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ABO Blood Group and Risk of Coronary Heart Disease in Two Prospective Cohort Studies

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Objective—Epidemiological data regarding the association between ABO blood groups and risk of coronary heart disease (CHD) have been inconsistent. We sought to investigate the associations between ABO blood group and CHD risk in prospective cohort studies.

Methods and Results—Two large, prospective cohort studies (the Nurses' Health Study [NHS] including 62 073 women and the Health Professionals Follow-up Study [HPFS] including 27 428 men) were conducted with more than 20 years of follow-up (26 years in NHS and 24 years in HPFS). A meta-analysis was performed to summarize the associations from the present study and previous studies. In NHS, during 1 567 144 person-years of follow-up, 2055 participants developed CHD; in HPFS, 2015 participants developed CHD during 517 312 person-years of follow-up. ABO blood group was significantly associated with the risk of developing CHD in both women and men (log-rank test; $P=0.0048$ and 0.0002, respectively). In the combined analysis adjusted for cardiovascular risk factors, compared with participants with blood group O, those with blood groups A, B, or AB were more likely to develop CHD (adjusted hazard ratios [95% CI] for incident CHD were 1.06 [0.99–1.15], 1.15 [1.04–1.26], and 1.23 [1.11–1.36], respectively). Overall, 6.27% of the CHD cases were attributable to inheriting a non-O blood group. Meta-analysis indicated that non-O blood group had higher risk of CHD (relative risk =1.11; 95% CI, 1.05–1.18; $P=0.001$) compared with O blood group.

Conclusion—These data suggest that ABO blood group is significantly associated with CHD risk. Compared with other blood groups, those with the blood type O have moderately lower risk of developing CHD. (*Arterioscler Thromb Vasc Biol.* 2012;32:2314-2320.)

Key Words: ABO ■ coronary heart disease ■ cohort study ■ meta-analysis

Human blood group antigens are glycoproteins and glycolipids expressed on the surface of red blood cells and a variety of human tissues, including epithelium, sensory neurons, platelets, and vascular endothelium.[1] It has long been acknowledged that human ABO blood type might affect the risk factors of cardiovascular disease. In non-O individuals, plasma levels of factor VIII–von Willebrand factor (vWF) complex are ≈25% higher than group O individuals.[2] Accumulating evidence indicates that elevated factor VIII–vWF levels are a risk factor for coronary heart disease (CHD).[3,4] Other studies also indicate that ABO blood group might influence plasma lipid levels.[5,6] Recently, several genome-wide association studies found that variants at ABO locus were associated with plasma lipid levels[7,8] and inflammatory markers, including soluble intercellular adhesion molecule 1,[9,10] plasma soluble E-selectin levels[11,12] and P-selectin levels,[10] and tumor necrosis factor-α,[13] which were markers of inflammation associated with the CHD risk.

A number of epidemiological studies have examined the relation between ABO blood type and risk of cardiovascular diseases. In 2008, a meta-analysis investigated the associations between several types of vascular disease and ABO blood groups.[14] A consistent relation between non-O blood group and an increased CHD risk was observed in cross-sectional case–control studies[15–17]; however, data from prospective cohort studies were inconsistent,[18–22] probably because of the small sample size of these cohort studies.

In this study, we conducted prospective analyses on human blood groups and CHD risk in 2 large cohorts: the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). In addition, we also combined our data with previously published prospective studies in a meta-analysis.

Patients and Methods

Study Population

The NHS cohort began in 1976 when 121 700 female nurses aged 30 to 55 years living in 11 U.S. states responded to a questionnaire

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regarding medical, lifestyle, and other health-related information. Questionnaires have been sent biennially to update this information. Diet intakes were assessed by food frequency questionnaire in 1980, 1984, 1986, 1990, 1994, 1998, and 2002. At baseline, we excluded those with a history of CHD, cancer, stroke, coronary artery bypass graft, or angina. After these exclusions, 62 073 women reporting their ABO blood group had follow-up from 1980 through 2006 and were included in the analyses.

