Blood group and ischemic stroke, myocardial infarction, and peripheral vascular disease: A meta-analysis of over 145,000 cases and 2,000,000 controls

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Objective: Cardiovascular illnesses have been associated to ABO blood types, specifically through an effect on von Willebrand factor and factor FVIII levels. We conducted a meta-analysis to comprehensively explore the relationship between blood groups and ischemic stroke, myocardial infarction, and peripheral vascular disease. *Materials and methods:* A comprehensive meta-analysis was undertaken to investigate blood groups and ischemic stroke (IS), myocardial infarction (MI) and peripheral vascular disease (PVD). Odds ratios (OR) were used to assess the relationship between blood groups and disease. RevMan v5,4 was used to statistically analyse the results. Risk of bias was assessed using the Newcastle-Ottawa scale. *Results:* A total of 72 studies (18 ischemic stroke, 37 myocardial infarction, 17 peripheral vascular disease) met our search criteria, totalling 145,499 cases and 2,113,736 controls. Mean age ranged between 18 and 90 years. Compared to blood group-O, non-O blood group had an increased association with IS (OR=1.13, 95%Cl: 1.07-1.21, $P < 0.001$), MI (OR=1.17, 95%Cl: 1.11-1.24, $P < 0.001$) and PVD (OR=1.15, 95%Cl: 1.04-1.28, $P=0.005$). Compared to blood group-O, blood group A had a stronger statistically significant association to IS (OR=1.19, $P=0.001$), MI (OR=1.22, $P < 0.001$) and PVD (OR=1.15, $P=0.03$). Blood group-B has the lowest risk associated with MI (OR=1.09, $P=0.01$). In addition, blood groups AB had a stronger statistically significant association to IS (OR=1.24, $P=0.01$), and MI (OR=1.20, $P < 0.001$) compared with the other blood groups. *Conclusions:* Compared to blood group-O, groups A and AB are strongly associated to ischemic stroke, myocardial infarction, and peripheral vascular disease.

Keywords: Ischemic stroke—Myocardial infarction—Peripheral vascular disease—Blood type—Meta-analysis

Abbreviations: IS, ischemic stroke; MI, myocardial infarction; PVD, peripheral vascular disease; vWF, von Willebrand factor; FVIII, factor FVIII levels; OR, odds ratio; SD, standard deviation; CI, confidence interval; CVT, cerebral venous thrombosis; RCT, randomised controlled trials

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Introduction

The ABO blood groups have been associated with the pathophysiology of cardiovascular diseases through an influence on two important blood clotting proteins, von Willebrand factor (vWF) and factor FVIII levels (FVIII).[1,2] These proteins circulate in the plasma as a complex and are vital in normal haemostasis.[1] The highest levels of FVIII and VWF are seen in non-O blood groups. Studies suggest a relationship between non-O blood groups and an increased risk of venous thromboembolism and other thrombotic episodes.[3] However, the association between ABO blood groups and ischemic stroke (IS), myocardial infarction (MI), peripheral vascular disease (PVD) remains less well defined.[4]

Blood type refers to autoantigens on an erythrocyte surface that results in four basic phenotypes O, A, B, and AB.[5] Antigens are polymorphic residues composed of carbohydrates, lipids, and proteins, which allow for the distinction between self and non-self, thus play a role in immunity.[6] Moreover, an A phenotypic expression arises from erythrocytes containing only the A antigen on their cell surface. B phenotype occurs if only B antigens are expressed on the surface. AB develops from the combination of both A and B antigens, while an O phenotype occurs when no modified antigens are present on the cell surface. Moreover, an AB phenotype is possible as the A and B alleles exhibit codominance. The distribution of the four ABO blood types, A, B, AB, and O, varies in populations throughout the world and is determined by the frequency of the three alleles of the ABO gene in different populations. Blood type O is the most common worldwide (45%), followed by group A (32.5%). Group B is less common (16%), and group AB is the least common (5.5%).[7]

To provide a more robust and reliable assessment of the role of blood groups we conducted a comprehensive meta-analysis and systematic review to determine whether ABO blood groups are associated with IS, MI, and PVD.

