0.20% for A, 0.19% for AB, and 0.21% for B. For idiopathic PE, the population attributable fraction was 33% for inheritance of non-O blood type. Among past and current smokers, participants with non-O vs. O-blood type had a HR for idiopathic PE of 2.56 (95% CI, 1.61–4.08). Among never smokers, the HR for idiopathic PE was 1.30 (95% CI, 0.82–2.05; $P_{\text{interaction}}=0.04$). In two large, prospective cohorts, ABO blood type was significantly associated with the risk of idiopathic and non-idiopathic PE, with even greater risk for idiopathic PE among current and past smokers with non-O blood type.

Keywords

Pulmonary embolism; inherited coagulation disorders; epidemiological studies

Introduction

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in the United States and encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE) (1). Acknowledging the importance of this condition, the U.S. Surgeon General issued a “Call to Action to Prevent Deep Venous Thrombosis and Pulmonary Embolism” in September of 2008 (2). Although several genetic predispositions to VTE are known, the majority of these inherited alterations occur at low frequencies in the general population, such that their clinical utility remains poorly defined (3). Therefore, characterisation of predisposing factors for VTE constitutes an important area of investigation, with the goal of improved risk stratification and appropriate implementation of prophylactic treatment strategies (4).

In addition to the rare, more highly penetrant genetic predispositions, such as factor V Leiden (5) and polymorphism of the prothrombin gene (6), prior studies have suggested an increased risk for VTE among individuals with non-O blood types, i.e. blood types A, AB, and B (7). However, few of these studies were prospectively designed with rigorous collection of important covariates or validated endpoints for idiopathic and secondary VTE. In addition, risk estimates have varied considerably across studies and possible interactions between ABO blood type and other predisposing exposures remains poorly defined. Therefore, we examined prospectively the relationship between blood type and the risk of pulmonary embolism (PE) in two large, well-defined cohort studies, with endpoints validated by medical record review and rigorously collected covariate data obtained prior to PE diagnosis.

Methods

Study population

All subjects were participants in the Nurses’ Health Study (NHS) or Health Professionals Follow-up Study (HPFS). These longitudinal studies have been described in detail previously (8, 9). The NHS began in 1976, when 121,700 female nurses between 30 and 55 years of age completed a baseline questionnaire about risk factors for cancer and cardiovascular disease. Subsequently, participants have completed a self-administered, mailed questionnaire biennially to update information on their lifestyle, diet, and medical history, including incident PE. The HPFS began in 1986 when 51,529 U.S. male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists, aged 40–75 years, completed a baseline questionnaire on diet, lifestyle, and medical conditions. This information was then updated with biennial questionnaires, including ascertainment of subsequent incident PE. The Human Research Committee at the Brigham and Women’s Hospital (Boston, MA, USA) approved the study.

Primary exposure data

In 1996, questionnaires for NHS and HPFS included ABO blood type, prompting participants to specify blood types O, A, AB, B or unknown. We recently demonstrated >90% concordance between self-reported blood type from these questionnaires and blood type determined serologically (9) or genotypically (10). For this analysis of ABO blood type and the risk of incident PE, we included all cohort participants without a prior history of PE, who provided their ABO blood type on the 1996 questionnaires.

Covariate data

Data for the other covariates in this analysis were obtained from the 1996 questionnaire, or if data from the 1996 questionnaire were not available, from the most recent previous questionnaire. We used body mass index (weight in kilograms/[height in meters]²) as a measure of total adiposity. A previously described and validated measure of physical activity was utilised (11, 12), in which participants were asked to average the time spent per week in eight different activities over the previous year and a weekly physical-activity level was derived by multiplying the time spent in each activity per week by its typical energy-expenditure requirements expressed in metabolic equivalents. Data were also ascertained regarding participants' race/ethnicity, smoking status (current, past, never), pack-years of smoking, menopausal status (NHS only), use of warfarin, non-steroidal anti-inflammatory drugs (NSAID), aspirin, or post-menopausal hormones (NHS only), and history of medical conditions, including rheumatologic disease (rheumatoid arthritis or systemic lupus erythematosus), hypertension, or coronary vascular disease (angina, myocardial infarction or coronary artery stenosis). Of the 144,082 participants who returned the 1996 questionnaires in the NHS and HPFS, 75% provided their ABO blood type.

