Genetically Determined ABO Blood Group and its Associations With Health and Disease

Groot, Hilde E; Villegas Sierra, Laura E; Said, M Abdullah; Lipsic, Erik; Karper, Jacco C; van der Harst, Pim

Published in:
Arteriosclerosis, thrombosis, and vascular biology

DOI:
10.1161/ATVBAHA.119.313658

Publication date:
2020

Arteriosclerosis, Thrombosis, and Vascular Biology

CLINICAL AND POPULATION STUDIES

Genetically Determined ABO Blood Group and its Associations With Health and Disease

Hilde E. Groot, Laura E. Villegas Sierra, M. Abdullah Said, Erik Lipsic, Jacco C. Karper, Pim van der Harst

OBJECTIVE: To determine the spectrum of phenotypes linked to the ABO blood group system, using genetic determinants of the ABO blood group system.

APPROACH AND RESULTS: We assessed the risk of 41 health and disease outcomes, and 36 linear traits associated with the ABO blood group system in the UK Biobank cohort. A total of 406 755 unrelated individuals were included in this study. Blood groups A, B, and O were determined based on allele combinations of previously established single-nucleotide polymorphisms rs8176746, rs8176719 in the ABO gene. Group AB was excluded because of its relative small sample size. Overall, 187 387 (46%) were male with a mean (SD) age of 57±8.1 years and a median total exposure of 64 person-years (interquartile range, 57–70). Of 406 755 individuals, 182 621 (44.9%) participants had blood group O, 182 786 (44.9%) had blood group A, and 41 348 (10.2%) had blood group B. ABO blood groups were associated with 11 health and disease outcomes ($P<2.19\times10^{-4}$). ABO blood groups were primarily associated with cardiovascular outcomes. Compared with individuals with blood group O, blood groups A and B were associated with increased odds of up to 1.56 (95% CI, 1.43–1.69) for thromboembolic events and decreased odds for hypertension (0.94 [95% CI, 0.92–0.97]).

CONCLUSIONS: The ABO blood group system is associated with several parameters of healthy aging and disease development. Knowledge of ABO blood groups might be of interest for more personalized approaches towards health maintenance and the prevention of diseases.

VISUAL OVERVIEW: An online visual overview is available for this article.

Key Words: ABO ■ aging ■ blood ■ genetics ■ hypertension ■ phenotype

The ABO blood group system was discovered by the Austrian pathologist Karl Landsteiner in 1901, who classified the blood groups based on the presence of A and B antigens on the surface of red blood cells after noting patterns of agglutination during blood transfusions.[1] Since the discovery of the ABO blood group system, several studies investigating the relationship between the ABO blood group system and various diseases have been conducted.[2] One of the discovered relationships is the association between ABO blood groups and blood coagulation.[3–5] Individuals with non-O blood groups demonstrate an increased risk for several thromboembolic diseases, including ischemic heart disease, pulmonary thromboembolism (PE), and deep vein thrombosis.[2,6] The associations between ABO blood group with thromboembolic diseases and bleeding risk are possibly mediated not only by the relationship between glycosyltransferase activity but also via plasma levels and biologic activity of VWF (von Willebrand factor), a carrier protein for coagulation factor VIII, which is reduced in O-group individuals.[3,7,8] In O-group individuals, reduced risks of thromboembolic diseases have been reported, although with regards to bleeding risk, its correlation with reduced VWF levels remains inconclusive.[5,9,10] The expression of A or B antigens, and thereby an individual's blood group, is the result of allelic combinations of genetic variants in the ABO gene on chromosome 9 (9q34.2).[5,11,12] In agreement with studies which used the ABO phenotype, genetically determined non-O blood groups were similarly associated with an increased risk of ischemic stroke and venous thromboembolism.[5] However, these studies included only a small number of participants or were

Correspondence to: Pim van der Harst, MD, PhD, Department of Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, the Netherlands. Email p.van.der.harst@umcg.nl

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/ATVBAHA.119.313658.

For Disclosures, see page 838.

Arterioscler Thromb Vasc Biol is available at www.ahajournals.org/journal/atvb

Nonstandard Abbreviations Acronyms

OR	odds ratio
PE	pulmonary thromboembolism
SNP	single-nucleotide polymorphism
VWF	von Willebrand factor

limited to one disease. Furthermore, most studies studied differences between blood group O and non-O, rather than studying blood group A, B, and AB separately.[2,5,13–16] The association between blood group and healthy aging remains unknown as well. Therefore, we aimed to genetically determine ABO blood groups in 406 755 individuals and provide a phenome-wide overview of the associations between ABO blood groups with prevalent and new-onset disease, as well as health in the UK Biobank.

Highlights

- The ABO blood group system has been linked to several diseases.
- However, a phenome-wide scan to assess the extent of these associations has not been performed yet.
- The ABO blood group system was associated with healthy aging and disease development.
- ABO blood groups were primarily associated with cardiovascular outcomes.
- The determination of ABO blood groups could serve in blood group individualized approaches towards health maintenance and prevention of diseases.

MATERIALS AND METHODS

The data that support the findings of this study are available in the UK Biobank study.

UK Biobank Participants

The UK Biobank study design and population have been described in detail elsewhere.[17] In brief, UK Biobank is a large community-based prospective study in the United Kingdom that recruited >500 000 participants aged 40 to 69 years old with the aim of improving prevention, diagnosis, and treatment of a plethora of illnesses including cancer, diabetes mellitus, stroke, and heart diseases. All participants gave informed consent for the study. UK Biobank has approval from the relevant institutional review boards, namely, the North West Multi-Center Research Ethics Committee for the United Kingdom, from the National Information Governance Board for Health and Social Care for England and Wales, and from the Community Health Index Advisory Group for Scotland.[18] The present study was conducted under application number 15 031 of the UK Biobank resource. The data from the UK Biobank resource are available for other researchers following an approved research proposal.[19]