The HPFS enrolled 51 529 men aged 40 to 75 years at baseline in 1986. The cohort participants are sent a biennial questionnaire regarding medical conditions and lifestyle characteristics, such as smoking status, medication use, and physical activity. Every 4 years, the participants are sent a food frequency questionnaire to assess their diet intakes. We excluded those who reported a history of myocardial infarction (MI), angina, coronary artery bypass graft, stroke, or cancer in the baseline questionnaire, resulting in a baseline population of 27 428 with ABO blood group data for the current analysis. This study was approved by the Harvard Institutional Review Board, and all participants provided written informed consent.

Assessment of ABO Blood Group

The assessment of ABO blood group has been described in detail elsewhere.[23] Briefly, in both the NHS and HPFS, participants were asked to report their blood type (A, B, AB, O, or unknown) and their Rh factor (positive, negative, or unknown) in the 1996 questionnaire. We conducted a validation study by performing serologic testing in a subsample of 98 subjects. The consistency of self-reported and serologically confirmed ABO blood type was 93% for NHS and 90% for HPFS, and the consistency of self-reported and serologically confirmed Rh type was 100% for NHS and 96% for HPFS. We also validated the self-report ABO blood type using germline genetic data in 187 participants from NHS and HPFS and found 92% concordance.[24] Of the participants in the NHS and HPFS who returned the 1996 questionnaire, 75% reported ABO blood group; of these, 92.3% also reported Rh factor type. The characteristics of those participants who provided blood type and those who did not were similar (data not shown).

Assessment of Covariates

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Physical activity was expressed as metabolic equivalents per hour, which were calculated with data from a self-report questionnaire that focused on the types and durations of activities over the previous year. Participants were also asked about recent smoking status (current, past, or never), alcohol intake, and aspirin use; history of hypertension, high blood cholesterol, and diabetes mellitus; and parental history of CHD before age 60. To represent the long-term intake of dietary factors and to reduce measurement error, we conducted analyses using updated dietary data by taking the average of all available dietary questionnaires.[25]

Ascertainment of CHD End Point

We identified incident cases of CHD (nonfatal MI or fatal CHD) that occurred after the return of the 1980 questionnaire but before June 1, 2006, in women (NHS) and occurred between the return of the 1986 questionnaire and June 1, 2006, in men (HPFS). We requested permission to review medical records of the participants who reported having an MI on each biennial questionnaire. A physician unaware of the self-reported risk factor status verified the report of MI through review of medical/hospital records by using the World Health Organization criteria of symptoms and either typical ECG changes or elevated cardiac enzymes.[26] Fatal CHD was confirmed by medical records or autopsy reports or by CHD listed as the cause of death on the death certificate, and there was evidence of previous CHD in the records. Deaths were ascertained from state vital statistics records and the National Death Index or reported by the family members and the postal system.

Statistical Analysis

We used Cox proportional hazards models to assess the association between the ABO blood group and risk of CHD. For multivariate analysis, we adjusted for the following potential confounders, which were updated at each 2-year cycle: age (continuous), smoking (never, past, or current with cigarette use of 1–14 per day, 15–24 per day, 25+ per day, missing), BMI (<22.0, 22.0–22.9, 23.0–24.9, 25.0–28.9, and ≥29.0 kg/m^2), alcohol intake (0 g/day, up to 5 g/day, 5–15 g/day, or >15 g/day), parental history of CHD before age 60 (yes/no), physical activity (metabolic equivalents h/wk in quintiles), aspirin use (<1 per week, 1–2 per week, 3–6 per week, 7–14 per week, and 15+ per week), menopausal status and postmenopausal hormone use (premenopausal, never, past, or current hormone use) in women, history of hypertension (yes or no), history of high blood cholesterol (yes or no), and history of diabetes mellitus (yes or no). We also adjusted for race/ethnicity (white or nonwhite) and dietary factors, which were updated at 4-year cycle: multiple vitamin or vitamin E supplement (yes or no), total energy intake, polyunsaturated, saturated, and transfats; long-chain omega-3 fatty acids, dietary fiber, and folate intake (all in quintiles). In secondary analyses, we conducted stratified analyses by age (<65 and ≥65 years), BMI (<25 and ≥25 kg/m^2), smoking (never or past and current smoking), alcohol intake (drinking and nondrinking), physical activity (median as cut point), and diabetes mellitus history (yes or no). Tests of interaction between ABO blood group and potential effect modifiers were assessed by entering the cross product of ABO blood group and the dichotomized covariate into the Cox proportional hazard model. We used the log-rank test to compare the CHD-free survival among ABO blood group and cumulative pure incidence curves with plot 1–Kaplan-Meier survival rate.[27]