PE case identification

As described previously (13), on each questionnaire, participants were asked whether they had been diagnosed with PE in the previous two years. For participants without a history of malignancy, medical records were obtained and reviewed by study physicians to confirm cases of PE. Incident cases for which the medical record included imaging diagnostic of PE were considered and confirmed. Imaging was considered diagnostic if a ventilation/perfusion lung scan was read by a radiologist as high probability for PE, or if there was a filling defect on contrast enhanced computed tomography of the pulmonary vasculature or on catheter-based pulmonary angiography. Diagnoses of DVT were not ascertained in NHS or HPFS, so all analyses include only incident cases of PE.

Confirmed cases were sub-coded as idiopathic or non-idiopathic PE. A diagnosis of non-idiopathic PE was made based on the presence of either: (i) history of active malignancy, or (ii) surgery or major trauma within one month of PE diagnosis. Idiopathic PE was defined by the absence of one or more of these provoking events.

Statistical analysis

The primary exposure was a participant's ABO blood type. We determined baseline study characteristics for participants within each ABO blood type. We used Cox proportional hazards models to calculate adjusted hazards ratios (HR) and 95% confidence intervals (CI) for idiopathic PE, non-idiopathic PE, and any PE. Follow-up was from the 1996 questionnaire to PE diagnosis, death, or end of the follow-up period (NHS, June 2006; HPFS, January 2006), whichever came first. The proportionality of hazards assumption was satisfied by p -values >0.05 by the Wald test for time-dependent variables, which were the cross-products of blood type and time. Among participants with O and non-O blood types, incident PE was compared using the log-rank test and cumulative incidence curves, which plot one minus the Kaplan–Meier survival rate (14). Population attributable fraction for PE due to non-O blood group was calculated: $PAF = Pd ([HR - 1] / HR)$, where Pd = prevalence of exposure among cases and HR = multivariable-adjusted HR by Cox proportional hazards models (15).

We evaluated effect modification by investigating Cox proportional hazards models after stratifying by other known risk factors for PE, including age (above or below the combined cohort median), sex (male, female), body mass index (BMI) (above or below the combined cohort median), physical activity (above or below the combined cohort median), smoking

status (never, past/current), pack-years of smoking (none, 1–20 pack-years, ≥ 21 pack-years), postmenopausal hormone use among women (never, past/current), history of hypertension (no, yes), history of regular aspirin use (< 1 time per week, ≥ 1 time per week), and history of regular NSAID use (no, yes). Tests of interaction between ABO blood group and potential effect modifiers were assessed by entering into the model the cross-product of ABO blood group and the dichotomised covariate. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA) and all p-values were derived from two-sided tests.

Results

From the 1996 questionnaires, 107,130 participants in the NHS and HPFS reported their blood type and had no prior history of PE. The clinical characteristics of these participants were highly similar to those who did not provide their blood type on the 1996 questionnaires. Mean follow-up time for the current analysis was 9.4 years. Baseline characteristics of the study subjects were highly similar by blood type (►Table 1). Between 1996 and 2006, 179 participants (139 women and 40 men) developed idiopathic PE and 320 participants (220 women and 100 men) developed non-idiopathic PE. During a combined 1,010,378 person-years of follow-up, blood type was significantly associated with the risk of developing PE, in age and multivariable-adjusted models (►Table 2). Compared to those with blood type O, participants with non-O blood type had HRs of 1.86 (95% CI, 1.35–2.57) for idiopathic PE, 1.29 (95% CI, 1.03–1.62) for non-idiopathic PE, and 1.46 (95% CI, 1.22–1.76) for any PE. The hazard ratios comparing blood types A, AB, and B with blood type O were similar (Table 2). For example, the hazard ratios for idiopathic PE were 1.86 (95% CI, 1.31–2.64) for blood type A, 1.78 (95% CI, 1.03–3.09) for AB, and 1.90 (95% CI, 1.22–2.99) for B, when compared to participants with blood type O. Highly similar results were noted in analyses excluding non-White participants (data not shown).

Comparisons of O vs. non-O blood type using the log-rank test demonstrated p-values of 0.0002 for idiopathic PE, 0.03 for non-idiopathic, and < 0.0001 for any PE (►Fig. 1). For idiopathic PE, the population attributable fraction was 33% for inheritance of non-O blood type. Age-adjusted absolute rates of idiopathic PE over 10 years of follow-up differed by blood type: 0.11% for O, 0.20% for A, 0.19% for AB, and 0.21% for B.