Genotyping and Imputation

The genotyping process and arrays used in the UK Biobank study have been described elsewhere in more detail.[18] Briefly, participants were genotyped using the custom UK Biobank Lung Exome Variant Evaluation Axiom (Affymetrix; n=49 949), which includes 807 411 single-nucleotide polymorphisms (SNPs) or the custom UK Biobank Axiom array (Affymetrix; n=452 713), which includes 820 967 SNPs (5). The arrays have insertion and deletion markers with >95% common content.[18,20] Imputed genotype data were provided by UK Biobank, based on merged UK10K and 1000 Genomes phase 3 panels.[21] Participants were excluded if there was no genetic data available or if there was a mismatch between genetic and reported sex (n=378). Furthermore, participants with high missingness, excess heterozygosity, or familial relatedness were excluded (n=963). Last, we excluded participants of whom we could not create blood group based on the allelic combinations in previous literature (unknown blood group), or who had blood group AB (n=15 529). The latter were excluded due to their very small sample size compared with the other blood groups (A, B, and O). We created a maximal independent set of 406 755 unrelated individuals with available information on blood group. Figure 1 shows a flowchart of the study sample selection.

ABO Determination

ABO blood group was determined using allele combinations of SNP rs8176746 and rs8176719 located in the ABO gene (Figure 2).[11] Alleles were matched according to previous literature, based on frequency.[11] Table I in the online-only Data Supplement contains a detailed list of the extracted SNPs. Information on blood groups A, B, and O was available for 406 755 participants.

Definition of Prevalent and New-Onset Disease and (Cardiovascular) Health

We studied the association with ABO in 41 phenotypes and 36 linear traits. Definitions used to define incident and prevalent outcomes are presented in Table II in the online-only Data Supplement. We used self-reported diagnoses and medication, and Hospital Episode Statistics data, as previously described.[22] Furthermore, 2 health variables were generated. Cardiovascular health was defined as the absence of diabetes mellitus, stroke, and myocardial infarction.[23] Total health was based on the World Health Organization's top 10 causes of deaths in high-income countries and defined as absence of coronary artery disease, stroke, Alzheimer disease, lung cancer, chronic obstructive pulmonary disorder, pneumonia, colon cancer, rectal cancer, diabetes mellitus, kidney diseases, and breast cancer before inclusion or during follow-up.[24] Follow-up for disease outcomes was censored on March 31, 2015, for participants from England, August 31, 2014, for participants from Scotland, and on February 28, 2015, for participants from Wales. Follow-up for death was from inclusion until January 31, 2016, for participants from England and Wales and until November 30, 2015, for participants from Scotland.

Vital Signs, Blood Count, and Longevity

At the baseline visit, vital signs and biological samples were collected, together with data of self-completed questionnaires,

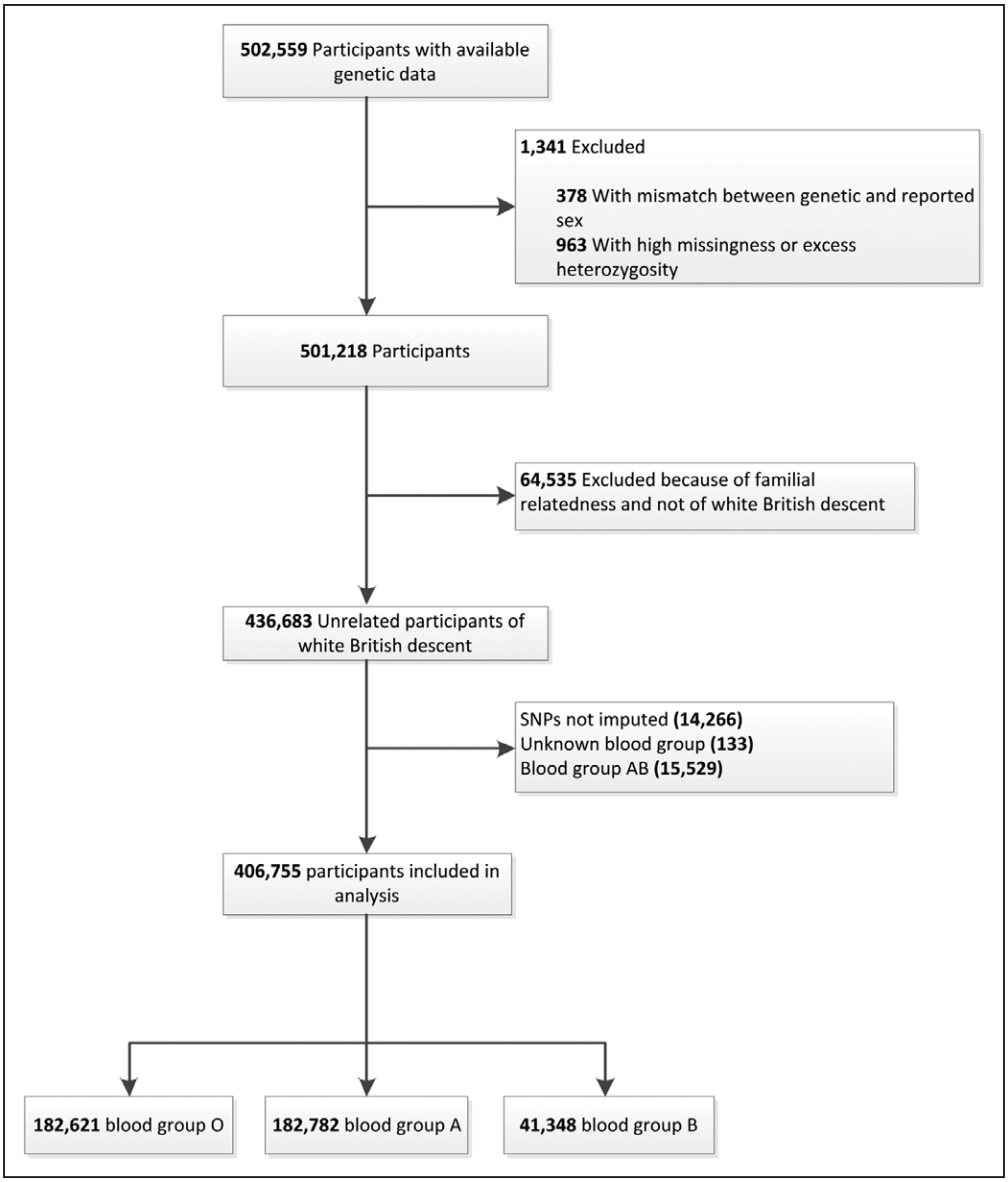

Figure 1. Flowchart for the selection of the analyzed study sample from the UK Biobank.
SNP indicates single-nucleotide polymorphism.

interviews, and physical measurements. Blood pressure was measured twice, automated or manually, and average values were used. Automated measurements were corrected as proposed by Stang et al.[25] Longevity was based on parental lifespan (field ID 1807 and 3526).