Meta-Analysis

The MEDLINE and EMBASE database was searched up to May 2010 for published articles on cohort studies that examined ABO blood group in relation to risk of CHD. Keywords used to identify relevant articles were as follows: cardiovascular disease (as standardized medical subject heading [MeSH] term) and (ABO blood group system). Together with the current study, a total of 7 studies were included in our meta-analysis. Data extraction was independently performed by 2 of the authors (M.A.H. and L.Q.) and there were no differences in the extracted information. We used the STATA version 9.2 statistical program (STATA, College Station, TX) to conduct the meta-analysis. Summary measures were calculated from the logarithm of the relative risks and corresponding standard errors of the individual studies using random effects models that incorporate both a within-study and an additive between-studies component of variance.[28] The heterogeneity of study results was calculated using the Cochran Q test[29] and the I^2 statistic.[29] Visual inspection of the funnel plot, Begg, and Egger tests were used to evaluate possible publication bias.[30,31]

Results

Baseline Characteristics

In both NHS and HPFS, the baseline characteristics of the participants were similar across the four ABO blood groups (Table 1). The distributions of the ABO blood groups were comparable between NHS and HPFS cohorts. The frequency for blood type O, A, B, and AB was 42.9%, 36.0%, 13.3%, and 7.8% in women and 43.0%, 37.2%, 12.3%, and 7.5% in men.

ABO Blood Group and CHD Risk

During up to 26 years of follow-up of 62 073 women (1 567 143 person-years) in the NHS, we confirmed 2055 CHD cases (including 1666 nonfatal MI and 389 fatal CHD); in HPFS, the period of follow-up was 20 years and 2015 CHD cases (including 1420 nonfatal MI and 595 fatal CHD) were

Table 1.   Baseline Characteristics of Study Subjects According to ABO Blood Type in NHS (1980) and HPFS (1986)

Characteristic	NHS				HPFS			
	O	A	B	AB	O	A	B	AB
No. of subjects	26 640	22 358	8263	4812	11 801	10 213	3365	2049
Percentage of subjects, %	42.9	36.0	13.3	7.8	43.0	37.2	12.3	7.5
Age, y	45.9 (7.1)	45.8 (7.1)	45.7 (7.1)	46.9 (6.9)	53.1 (9.0)	53.0 (8.8)	53.1 (8.9)	53.1 (9.4)
White, %	96.9	97.8	96.2	96.3	95.8	96.6	93.3	93.8
BMI, kg/m^2	24.3 (4.5)	24.2 (4.2)	24.3 (4.9)	24.1 (4.6)	25.4 (3.1)	25.4 (3.1)	25.4 (3.1)	25.4 (3.1)
Physical activity, METs*	14.3 (19.1)	13.9 (19.3)	14.5 (17.8)	15.2 (17.6)	21.5 (29.2)	21.4 (28.4)	21.9 (29.9)	22.6 (34.0)
Current smoking, %	26.8	25.7	26.4	26.2	8.9	8.5	9.2	9.9
Alcohol intake, g/d	5.16 (9.08)	5.04 (9.63)	5.11 (8.88)	5.37 (8.07)	11.6 (15.6)	11.5 (14.9)	11.1 (14.7)	11.2 (15.4)
Postmenopausal, %	28.6	28.1	28.0	32.5	—	—	—	—
Current PMH users, %	23.5	22.5	20.7	21.2	—	—	—	—
Total energy intake, kcal/d	1761 (519)	1761 (501)	1746 (496)	1757 (550)	2019 (618)	2015 (616)	1964 (603)	2000 (632)
History of hypertension, %	14.4	13.6	14.0	14.8	18.9	18.2	18.0	20.7
History of high cholesterol, %	4.6	4.8	4.7	5.3	9.9	11.4	11.2	11.7
History of diabetes mellitus, %	1.51	1.51	1.67	1.70	1.69	1.78	1.72	3.03
Family history of CHD, %	15.5	15.6	16.2	16.0	12.0	12.4	11.8	14.7

NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study; BMI, body mass index; METs, metabolic equivalents; PMH, postmenopausal hormones; CHD, coronary heart disease. The continuous variables are presented as mean (SD) and the categories variables presented as percentage.