The association between blood type and risk of idiopathic PE did not statistically significantly differ according to strata of age, sex, BMI, physical activity, post-menopausal hormone use, hypertension, aspirin use, or NSAID use (►Table 3). However, we did observe differences by smoking status (►Fig. 2). Compared to O-blood type, non-O-blood type conferred a HR for idiopathic PE of 1.30 (95% CI, 0.82–2.05) among never smokers and 2.56 (95% CI, 1.61–4.08) among past or current smokers ($P_{\text{interaction}}=0.04$).

Discussion

In two large prospective cohorts, we observed a nearly two times increased risk of idiopathic PE among participants with non-O blood type, when compared to those with blood type O. For inheritance of non-O blood type, the population attributable fraction was 33% for idiopathic PE. In addition, non-O blood type conferred a statistically significantly increased risk of non-idiopathic PE and any PE in our study population. The risk of PE with non-O blood type was more pronounced among current or past smokers in comparison to never smokers, suggesting a possibly important interaction between an inherited predisposition and environmental exposure.

A number of case-control studies over the past several decades have demonstrated an association of ABO blood type with the risk of VTE, primarily suggesting an increased

frequency of blood types A or B and a decreased frequency of blood type O among cases compared with selected groups of controls (16–19). A meta-analysis of studies including idiopathic and non-idiopathic VTE demonstrated a pooled odds ratio (OR) of 1.79 (95% CI, 1.56–2.05) for VTE among participants with non-O versus O blood type (7). However, significant heterogeneity was observed among studies and the findings of the individual studies were inconsistent, with ORs of 1.1 (non-significant) to 3.9.

In the current prospective study, with a uniform base population and rigorous ascertainment of case status and important co-variables, we noted HRs of 1.86 for idiopathic PE and 1.29 for non-idiopathic PE. These findings suggest blood type is associated with additional risk in patients already at high risk for PE due to recent surgery, trauma or cancer; however, blood type may play a larger role in the development of idiopathic PE. A study of ABO blood type and VTE risk in the Longitudinal Investigation of Thromboembolism Etiology (LITE) cohort (20) similarly noted a greater point estimate of risk for idiopathic VTE (OR, 1.83; 95% CI, 1.33–2.52) than secondary VTE (OR, 1.46; 95% CI, 1.11–1.92). Nevertheless, cross study comparisons should be made cautiously given the use by prospective cohort studies of differing definitions of “non-idiopathic” PE (21–23), which depend on availability of data for provoking events, such as active malignancy or recent surgery, trauma, air travel, or immobilisation.

Although some studies have suggested an increased risk for VTE predominantly with blood type A (7), we noted similar hazard ratios for blood types A, AB, and B, when compared to blood type O. This finding would appear to support a protective role for blood type O, as opposed to a specific detrimental effect of either blood type A or B. The protective role for blood type O may in part be explained by the differential survival of circulating von Willebrand factor (vWF) and clotting factor VIII in subjects with blood type O compared to those with non-O blood type (24–26). Specifically, subjects with blood type O have approximately 25% lower levels of circulating vWF than those with blood types A or B (27), and correspondingly lower levels of circulating factor VIII, as vWF acts as a carrier molecule for factor VIII in blood. More recently, these lower levels of vWF and factor VIII have been related to a shorter half-life of vWF in the circulation, due to increased clearance (24, 25). Given the previously demonstrated associations of vWF and factor VIII with risk of VTE (28), alterations in circulating vWF and factor VIII levels due to differences in ABO glycosylation may be partly responsible for the association of blood type with risk of VTE (29).

Another mechanism is suggested by the results of several recently performed genome-wide association studies (GWAS), which attempt to characterise common genetic determinants of complex traits (30). In five recent studies, single nucleotide polymorphisms (SNPs) at the *ABO* gene locus were found to be genetic determinants of circulating levels of soluble E-selectin, soluble P-selectin, soluble intercellular adhesion molecule-1 (ICAM-1), and tumour necrosis factor-alpha (TNF- α) (31–35). In each of these studies, the most statistically significant SNPs were proxies for defining the O vs. non-O allele.