Statistical Analysis

We excluded outcomes with a prevalence of 1% or less from the analyses. Logistic regression analyses were performed to assess the effect of blood group on combined previous and new-onset disease outcomes. Odds ratios (ORs) with 95% CI and standardized beta (β) were calculated between blood groups (A versus O [reference], B versus O [reference], and A versus B [reference]), and non-O versus O (reference). Logistic regression analyses were adjusted for age at moment of last follow-up, sex, genotyping chip, and the first 30 principal components (to adjust for population structure) provided by UK Biobank. Furthermore, Cox regression analyses were performed for the significant associations found in the logistic regression analyses, adjusted for age at moment of last follow-up, sex, genotyping chip, and the first 30 principal components. The time frame used for the Cox regression analyses was from birth until last follow-up. Linear regression analyses were performed to assess the effect of blood group on anthropometric measurements, hemodynamics, laboratory measurements, longevity, and pulmonary function at baseline. Linear regression analyses were adjusted for age at baseline visit, sex, genotyping chip, and the first 30 principal components. We considered a 2-sided $P<2.19\times10^{-4}$ ($P<0.05$ divided by the number of independent tests, calculated using the Galwey method, ie, 0.05/228) statistically significant for all analyses.[26] We tested for interactions between blood group and risk factors of thrombosis (sex, body mass index, smoking, cancer, oral contraceptive use, and menopause[27]) on the outcome of thrombosis. We considered a P value of 0.05 as

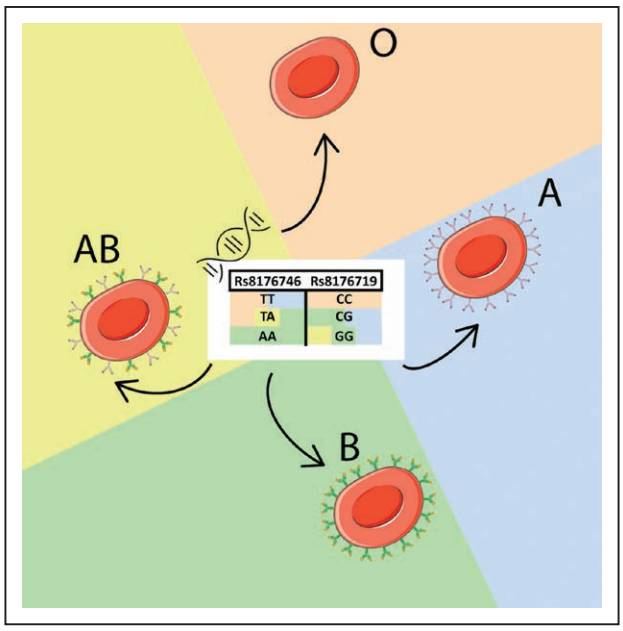

Figure 2. Genetic determination of ABO blood groups.

statistical significant for interaction. All analyses were performed using Stata version 15.

RESULTS

Population Characteristics

From the 502 559 individuals with available genotype, we included a total of 406 755 individuals for the present analyses (Figure 1). Participants with blood group AB (n=15 529 [3.7%]) were excluded because of the small sample size in comparison with blood groups O (n=182 621 [44.9%]), A (n=182 786 [44.9%]), and B (n=41 348 [10.2%]; Table 1). Overall, 187 387 (46%) were male with a mean age of 57±8.1 years and a median total exposure of 64 person-years (interquartile range, 57–70). Baseline characteristics, including the most common diseases in medical history and during up to 7 years (median 6 years [interquartile range, 5–7]) of follow-up, are provided in Table 1. All-cause mortality, cardiovascular mortality, and mortality due to cancer are shown per age group of 5 years (Table 2).

Disease

The significant associations of the different blood groups with 34 independent clinical outcomes and 23 linear traits are shown in Figures 3 and 4. The prevalence rates of the clinical outcomes associated with blood groups are shown in Table III in the online-only Data Supplement. Full details of the associations are presented in Tables IV and V in the online-only Data Supplement. Associations with blood group AB are attached as supplementary information (Table VI in the online-only Data Supplement). The observed associations with traits and disease outcomes differed per blood group and for combined non-O blood groups, that is, blood group A or B.

Individuals with non-O blood groups, that is, blood group A or B, were at up to 1.6 times (OR, 1.56 [95% CI, 1.43–1.69]) higher risk of thromboembolic events, compared with individuals with blood group O. They had a nominally lower risk of gastrointestinal bleeding compared with individuals with blood group O, although not statistically significant (OR, 0.95 [95% CI, 0.91–0.99]). Non-O blood groups were also associated with a lower risk of hypertension compared with blood group O (OR, 0.97 [95% CI, 0.95–0.98]; and OR, 0.94 [95% CI, 0.92–0.97], for blood group A and B, respectively; Figure 3).

Blood group A was associated with a higher risk of heart failure (OR, 1.14 [95% CI, 1.07–1.21]), atherosclerosis (OR, 1.05 [95% CI, 1.03–1.08]), hyperlipidemia (OR, 1.09 [95% CI, 1.07–1.11]) compared with blood group O (Figure 3). Additionally, blood group A was associated with a higher risk of atopy (OR, 1.03 [95% CI, 1.01–1.04)] compared with blood group O. Compared with blood group B, blood group A was associated with an increased risk of hyperlipidemia (OR, 1.08 [95% CI, 1.04–1.11]) and an increased risk of sleep apnea (OR, 1.23 [95% CI, 1.08–1.39]; Figure 3). There was no appreciable change in risk associated with other outcomes.