*In NHS, the physical activity data in 1986 was used.

documented in 27 428 subjects (517 313 person-years). The incident rates of CHD per 100 000 person-years were 125, 128, 142, and 161 for those with blood type O, A, B, and AB in women and 373, 382, 387, and 524 for those with blood type O, A, B, and AB in men. The cumulative incidence of CHD was statistically significantly different among the 4 ABO blood groups in both cohorts (log-rank test; *P*=0.0048 in NHS and 0.0002 in HPFS, respectively; Figure 1). In the combined analysis, compared with participants with blood group O, those with blood groups A, B, or AB were more likely to develop CHD (age–adjusted hazard ratios [95% CI] for CHD, 1.05 [0.98–1.13], 1.11 [1.01–1.23], and 1.23 [1.10–1.37], respectively) (Table 2). The associations were not substantially altered by multivariate adjustment for other potential risk factors and dietary factors (multivariate–adjusted hazard ratios [95% CI] for CHD, 1.08 [1.00–1.16], 1.11 [1.00–1.24], and 1.20 [1.07–1.36], respectively) (Table 2). The associations of the risks of CHD with ABO blood groups were not substantially altered by excluding patients with diabetes mellitus diagnosed at baseline. In addition, restriction of the analysis to whites only (97.1% in NHS and 95.7% in HPFS) did not alter these associations; compared with the O blood group, the A, B, and AB groups had increasing risk of CHD (combined hazard ratios [95% CI] for CHD, 1.08 [1.00–1.16], 1.10 [1.00–1.21], and 1.20 [1.07–1.35]).
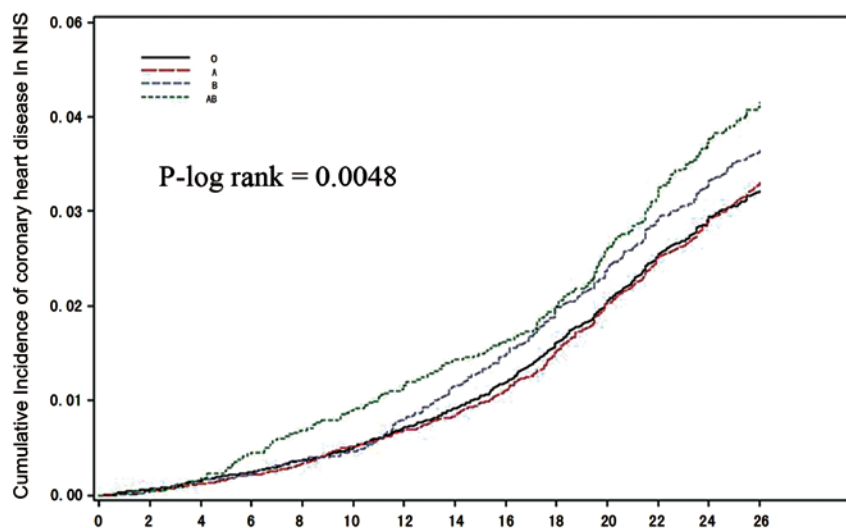
We also examined the risk of CHD by comparing the non-O blood type (A, B and AB) with the O blood type. Compared with participants reporting blood group O, those with non-O blood type had an age–adjusted hazard ratio of 1.09 (95% CI, 1.03–1.17). Adjustment for other potential risk factors for CHD did not materially alter the associations (hazard ratio, 1.10; 95% CI, 1.03–1.18). The population attributable risk of the non-O blood group (A, B, and AB) for CHD was 6.27%. In contrast, we did not find an association between Rh type

and CHD risk in either cohort or in the combined analyses; compared with participants who were Rh-positive, those who were Rh-negative experienced a multivariate-adjusted hazard ratio of 0.98 (95% CI, 0.90–1.06; *P*=0.58) in the combined samples (Table 3).