E-selectin and P-selectin are transmembrane glycoproteins expressed on the surface of endothelial cells, which bind glycosylated ligands important for leukocyte and platelet adhesion to sites of vascular inflammation (36). P-selectin is also expressed on the surface of activated platelets, where it helps mediate attachment to the vessel wall, other platelets and leukocytes (37). Also important for leukocyte adhesion and migration, ICAM-1 is a member of the immunoglobulin gene superfamily that is expressed on the surface of endothelial cells and binds leukocyte integrins. Interestingly, expression of endothelial E-selectin and ICAM-1 are upregulated in response to inflammatory mediators, including TNF- α (38). The extracellular domains of E-selectin, P-selectin and ICAM-1 are shed into the circulation

(39), where their levels have been linked to incident cardiovascular disease and diabetes mellitus (40, 41). Therefore, another possible mechanism linking ABO blood group antigens with the risk of VTE may involve the alteration of vascular inflammation and integrity, as mediated by levels of glycoproteins such as selectins and vascular adhesion molecules.

In the current study, we noted a greater increase in risk for VTE due to non-O blood type among smokers, with a hazard ratio of 2.6. Given its prospective design, our study avoids some of the difficulties associated with retrospective case-control studies, such as recall, selection, and survival biases, providing an ideal opportunity to evaluate effect modifiers of the relationship between ABO blood group and VTE risk. If this finding is validated in other studies, it points to a notable interaction between an inherited predisposition and an environmental exposure. Also of interest is the association of smoking with circulating inflammatory markers, such as ICAM-1, suggesting a possible overlapping pathophysiology of smoking with ABO blood group antigens on risk of VTE (42).

Several genetic predispositions to VTE are known, including factor V Leiden (FVL) and a prothrombin gene polymorphism, with larger relative risks for VTE (5, 6). However, these abnormalities occur at much lower frequencies in the general population than the presence of non-O blood type and therefore are less influential at the population level (7). This is of particular interest, since a recent GWAS of idiopathic VTE identified only polymorphisms at the factor V and ABO loci as associated with VTE at the level of genome-wide significance (43). Although the sample size of this study was modest for a GWAS design, the study does indicate that other genetic factors are unlikely to be identified with as statistically strong an association with VTE risk as the ABO locus. Further work to incorporate blood type into clinical management algorithms for VTE may be warranted, with genotypically-defined blood group alleles likely to add further information beyond that provided by serology alone (44–46).

A limitation of our study is the predominance of White participants, somewhat limiting the generalisability of our results. Although the distribution of blood type does vary between the world's populations, data have not suggested that the underlying mechanism relating blood type to thrombosis is different by race/ethnicity. In addition, the distribution of blood type among our study participants was similar to that of the U.S. White population (9).

We cannot rule out the presence of residual confounding. Nevertheless, age-adjusted hazard ratios for PE by blood type did not change substantially when other predisposing factors were included in multivariable models, and the risk of detecting a false association due to population stratification was low, given the prospective cohort design, primarily non-Hispanic European-American ancestry of the study population, and paucity of evidence for variation in PE risk in the ancestral population (47). The use of self-reported ABO blood type likely introduced a modest degree of exposure misclassification. Nevertheless, two separate validation studies have demonstrated > 90% concordance between self-report and blood type determined serologically (9) or genotypically (10) in NHS and HPFS, indicating that misclassification is unlikely to have meaningfully altered our results. Furthermore, self-reported ABO blood type in NHS and HPFS similarly predicted risk of pancreatic cancer in comparison with genotypically defined ABO blood type in a consortium of 12 prospective cohort studies (9, 10). Moreover, any modest misclassification generated by the use of self-report was non-differential with respect to case status and highly unlikely to introduce bias, as blood type was reported by participants prior to pancreatic cancer diagnosis.

The prospective design of this study avoided recall or selection bias; further strengths included prospective covariate information ascertained at the time of initiation of follow-up;

physician record review to establish PE diagnoses; high follow-up rates in both cohorts; and a large number of subjects with information on blood type.

In sum, prospective data from two large cohort studies with rigorous case definition and ascertainment of important covariates demonstrated a statistically significant association between ABO blood type and the risk of PE. Further investigation is needed to confirm a greater risk for non-O blood type among smokers compared with non-smokers.