In addition to an increased risk of thromboembolic diseases and hypertension, blood group B was associated with an increased risk of myocardial infarction in comparison to blood group O (OR, 1.13 [95% CI, 1.06–1.20]; Figure 3).

No associations were observed between the different blood groups and cancer.

The significant associations between ABO blood group and diseases remained significant after cox regression analysis (Table 3).

Healthy Aging

We investigated the association between blood groups with cardiovascular and total health and found non-O individuals had worse cardiovascular and total health and reduced longevity compared with individuals with blood group O (OR, 0.95 [95% CI, 0.92–0.97]; OR, 0.97 [95% CI, 0.96–0.99]; β, −0.03 [95% CI, −0.05 to −0.02]). More specifically, this was seen in individuals with blood group A compared with individuals with blood group O (cardiovascular health: OR, 0.95 [95% CI, 0.93–0.97]; total health: OR, 0.97 [95% CI, 0.96–0.99]; β, −0.03 [95% CI, −0.05 to −0.02], respectively; Tables III and IV in the online-only Data Supplement). No differences in cardiovascular or total health, nor in longevity were observed between blood group A and B or between B and O.

Table 1. Descriptive Statistics

	O (n=182 621)	A (n=182 786)	B (n=41 348)
Male	84 460 (46.2%)	83 885 (45.9%)	19 033 (46.0%)
Age, mean (SD), y	57.0 (8.1)	57.1 (8.1)	56.5 (8.2)
Years of exposure, median (IQR), y	64.3 (56.6–69.8)	64.5 (56.8–69.8)	63.6 (55.9–69.3)
Smoking behavior			
Never or <100 cigarettes	100 351 (56.4%)	100 419 (56.4%)	23 553 (58.6%)
Stopped >12 mo	57 325 (32.2%)	57 780 (32.5%)	12 037 (29.9%)
Stopped ≤12 mo	888 (0.5%)	807 (0.5%)	207 (0.5%)
Active occasionally	4989 (2.8%)	4908 (2.8%)	1210 (3.0%)
Active daily	14 351 (8.1%)	14 061 (7.9%)	3196 (7.9%)
Body mass index, kg/m^2	27.4 (4.8)	27.4 (4.8)	27.4 (4.86)
Hyperlipidemia	39 189 (21.5%)	41 633 (22.8%)	9188 (22.2%)
Statin use	30 311 (16.6%)	32 466 (17.8%)	7051 (17.1%)
Nonstatin lipid lowering medication	2217 (1.2%)	2402 (1.3%)	525 (1.3%)
Cholesterol, mmol/L	5.7 (1.1)	5.7 (1.2)	5.6 (1.1)
HDL, mmol/L	1.4 (0.4)	1.5 (0.4)	1.4 (0.4)
LDL, mmol/L	3.5 (0.9)	3.6 (0.9)	3.5 (0.9)
Triglycerides, mmol/L	1.5 (1.0–2.2)	1.5 (1.0–2.1)	1.5 (1.0–2.2)

HDL indicates high-density lipoprotein; IQR, interquartile range; and LDL, low-density lipoprotein.

Interactions of Blood Group and Risk Factors for Thrombosis Diseases

We studied possible interactions between blood groups and known risk factors for thrombosis (sex, body mass index, smoking, cancer, oral contraceptives, and menopause[27]). A significant interaction was observed for sex and blood group. Within blood groups A and B, men had higher odds for developing thrombosis, deep vein thrombosis, and PE compared with men with blood group O (Table VII in the online-only Data Supplement). Within blood group A, individuals with a medical history of cancer had lower odds for developing thrombosis, thromboembolism, or PE, compared with individuals with blood group O. A similar phenomenon was observed when blood groups A and B were combined. Within blood group A, women in menopause had lower odds for developing thrombosis, deep vein thrombosis, thromboembolism, or PE compared with women in menopause with blood group O.

DISCUSSION

In this large community-based population, we determined ABO blood group phenotypes based on inherited allelic combinations and observed numerous associations between the ABO blood group system with healthy aging and the development of a multitude of diseases. The ABO blood groups were primarily associated with cardiovascular outcomes. The present study observed that individuals with blood group A and B were at higher risk of developing thromboembolic diseases, but lower risk of hypertension, when compared with O-group individuals. Individuals with blood group A were at higher risk of developing hyperlipidemia, atherosclerosis, and heart failure compared with blood group O, whereas individuals with blood group B were at higher risk of myocardial infarction compared with individuals with blood group O. The observed differences suggest blood group-specific approaches for the maintenance of human health and the prevention and treatment of a multitude of diseases.

ABO and Disease

Our results are concordant with previous smaller observational reports suggesting an increased risk of thromboembolic events in non-O blood group individuals compared to individuals with blood group O.[28] In both blood groups A and B, we observed similar increased risks of developing thromboembolic events compared with blood group O. Interestingly, we did not observe the same effects on blood cell characteristics between individuals with blood group A or B compared to blood group O. Because thrombosis is a well-balanced and complex process, which is affected by a plethora of factors, there could be different biological mechanisms (ie, cell functionality, number of cell receptors) involved in the increased risk of thromboembolic events in blood group A and blood B individuals, besides the already established relation with VWF.[9] Molecular studies are necessary to further unravel these differences between blood group A and blood group B. Nevertheless, this study provides an elegant overview for future research possibilities. In addition, it might be of interest to take sex differences into account because we observed interactions between sex and blood groups in the development of thromboembolic disease.