In the stratified analyses, the association between ABO blood group and risk of CHD was not modified by age, physical activity, alcohol consumption, smoking status, or diabetes mellitus history in men or women. In women, menopausal status did not modify the association between ABO blood group and CHD risk. We found a significant interaction between the BMI and ABO blood type in relation to CHD risk in women (*P* for interaction=0.026). Compared with the O blood group, the non-O blood type (A, B, and AB) had a stronger relationship with CHD risk in overweight and obese women than those with BMI <25 kg/m^2. However, this interaction was not confirmed in men (*P* for interaction =0.75; data not shown).

Meta-Analysis

Characteristics of the 7 prospective cohort studies included in the meta-analysis are shown in Table I in the online-only Data Supplement. The study populations included both men and women, predominantly white populations. Based on data from all prospective studies combined, which included 114 648 participants and 5741 cases of CHD, the pooled relative risk was 1.06 (95% CI, 0.96–1.17; *P*=0.266) for non-O blood group compared with O blood group. There was significant heterogeneity among the studies (I^2, 58%; 95% CI, 4%–82%; *P* value for homogeneity test=0.026). In the meta-regression analysis, the mean age, sex, publication year, follow-up period, and sample size did not modify the associations (*P*>0.05). Cumulative meta-analysis indicated that only the study by Suadicani et al[21] was significantly inversely
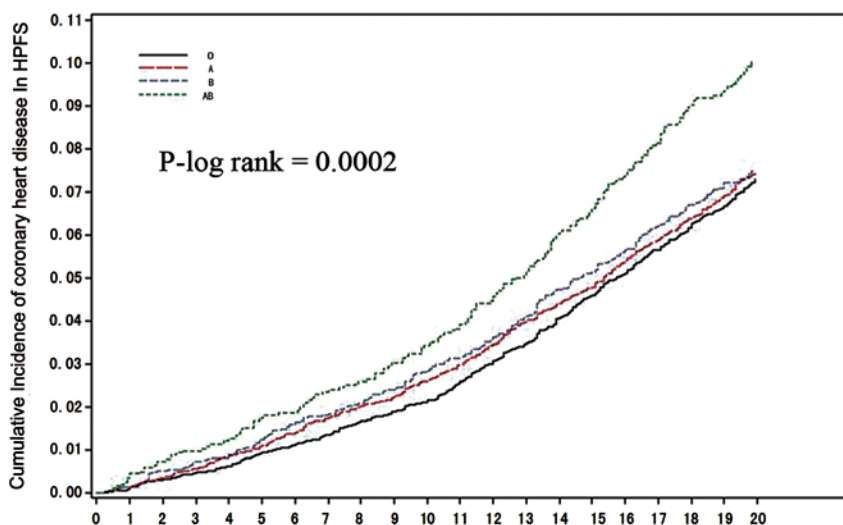
Figure 1. Cumulative incidence curves for coronary heart disease by ABO blood group in Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). Number of participants at risk is shown for selected times.

associated with CHD risk. After excluding this study, the heterogeneity test was not significant (I^2, 0%; 95% CI, 0%–75%; P value for homogeneity test =0.68) and the pooled relative risk was 1.11 (95% CI, 1.05–1.18; P=0.001; Figure 2). We then conducted a sensitivity analysis by omitting 1 study at a time and calculating the pooled estimate for the remaining studies. The pooled relative risks did not change, ranging from 1.09 (95% CI, 1.03–1.17) to 1.12 (95% CI, 1.03–1.21), indicating that the overall results were not excessively influenced by any 1 study of the remaining 6 cohorts. Visual inspection of the funnel plot (Figures I and II in the online-only Data

Supplement) and the Begg (P=0.71) and Egger (P=0.74) tests did not suggest a publication bias.