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What is known about this topic?

- Retrospective case-control studies have suggested an increased incidence of venous thromboembolism (VTE) in subjects with blood type A or B and reduced incidence in subjects with blood type O.
- Risk estimates across studies are quite heterogeneous and potential effect modifiers have not been defined for the relationship between ABO and the risk of VTE.

What does this paper add?

- Our prospective study in two large cohorts demonstrates a nearly two-fold increase in the risk for idiopathic pulmonary embolism (PE) in subjects with blood types A, B, and AB, when compared to those with blood type O.
- A statistically significant increased risk is noted among non-O subjects for idiopathic, non-idiopathic, and any PE.
- For idiopathic PE, the population attributable fraction was 33% due to inheritance of non-O blood type.
- The risk of idiopathic PE with non-O blood type was more pronounced among current or past smokers in comparison to never smokers, suggesting a possibly important interaction between an inherited predisposition and environmental exposure.

Figure 1. Cumulative pure incidence curves for pulmonary embolism by ABO blood type
A) Idiopathic pulmonary embolism. B) Any pulmonary embolism.

Figure 2. Cumulative pure incidence curves for pulmonary embolism by ABO blood type and smoking status
A) Idiopathic pulmonary embolism. B) Any pulmonary embolism.

Table 1

Baseline characteristics of study subjects according to ABO blood type.

Characteristic	ABO blood type			
	O	A	AB	B
No. (%) of subjects	46,080 (43.0)	38,519 (36.0)	8,440 (7.9)	14,091 (13.2)
Age (mean $\pm$ SD, years)	62.5 (+/-7.7)	62.3 (+/-7.7)	63.7 (+/-7.8)	62.2 (+/-7.6)
Female gender (%)	71.9	71.1	72.6	73.7
White race/ethnicity (%)	97.0	97.9	96.3	96.1
Body-mass index (mean $\pm$ SD, kg/m ²)	26.5 (+/-4.9)	26.5 (+/-4.9)	26.3 (+/-4.8)	26.5 (+/-4.8)
Physical activity level (mean $\pm$ SD, MET-hr/wk)	22.7 (+/-29.3)	22.8 (+/-29.8)	22.8 (+/-28.9)	22.3 (+/-28.7)
Smoking status (%)				
Never	45.0	46.2	44.6	45.0
Past	44.4	43.6	44.0	44.2
Current	10.6	10.2	11.4	10.8
Menopausal status* (%)				
Pre-menopausal	6.3	6.6	4.9	6.8
Post-menopausal, never used HRT	31.1	30.3	33.0	31.1
Post-menopausal, past use of HRT	43.1	43.7	40.6	42.5
Post-menopausal, current use of HRT	19.5	19.4	21.5	19.6
Warfarin use (%)	1.8	2.3	2.7	2.0
NSAID use (%)	31.0	30.8	30.3	31.2
Aspirin use (%)	41.0	42.1	43.1	42.9
Hypertension (%)	36.5	34.7	38.0	35.7
Coronary vascular disease [†] (%)	10.0	9.6	11.3	10.1
Rheumatologic disease [‡] (%)	6.0	5.8	7.1	6.1

NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; SD, standard deviation; MET-hr/wk, metabolic equivalent task hours per week; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

* Data from NHS participants only.

[†] Coronary vascular disease includes any history of angina, myocardial infarction, or coronary artery stenosis.

[‡] Rheumatologic disease includes any history of systemic lupus erythematosus or rheumatoid arthritis in NHS and any history of rheumatoid arthritis in HPFS (history of systemic lupus erythematosus was not assessed in HPFS).

Table 2

Age-adjusted and multivariable-adjusted hazard ratios and 95% confidence intervals for incident pulmonary embolism by ABO blood type.