Our analyses indicated an increased risk of hyperlipidemia in individuals with blood group A compared to both

Table 2. Age-Adjusted Mortality Rates in Blood Group O, A, and B

Age Category	<45 y			45–49			50–54			55–59			60–64			65–69			≥70 y		
Blood Group	O	A	B	O	A	B	O	A	B	O	A	B	O	A	B	O	A	B	O	A	B
Number	18651	18308	4766	24564	23902	5748	27768	27759	6628	32891	32856	7411	43824	44717	9439	33811	34204	7140	1112	1040	216
All cause	130 (0.7%)	126 (0.7%)	30 (0.6%)	257 (1.0%)	257 (1.1%)	60 (1.0%)	451 (1.6%)	439 (1.6%)	119 (1.8%)	800 (2.4%)	793 (2.4%)	165 (2.2%)	1575 (3.6%)	1532 (3.4%)	338 (3.6%)	1926 (5.7%)	1919 (5.6%)	412 (5.8%)	82 (7.4%)	87 (8.4%)	13 (6.0%)
Cardiovascular	16 (0.1%)	17 (0.1%)	9 (0.2%)	55 (0.2%)	54 (0.2%)	10 (0.2%)	82 (0.3%)	70 (0.3%)	15 (0.2%)	138 (0.4%)	177 (0.5%)	34 (0.5%)	311 (0.7%)	354 (0.8%)	75 (0.8%)	445 (1.3%)	413 (1.2%)	91 (1.3%)	18 (1.6%)	15 (1.4%)	1 (0.5%)
Cancer (malignant)	70 (0.4%)	58 (0.3%)	8 (0.2%)	119 (0.5%)	140 (0.6%)	23 (0.4%)	269 (1.0%)	270 (1.0%)	77 (1.2%)	475 (1.4%)	469 (1.4%)	101 (1.4%)	951 (2.2%)	875 (2.0%)	187 (2.0%)	1102 (3.3%)	1091 (3.2%)	235 (3.3%)	44 (4.0%)	55 (5.3%)	11 (5.1%)

blood group O as well as blood group B, which is also in line with previous studies. Earlier research has associated blood group A with higher total cholesterol levels as well as low-density lipoprotein cholesterol compared with both blood groups B and O.[29] However, in a study including 6476 individuals with Asian backgrounds, cholesterol levels were increased in individuals with blood group A or B compared to blood group O but not higher in individuals with A compared to B.[13] The difference in outcomes between this study in Asians and our study might be because of the larger sample size of our study (66× larger). Whether epigenetic factors play a role in these differences remains to be investigated. In addition, previous reports have also shown that non-O blood group patients affected by familial hypercholesterolemia were at a 2-fold increased risk of cardiovascular diseases compared with O blood group patients.[30]

Interactions Between ABO Blood Group and Risk Factors for Thromboembolic Diseases

The present study provides information on the sex differential for thromboembolic diseases in the context of ABO blood group in the general population. The interaction between blood group and sex has been previously observed in patients with persistent antiphospholipid antibodies.[31] We did not find an interaction with use of contraceptive medication. This might be explained due to the small number of women (<1%) still using contraceptive medication in this group of middle-aged women from the UK Biobank (median age when quitted oral contraceptives was 30 years [interquartile range, 24–35 years). Of interest is the interaction between blood group and cancer. Previous literature reported non-O blood groups to be a risk factor for venous thromboembolism in adult patients with malignant gliomas and children with acute lymphoblastic leukemia.[32,33] Also in the Longitudinal Investigation of Thromboembolism Etiology study, an increased risk of venous thromboembolism due to cancer was observed in non-O individuals compared with individuals with blood group O.[34] The present analyses add to these previous findings, indicating individuals with blood group O and a medical history of cancer had higher odds of developing thrombosis, thromboembolism or PE compared with blood group A or A + B combined. Although the mechanism underlying the interaction between blood group and cancer requires further research, the ABO blood group might play a role in counseling, risk stratification and thromboprophylaxis in individuals with cancer.

ABO and Healthy Aging

We also investigated whether specific blood groups were associated with cardiovascular and total health. Individuals with blood group A had worse perspectives for healthy aging compared with individuals with blood group O. No associations were observed between blood group B

versus O, suggesting the association may be specific for blood group A and not non-O blood groups in general. Another explanation could be the small sample size of blood group B compared with blood group A and blood group O. Our finding is in line with previous literature and indicates potential implications for the maintenance of health and prevention of diseases in different blood groups within the ABO system.[34] Individuals with blood group A may benefit from early preventive interventions to reduce their risk of poor cardiovascular or total health.

Strengths and Limitations

The major strengths of this study were the large sample size, variety of examined traits and disease outcomes, adjustment for multiple covariates, and the prospective design of the UK Biobank. However, this study has some limitations. We excluded individuals with blood group AB from our main analysis because of the relative large difference in sample size compared with blood group O, A, and B. We included this information in the online-only Supplement Data. Nevertheless, in contrast to previous studies, we were able to study individuals with blood groups A and B separately rather than only as a combined non-O group. A second limitation was that we were not able to take into account the possible role of the Rhesus and other blood group systems, which could provide other and more detailed insights. Furthermore, we determined the ABO phenotype based on previously reported SNP allele combinations, but because blood group has not been determined in UK Biobank blood samples, comparison of the genetically determined phenotype and laboratory determined phenotype was not possible. The distribution of the ABO blood groups was,