Discussion

In the 2 large, prospective cohorts of the NHS and HPFS, we observed a significantly elevated risk of incident CHD for participants with blood group A or B or AB, compared with those with blood group O. The highest risk was observed for blood group AB, followed by blood groups B and A. The association between ABO blood group and CHD risk was not significantly modified by other known risk factors for CHD,

Table 2.   Age-Adjusted and Multivariable-Adjusted Hazard Ratios and 95% CIs for Coronary Heart Disease by ABO Blood Type

Cohort	O	A	B	AB
NHS				
No. of cases/No. of person-years	841/673 089	723/564 896	296/208 358	195/120 801
Age-adjusted HR (95% CI)	1.0	1.04 (0.94–1.15)	1.14 (1.00–1.30)	1.20 (1.02–1.40)
Multivariate model 1 HR (95% CI)*	1.0	1.06 (0.96–1.17)	1.15 (1.00–1.31)	1.20 (1.03–1.41)
Multivariate model 2 HR (95% CI)†	1.0	1.08 (0.97–1.21)	1.15 (0.99–1.33)	1.24 (1.05–1.48)
HPFS				
No. of cases/No. of person-years	833/223 128	737/192 687	246/63 531	199/37 966
Age-adjusted HR (95% CI)	1.0	1.07 (0.96–1.18)	1.10 (0.95–1.27)	1.26 (1.07–1.48)
Multivariate model 1 HR (95% CI)*	1.0	1.08 (0.97–1.19)	1.08 (0.93–1.25)	1.18 (1.00–1.39)
Multivariate model 2 HR (95% CI)†	1.0	1.08 (0.97–1.19)	1.08 (0.93–1.25)	1.17 (1.00–1.38)
Combined				
Age-adjusted HR (95% CI)	1.0	1.05 (0.98–1.13)	1.11 (1.01–1.23)	1.23 (1.10–1.37)
Multivariate model 1 HR (95% CI)	1.0	1.07 (0.99–1.15)	1.11 (1.01–1.23)	1.19 (1.06–1.33)
Multivariate model 2 HR (95% CI)	1.0	1.08 (1.00–1.16)	1.11 (1.00–1.24)	1.20 (1.07–1.36)

NHS indicates Nurses' Health Study; HR, hazard ratios; HPFS, Health Professionals Follow-up Study; HR, hazard ratios; BMI, body mass index; MET, metabolic equivalent.

*Adjusted for age (continuous), smoking (never, past, or current with cigarette use of 1–14 per day, 15–24 per day, 25+ per day, missing), BMI (<23.0, 23.0–25.0, 25.0–29.0, and ≥29.0), alcohol intake (0 g per day, up to 5 g per day, 5–15 g per day, and >15 g per day), parental history of myocardial infarction before age 60 (yes/no), physical activity (MET h/wk in quintiles), aspirin use (<1 per week, 1–2 per week, 3–6 per week, 7–14 per week, and 15+ per week), history of hypertension and high blood cholesterol and type 2 diabetes mellitus (yes or no), race/ethnicity (white or nonwhite), and menopausal status and postmenopausal hormone use (premenopausal, never, past, or current hormone use) in women.

†Adjusted for covariates in model 1 plus dietary factors including multiple vitamin or vitamin E supplement (yes or no), total energy intake, polyunsaturated, saturated, and transfats; long-chain omega-3 fatty acids, dietary fiber, and folate intake (all in quintiles).

including age, sex, alcohol consumption, smoking, physical activity, or diabetes mellitus history. In total, 6.27% of CHD cases were attributable to a non-O blood group (A, B, or AB blood types). A meta-analysis of 6 prospective studies indicated that non-O blood group was associated with an 11% increased risk of CHD compared with O blood group.