Materials and methods

Search criteria

Four investigators followed PRISMA and Cochrane guidelines, and independently searched MEDLINE and Google Scholar up to March 2022 using the key terms: *ischaemic stroke, cerebral ischemia, myocardial infarction, myocardial ischemia, ischaemic heart disease, coronary heart disease, myocardial ischaemia, peripheral vascular disease, peripheral artery disease, coronary heart disease, coronary artery disease, ischemic disease, blood type, and blood group*. All languages were searched. Boolean operators "AND" and "OR" were used to combine search terms. References within relevant studies were hand-searched.

Inclusion criteria

Randomised controlled trials or observational studies (case-control, cross-sectional, cohort studies) that explicitly examined the association between blood type or blood group on IS, MI, and PVD were included. Included studies were in adults (aged≥18 years) of either gender and any ethnicity. Studies were excluded if blood group data was not presented in cases and controls.

Outcome measures

Primary outcome was assessed as the distribution of the different blood groups in IS, MI and PVD. Comparisons were generated with the reference blood group-O. Clinical diagnosis of IS was confirmed using TOAST (trial of ORG 10172 in acute stroke treatment) criteria, neuro-imaging scans CT or MRI. Clinical diagnosis of MI was confirmed using WHO criteria, ECG, or elevated cardiac enzymes changes. Clinical diagnosis of PVD was confirmed using physical exam and angiogram, or magnetic resonance angiography (MRA).

Risk of Bias

The quality of the included studies was initially visually assessed for publication bias through the generation of funnel plots and the effect size against the standard error. The quality of the reports was evaluated using the risk of bias assessed using the Newcastle-Ottawa scale.[8] Risk of bias for each report was rated independently from unclear, low, or high by two independent investigators and any discrepancies were resolved by discussion.

Data analysis

The meta-analysis was conducted using Review Manager (RevMan, v5.4 Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). Odds ratios (OR) were used on the original measurement scale to determine the magnitude of the impact on the disease. Pooled estimates of each outcome for each blood group were obtained via the DerSimonian and Laird method using a random-effects model.[9] The I^2 statistic was used to assess heterogeneity of trial results used to construct pooled estimates of effect.[10] Statistical significance threshold was accepted as $P < 0.05$.

Results

Blood type and IS

A total of 18 studies comprising 12 case-control[11–22] (3,478 IS cases & 39,932 controls) and 6 cohort studies[23–28] (74,262 IS cases & 1,197,742 controls) totalling 77,740 IS patients and 1,237,674 controls met our inclusion criteria (Fig. 1). Mean age of IS cases and controls ranged between 18 and 90 years. All studies were published in English from 1976 to 2021. The risk of IS was significantly