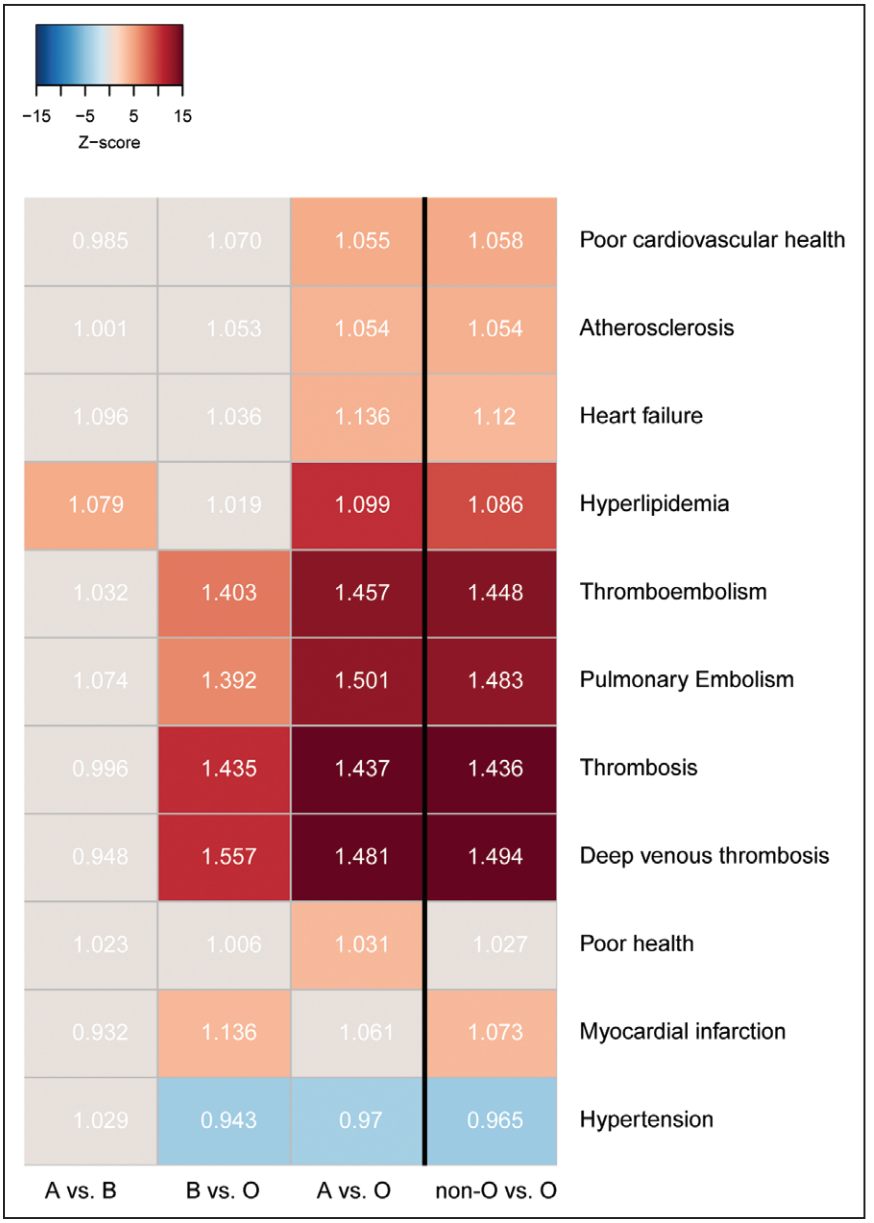

Figure 3. Heatmap of Z scores for associations in UK Biobank with blood group.
Odds ratios are provided for these associations. Significant associations are colored. Nonsignificant associations are gray.

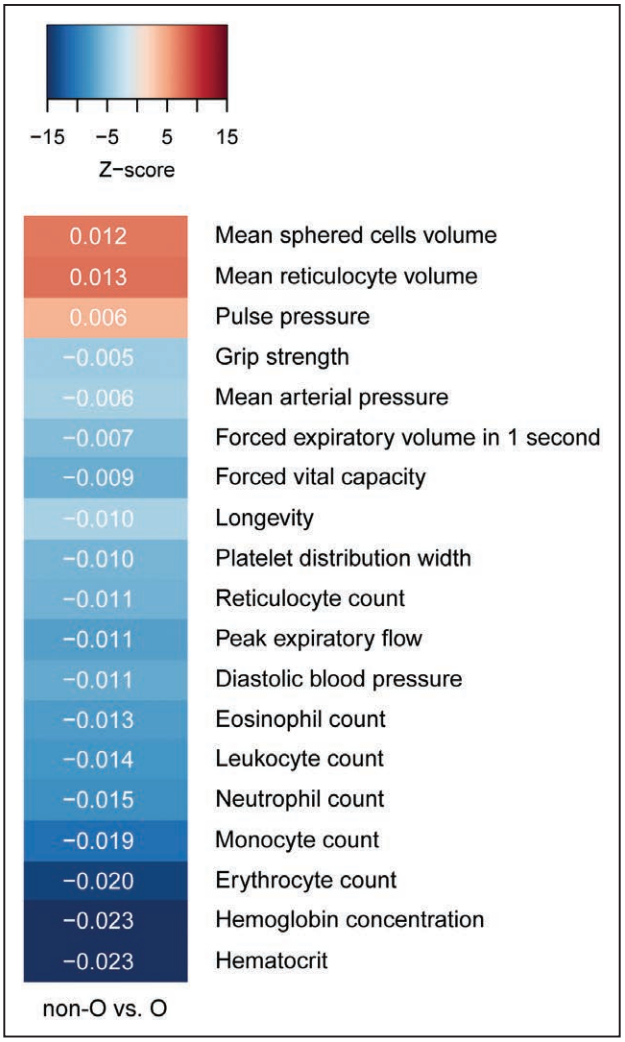

Figure 4. Heatmap of Z scores for significant associations in UK Biobank on linear outcomes in non-O vs O blood groups. Standardized β are provided for these associations.

however, consistent with previously reported distributions in the United Kingdom.[36]

Finally, some data were self-reported and incident cases of, for example, hypertension and diabetes mellitus may have been missed if they were diagnosed and treated in outpatient settings and not reported by the participant during one of the follow-up visits at the UK Biobank assessment center. However, any possible measurement errors or misclassifications are likely biased towards the null and would, therefore, underestimated the presented risks associated with the ABO blood groups.

Future Perspectives

The differences between individuals with blood groups A and B invite further studies on the pathophysiological mechanisms underlying the increased risk of thromboembolic diseases, as well as the associations with hyperlipidemia, atherosclerosis, myocardial infarction, and heart failure.