	ABO blood type				
	O (Referent)	A	AB	B	A, AB, and B (non-O)
No. of person-years	435,158	363,330	78,872	133,018	575,220
Idiopathic PE					
No. of cases	52	80	17	30	127
Age-adjusted HR (95%CI)	1.00	1.85 (1.31–2.63)	1.75 (1.01–3.02)	1.90 (1.21–2.98)	1.85 (1.34–2.55)
Multivariable-adjusted HR (95%CI) *	1.00	1.86 (1.31–2.64)	1.78 (1.03–3.09)	1.90 (1.22–2.99)	1.86 (1.35–2.57)
Non-idiopathic PE					
No. of cases	119	121	28	52	201
Age-adjusted HR (95%CI)	1.00	1.23 (0.96–1.59)	1.21 (0.80–1.83)	1.45 (1.05–2.01)	1.28 (1.02–1.61)
Multivariable-adjusted HR (95%CI) *	1.00	1.24 (0.96–1.60)	1.22 (0.81–1.84)	1.47 (1.06–2.04)	1.29 (1.03–1.62)
Any PE					
No. of cases	171	201	45	82	328
Age-adjusted HR (95%CI)	1.00	1.42 (1.16–1.74)	1.38 (0.99–1.91)	1.59 (1.22–2.07)	1.45 (1.21–1.75)
Multivariable-adjusted HR (95%CI) *	1.00	1.43 (1.17–1.75)	1.39 (1.00–1.93)	1.60 (1.23–2.08)	1.46 (1.22–1.76)

PE, pulmonary embolus; HR, hazard ratio; CI, confidence interval.

* Adjusted for age, body-mass index, level of physical activity, smoking status, pack-years of smoking, cohort (which also adjusts for gender), race/ethnicity, rheumatologic disease, hypertension, coronary vascular disease, menopausal status, warfarin use, non-steroidal anti-inflammatory use, and aspirin use.

Table 3
Stratified analyses of incident idiopathic pulmonary embolism and ABO blood type.

Characteristic	No. of cases	ABO blood type Hazard ratio [†] (95% CI)		P-value, interaction
		O	Non-O	
Age [*]				
< 62 years	73	1.00	2.50 (1.45–4.31)	0.16
≥ 62 years	106	1.00	1.55 (1.03–2.32)	
Gender				
Male	40	1.00	1.41 (0.74–2.70)	0.36
Female	139	1.00	2.02 (1.40–2.94)	
Race/ethnicity				
White	176	1.00	1.86 (1.35–2.58)	-
Other [‡]	3	-	-	
Body-mass index [*]				
< 25.7 kg/m ²	59	1.00	1.71 (0.98–2.97)	0.69
≥ 25.7 kg/m ²	120	1.00	1.94 (1.31–2.89)	
Physical activity [*]				
< 13.5 MET-hrs/wk	102	1.00	1.68 (1.11–2.56)	0.45
≥ 13.5 MET-hrs/wk	77	1.00	2.16 (1.30–3.59)	
Smoking status				
Never	79	1.00	1.30 (0.82–2.05)	0.04
Past / current	100	1.00	2.56 (1.61–4.08)	
Pack-years of smoking				
None	79	1.00	1.30 (0.82–2.05)	0.07
1–20	49	1.00	2.63 (1.34–5.14)	
≥ 21	51	1.00	2.54 (1.33–4.84)	
Post-menopausal hormone use [§]				
Current	76	1.00	1.68 (1.04–2.73)	0.20

Characteristic	No. of cases	ABO blood type Hazard ratio [‡] (95% CI)		P-value, interaction
		O	Non-O	
Never and past	56	1.00	2.25 (1.23–4.12)	
Hypertension				
No	93	1.00	1.82 (1.16–2.85)	0.87
Yes	86	1.00	1.91 (1.20–3.04)	
Regular aspirin use				
< 1 time per week	99	1.00	2.08 (1.33–3.23)	0.46
≥ 1 time per week	80	1.00	1.63 (1.01–2.61)	
Regular NSAID use				
No	108	1.00	2.19 (1.42–3.36)	0.25
Yes	71	1.00	1.49 (0.91–2.44)	

CI, confidence interval; MET-hr/wk, metabolic equivalent task hours per week; NSAID, non-steroidal anti-inflammatory drug.

* Dichotomised at the median of age, body-mass index and physical activity.

[‡] Adjusted for age, body-mass index, level of physical activity, smoking status, pack years of smoking, prospective cohort (which also adjusts for gender), race/ethnicity, rheumatologic disease, hypertension, coronary vascular disease, menopausal status, warfarin use, non-steroidal anti-inflammatory use, and aspirin use, excluding the stratification variable.

[‡] Too few non-White participants were available for a separate analysis in this subgroup.

[§] Data from Nurses' Health Study participants only.