Table 3.   Age-Adjusted and Multivariable-Adjusted Hazard Ratios and 95% CIs for Coronary Heart Disease by ABO Blood Type and Rh Factor Type

	Rh Factor			ABO Blood Group		
Cohort	Positive	Negative	P Value	O	Non-O	P Value
NHS						
No. of cases/No. of person-years	1453/1 163 643	465/3 31 107		841/673 089	1214/894 055	
Age-adjusted HR (95% CI)	1.0	1.05 (0.94–1.16)	0.40	1.0	1.08 (0.99–1.18)	0.07
Multivariate model 1 HR (95% CI)*	1.0	1.03 (0.93–1.14)	0.59	1.0	1.10 (1.01–1.20)	0.037
Multivariate model 2 HR (95% CI)†	1.0	1.05 (0.93–1.18)	0.43	1.0	1.12 (1.02–1.24)	0.02
HPFS						
No. of cases/No. of person-years	1238/350 224	333/94 291		833/223 128	1182/294 184	
Age-adjusted HR (95% CI)	1.0	0.88 (0.78–1.00)	0.049	1.0	1.10 (1.01–1.21)	0.03
Multivariate model 1 HR (95% CI)*	1.0	0.91 (0.80–1.03)	0.13	1.0	1.09 (1.00–1.20)	0.057
Multivariate model 2 HR (95% CI)†	1.0	0.90 (0.79–1.02)	0.095	1.0	1.09 (0.99–1.20)	0.06
Combined						
Age-adjusted HR (95% CI)	1.0	0.97 (0.90–1.06)	0.53	1.0	1.09 (1.03–1.17)	0.005
Multivariate model 1 HR (95% CI)	1.0	0.98 (0.90–1.06)	0.57	1.0	1.10 (1.03–1.17)	0.0045
Multivariate model 2 HR (95% CI)	1.0	0.98 (0.90–1.06)	0.58	1.0	1.10 (1.03–1.18)	0.004

NHS indicates Nurses' Health Study; HR, hazard ratios; HPFS, Health Professionals Follow-up Study; BMI, body mass index; MET, metabolic equivalent.

*Adjusted for age (continuous), smoking (never, past, or current with cigarette use of 1–14 per day, 15–24 per day, 25+ per day, missing), BMI (<23.0, 23.0–25.0, 25.0–29.0, and ≥29.0), alcohol intake (0 g per day, up to 5 g per day, 5–15 g per day, and >15 g per day), parental history of myocardial infarction before age 60 (yes/no), physical activity (MET h/wk in quintiles), aspirin use (<1 per week, 1–2 per week, 3–6 per week, 7–14 per week, and 15+ per week), history of hypertension and high blood cholesterol and type 2 diabetes mellitus (yes or no), race/ethnicity (white or nonwhite), and menopausal status and postmenopausal hormone use (premenopausal, never, past, or current hormone use) in women.

†Adjusted for covariates in model 1 plus dietary factors including multiple vitamin or vitamin E supplement (yes or no), total energy intake, polyunsaturated, saturated, and transfats; long-chain omega-3 fatty acids, dietary fiber, and folate intake (all in quintiles).
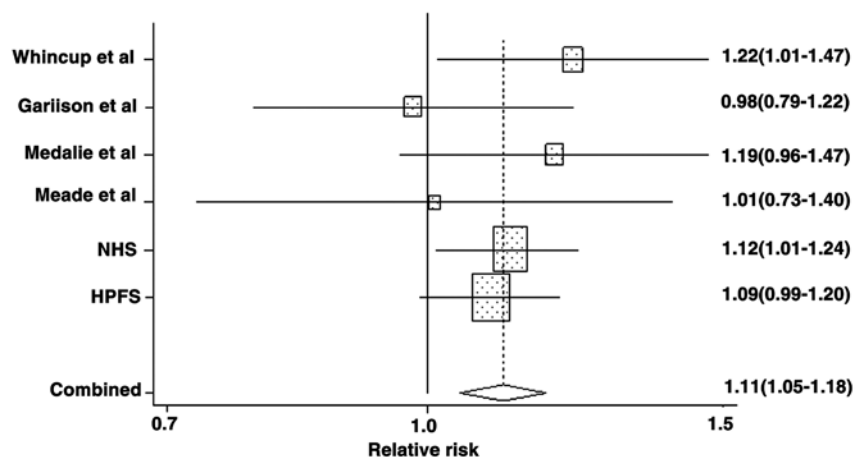
Figure 2. Forest plot showing the relative risk (RR) of coronary heart disease for non-O blood group for individual cohort studies and all studies combined. Bars and the diamond indicate 95% confidence intervals. The size of the squares corresponds to the weight of the study in the meta-analysis.