Table 3. Cox Regression Analysis Between Blood Groups and Significantly Associated Diseases (Based on Logistic Regression Analysis)

	HR	95% CI	*P* Value
Non-O vs O			
Atherosclerosis	1.05	1.03–1.07	5.90×10^{-6}
Heart failure	1.10	1.04–1.16	4.16×10^{-4}
Hypertension	0.97	0.96–0.98	2.10×10^{-7}
Hyperlipidemia	1.08	1.06–1.10	5.20×10^{-13}
Myocardial infarction	1.08	1.05–1.12	4.03×10^{-6}
Thrombosis	1.44	1.39–1.50	2.02×10^{-89}
Deep venous thrombosis	1.51	1.44–1.59	5.29×10^{-66}
Pulmonary embolism	1.47	1.39–1.55	1.46×10^{-43}
Thromboembolism	1.44	1.37–1.51	2.53×10^{-46}
A vs O			
Atherosclerosis	1.05	1.03–1.07	3.47×10^{-5}
Heart failure	1.11	1.05–1.18	1.99×10^{-4}
Hypertension	0.98	0.97–0.99	6.07×10^{-5}
Hyperlipidemia	1.09	1.07–1.12	3.08×10^{-16}
Thrombosis	1.44	1.39–1.50	3.05×10^{-82}
Deep venous thrombosis	1.50	1.43–1.58	1.37×10^{-59}
Pulmonary embolism	1.48	1.40–1.57	2.02×10^{-42}
Thromboembolism	1.44	1.37–1.52	7.28×10^{-44}
B vs O			
Hypertension	0.95	0.93–0.97	1.29×10^{-7}
Myocardial infarction	1.15	1.08–1.21	2.14×10^{-6}
Thrombosis	1.45	1.37–1.54	1.68×10^{-34}
Deep venous thrombosis	1.55	1.44–1.68	3.64×10^{-29}
Pulmonary embolism	1.42	1.28–1.54	3.34×10^{-13}
Thromboembolism	1.42	1.30–1.54	2.04×10^{-16}
A vs B			
Hyperlipidemia	1.08	1.04–1.12	1.43×10^{-5}

HR indicates hazard ratio.

Conclusions

Our study identified connections between the ABO blood group system with healthy aging and disease development. The determination of ABO blood groups could serve in blood group individualized approaches towards health maintenance and prevention of diseases.

ARTICLE INFORMATION

Received July 26, 2019; accepted November 22, 2019.

Affiliations

From the Department of Cardiology, University of Groningen, University Medical Center Groningen, the Netherlands (H.E.G., L.E.V.S., M.A.S., E.L., J.C.K., P.v.d.H.); and University of Antioquia, School of Medicine, Medellín, Colombia (L.E.V.S.).

Acknowledgments

We thank the Centre for Information Technology of the University of Groningen for their support and for providing access to the Peregrine high-performance computing cluster. We thank N. Verweij; Ruben N. Eppinga, MD; Tom Hendriks, MD; Yordi J. van de Vegte, BSc; M. Yldau van der Ende, BSc; Yanick Hagemeijer,

MSc; and Jan-Walter Benjamins, BEng (Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands), for their contributions to the extraction and processing of data in the UK Biobank. None of the contributors received compensation except for their employment at the University Medical Center Groningen. This research has been conducted using the UK Biobank Resource under Application Number 15031.

Disclosures

None.