Associations between ABO blood groups and CHD have been investigated for several decades. However, the results have been conflicting, especially for the prospective cohort studies. Recently a meta-analysis reported that individuals with non-O blood group had a statistically significantly higher risk of MI than those with O blood group; however, restricting the analysis to the prospective cohorts did not find significant associations.[14] This might be because of the small sample size of these studies.

The mechanisms underlying the associations between ABO blood group and CHD risk remain unclear. However, several lines of evidence support its potential cardiovascular effects. Several studies have reported that plasma levels of factor VIII–vWf complex in non-O individuals were ≈25% higher than in group O individuals.[2] The vWf has an important role in hemostasis and thrombosis by mediating platelet adhesion to the vascular wall, especially under high shear stress conditions. Along with fibrinogen, vWF also participates in platelet aggregation[32,33] and plays a role in the development of atherosclerosis. ABO blood group has been associated with plasma lipid levels; in particular, the A blood group has been noted to have higher levels of serum total cholesterol[5,6] and low-density lipoprotein cholesterol.[5]

Recent genetic studies lend further support to the relation between ABO blood type and cardiovascular risk. The *ABO* gene is located on chromosome 9q34 with 3 variant alleles (A, B, and O), which encodes glycosyltransferases with different substrate specificities and determines blood type.[34] We recently found that the ABO locus was associated with the plasma soluble E-selectin levels in the NHS,[11] consistent with findings from another genome-wide association study.[12] ABO locus was also associated with plasma soluble intercellular adhesion molecule 1[9,10] and soluble P-selectin concentrations.[10] In addition, ABO locus was related to tumor necrosis factor-α,[13] which can mediate endothelial cell activation by increasing the expression of adhesion molecules including intercellular adhesion molecule 1, vascular adhesion molecule 1, and E-selectin.[35,36] All of these inflammatory markers have been associated with increased CHD risk.[37–39]

Our findings are less likely to be false positive because of consistent replications in 2 independent cohorts and because the meta-analysis confirmed these associations. Also, the prospective analyses minimized selection bias. Nevertheless, there are several potential limitations that need to be considered. First, participants included in this study are of different ethnicities. It is known that the prevalence of blood types varies across different ethnic groups. However, 97.1% participants in NHS and 95.7% in HPFS were white. When we restricted the analysis to whites, the associations were not appreciably altered. However, it still remains to be determined whether our findings apply to other ethnicities. Also, population stratification might be a potential confounding in our analysis. However, population stratification has negligible influence on genetic analysis in our study samples, including analysis on ABO blood type.[11] In addition, the cryptic relatedness might bias the associations. Nevertheless, our previous genome-wide analyses have indicated that cryptic relatedness was very rare in our study samples and less likely affected our current analysis.[11] Second, although genetic studies have found associations between the ABO locus and risk factors of CHD, it is possible that the ABO locus might be only a marker for other genes because of linkage disequilibrium and might not be directly involved in regulating these risk factors and associated with CHD risk. Also, lack of information about genotypic variation at the *ABO* gene locus in the whole study samples limited us to distinguish the exact genotype of ABO blood group. Third, because the blood group in our study was self-reported, measurement errors are inevitable. However, because our participants are healthcare professionals, they tend to report their blood type more accurately than the general population. Our validation study indicated that more than 90% of the participants reported their blood group correctly. In addition, in prospective studies, nondifferential measurement errors are likely to attenuate the associations toward null. Finally, although we adjusted for the lifestyle and dietary factors in our analyses, residual confounding because of unmeasured factors might still remain. However, the consistency of findings in NHS and HPFS and the relative homogeneity of the 2 cohorts with similar educational level and socioeconomic status reduces the likelihood that residual confounding can fully explain the findings in the present study.

In summary, our results from the 2 large, prospective cohorts and a meta-analysis of prospective studies suggest that ABO blood group is associated with CHD risk independent of

other risk factors. Further studies are needed to confirm these findings and to investigate the potential mechanisms underlying the links between ABO blood type and CHD risk.

Disclosures

None.

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