REFERENCES

1. Dean L. *Blood Groups and Red Cell Antigens*. Bethesda: National Center for Biotechnology Information; 2005; Chapter 5:1-9. The ABO blood group.
2. Chen Z, Yang SH, Xu H, Li JJ. ABO blood group system and the coronary artery disease: an updated systematic review and meta-analysis. *Sci Rep*. 2016;6:23250. doi: 10.1038/srep23250
3. Larson NB, Bell EJ, Decker PA, Pike M, Wassel CL, Tsai MY, Pankow JS, Tang W, Hanson NQ, Alexander K, et al. ABO blood group associations with markers of endothelial dysfunction in the Multi-Ethnic Study of atherosclerosis. *Atherosclerosis*. 2016;251:422–429. doi: 10.1016/j.atherosclerosis.2016.05.049
4. Johansson Å, Alfredsson J, Eriksson N, Wallentin L, Siegbahn A. Genome-Wide Association Study identifies that the ABO Blood Group system influences interleukin-10 levels and the risk of clinical events in patients with acute coronary syndrome. *PLoS One*. 2015;10:e0142518. doi: 10.1371/journal.pone.0142518
5. Wiggins KL, Smith NL, Glazer NL, Rosendaal FR, Heckbert SR, Psaty BM, Rice KM, Lumley T. ABO genotype and risk of thrombotic events and hemorrhagic stroke. *J Thromb Haemost*. 2009;7:263–269. doi: 10.1111/j.1538-7836.2008.03243.x
6. Vasan SK, Rostgaard K, Majeed A, Ullum H, Titlestad KE, Pedersen OB, Erikstrup C, Nielsen KR, Melbye M, Nyrén O, et al. ABO Blood Group and risk of thromboembolic and arterial disease: A Study of 1.5 million blood donors. *Circulation*. 2016;133:1449–1457; discussion 1457. doi: 10.1161/CIRCULATIONAHA.115.017563
7. Souto JC, Almasy L, Muñiz-Diaz E, Soria JM, Borrell M, Bayén L, Mateo J, Madoz P, Stone W, Blangero J, et al. Functional effects of the ABO locus polymorphism on plasma levels of von Willebrand factor, factor VIII, and activated partial thromboplastin time. *Arterioscler Thromb Vasc Biol*. 2000;20:2024–2028. doi: 10.1161/01.atv.20.8.2024
8. Tirado I, Mateo J, Soria JM, Oliver A, Martínez-Sánchez E, Vallvé C, Borrell M, Urrutia T, Fontcuberta J. The ABO blood group genotype and factor VIII levels as independent risk factors for venous thromboembolism. *Thromb Haemost*. 2005;93:468–474. doi: 10.1160/TH04-04-0251
9. Jenkins PV, O'Donnell JS. ABO blood group determines plasma von Willebrand factor levels: a biologic function after all? *Transfusion*. 2006;46:1836–1844. doi: 10.1111/j.1537-2995.2006.00975.x
10. Kahr MK, Franke D, Brun R, Wisser J, Zimmermann R, Haslinger C. Blood group O: a novel risk factor for increased postpartum blood loss? *Haemophilia*. 2018;24:e207–e212. doi: 10.1111/hae.13537
11. Melzer D, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, Lauretani F, Murray A, Gibbs JR, Paolisso G, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). *PLoS Genet*. 2008;4:e1000072. doi: 10.1371/journal.pgen.1000072
12. van Hylckama Vlieg A, Flinterman LE, Bare LA, Cannegieter SC, Reitsma PH, Arellano AR, Tong CH, Devlin JJ, Rosendaal FR. Genetic variations associated with recurrent venous thrombosis. *Circ Cardiovasc Genet*. 2014;7:806–813. doi: 10.1161/CIRCGENETICS.114.000682
13. Chen Y, Chen C, Ke X, Xiong L, Shi Y, Li J, Tan X, Ye S. Analysis of circulating cholesterol levels as a mediator of an association between ABO blood group and coronary heart disease. *Circ Cardiovasc Genet*. 2014;7:43–48. doi: 10.1161/CIRCGENETICS.113.000299
14. Gotsman I, Keren A, Zwas DR, Lotan C, Admon D. Clinical impact of ABO and Rhesus D Blood Type Groups in patients with chronic heart failure. *Am J Cardiol*. 2018;122:413–419. doi: 10.1016/j.amjcard.2018.04.018
15. Takagi H, Umemoto T; All-Literature Investigation of Cardiovascular Evidence (ALICE) Group. Meta-analysis of Non-O Blood Group as an independent risk factor for coronary artery disease. *Am J Cardiol*. 2015;116:699–704. doi: 10.1016/j.amjcard.2015.05.043
16. Franchini M, Mengoli C, Capuzzo E, Terenziani I, Bonfanti C, Lippi G. Correlation between ABO Blood Group, and conventional hematological and metabolic parameters in blood donors. *Semin Thromb Hemost*. 2016;42:75–86. doi: 10.1055/s-0035-1564843
17. UK Biobank. *UK Biobank: Protocol for a Large-Scale Prospective Epidemiological Resource*. 2007. http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf.
18. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K et al. Genome-wide genetic data on ~500,000 UK biobank participants. *bioRxiv*. 2017.
19. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779. doi: 10.1371/journal.pmed.1001779
20. UK Biobank. *Genotyping and Quality Control of UK Biobank, a Large-scale, Extensively Phenotyped Prospective Resource*. 2018. https://biobank.ctsu.ox.ac.uk/crystal/docs/genotyping_qc.pdf.
21. Marchini J. *UK Biobank Phasing and Imputation Documentation*. 2018:13. https://biobank.ctsu.ox.ac.uk/crystal/docs/impute_ukb_v1.pdf. Accessed August 18, 2017.
22. Said MA, Eppinga RN, Lipsic E, Verweij N, van der Harst P. Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. *J Am Heart Assoc*. 2018;7:e007621. doi: 10.1161/JAHA.117.007621
23. Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, et al. Association of Cardiometabolic Multimorbidity With Mortality. *JAMA*. 2015;314:52–60. doi: 10.1001/jama.2015.7008
24. The top 10 causes of death. *WHO*. 2018. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
25. Stang A, Moebus S, Möhlenkamp S, Dragano N, Schmermund A, Beck EM, Siegrist J, Erbel R, Jöckel KH; Heinz Nixdorf Recall Study Investigative Group. Algorithms for converting random-zero to automated oscillometric blood pressure values, and vice versa. *Am J Epidemiol*. 2006;164:85–94. doi: 10.1093/aje/kwj160
26. Galwey NW. A new measure of the effective number of tests, a practical tool for comparing families of non-independent significance tests. *Genetic epidemiology*. 2009;33:559–568. doi: 10.1002/gepi.20408
27. Rosendaal FR. Causes of venous thrombosis. *Thromb J*. 2016;14(suppl 1):24. doi: 10.1186/s12959-016-0108-y
28. Wu O, Bayoumi N, Vickers MA, Clark P. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. *J Thromb Haemost*. 2008;6:62–69. doi: 10.1111/j.1538-7836.2007.02818.x
29. George VT, Elston RC, Amos CI, Ward LJ, Berenson GS. Association between polymorphic blood markers and risk factors for cardiovascular disease in a large pedigree. *Genet Epidemiol*. 1987;4:267–275. doi: 10.1002/gepi.1370040405
30. Paquette M, Dufour R, Baass A. ABO blood group is a cardiovascular risk factor in patients with familial hypercholesterolemia. *J Clin Lipidol*. 2018;12:383–389.e1. doi: 10.1016/j.jacl.2017.12.001
31. Shusterman M, Golub E, Mowrey WB, Broder A. The association between ABO blood types and venous thromboembolism in individuals with a positive antiphospholipid profile is varied by sex. *Lupus*. 2018;27:319–326. doi: 10.1177/0961203317721352
32. Streiff MB, Segal J, Grossman SA, Kickler TS, Weir EG. ABO blood group is a potent risk factor for venous thromboembolism in patients with malignant gliomas. *Cancer*. 2004;100:1717–1723. doi: 10.1002/cncr.20150
33. Mizrahi T, Leclerc JM, David M, Ducruet T, Robitaille N. ABO Group as a thrombotic risk factor in children with acute lymphoblastic leukemia: a Retrospective Study of 523 patients. *J Pediatr Hematol Oncol*. 2015;37:e328–e332. doi: 10.1097/MPH.0000000000000333
34. Ohira T, Cushman M, Tsai MY, Zhang Y, Heckbert SR, Zakai NA, Rosamond WD, Folsom AR. ABO blood group, other risk factors and incidence of venous thromboembolism: the longitudinal investigation of thromboembolism etiology. *J Thromb Haemost*. 2007;5:1455–1461. doi: 10.1111/j.1538-7836.2007.02579.x
35. Franchini M, Mengoli C, Bonfanti C, Rossi C, Lippi G. Genetic determinants of extreme longevity: the role of ABO blood group. *Thromb Haemost*. 2016;115:458–460. doi: 10.1160/TH15-05-0379
36. NHS Blood and Transplant. https://www.blood.co.uk/why-give-blood/blood-types/. Accessed October 16, 2019.