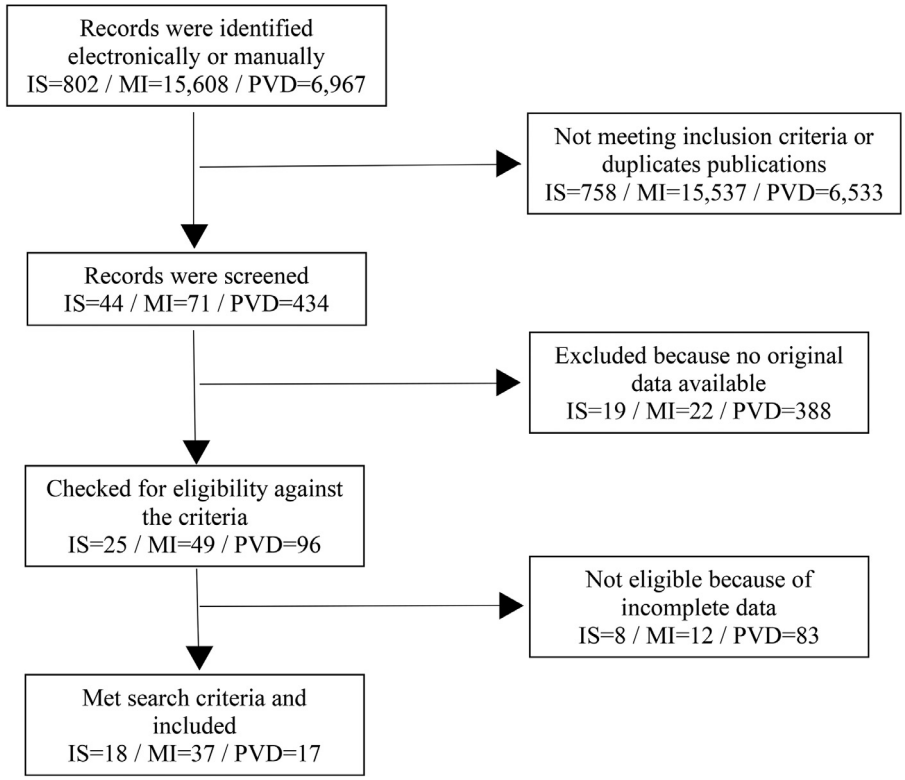

Fig. 1. *Flow chart of literature search.*

increased in patients with non-O blood group compared with blood group-O (OR=1.13, 95%CI: 1.07-1.21, $P < 0.001$) (Fig. 2A), with moderate[10] inter-study heterogeneity ($I^2 = 54.0\%$, $P < 0.01$). Data on stroke subtype was not available.

A blood subgroup analysis to determine any statistically significant difference between the subtypes was undertaken in the 12 case-control and 6 cohort studies (supplementary Fig. S1A). Subjects in blood group non-O had a statistically associated with IS compared with blood group-O among case-control studies (OR=1.18, 95%CI: 1.07-1.31, P=0.001). In comparison to the case-control studies, there was a lower (but statistically significant) incidence of non-O phenotype compared with blood group-O in the cases than in the controls resulting in a lower pooled OR of 1.11 (95%Cl:1.02-1.20, P=0.01) among cohort studies (Supplementary Fig. S1).

A subgroup analysis by individual blood groups (Fig. 3A) show that those with blood group-A had a statistically significant increase in IS compared with blood group-O (OR=1.19, 95%CI: 1.07-1.32, P=0.001). Blood group-AB had a statistically significant increase in IS compared with blood group-O (OR=1.24, 95%CI: 1.04-1.48, P=0.01). However, there was no statistically significant difference in IS between blood groups-B or O (OR=1.03, 95%CI: 0.93-1.14, P=0.54).

A symmetrical funnel plot suggested no significant publication bias. The risk of bias for the reports was evaluated by Newcastle-Ottawa scale (Supplementary Fig. S2A.1).

Blood type and MI

A total of 37 studies comprising 23 case-control[29–51] (10,037 MI cases & 399,821 controls), 9 cohort[52–56] (9,081 MI cases & 254,800 controls) and 5 cross-sectional[57–64] (6,276 MI cases and 16,516 controls) met our inclusion criteria (Fig. 1). Mean age of MI cases and controls ranged between 18 and 90 years. All studies were published in English from 1962 to 2019, a total of 25,394 MI patients and 671,137 controls were included. The risk of MI was significantly increased in patients with non-O blood group compared with blood group-O (OR=1.17, 95%CI: 1.11-1.24, $P < 0.001$) (Fig. 2B), with moderate inter-study heterogeneity ($I^2 = 62.8\%$, $P < 0.01$).

A subgroup analysis to determine any statistically significant difference between the subtypes was undertaken in the 23 case-control studies, 9 cohort studies, and 5 cross-sectional studies (supplementary Fig. S1B). Subject in blood group non-O had a statistically associated with MI compared with blood group-O among case-control studies (OR=1.21, 95%CI: 1.12-1.30, $P < 0.001$).

A subgroup analysis by individual blood groups (Fig. 3B) show that those with blood group-A had a statistically significant increase in MI compared with blood group-O (OR=1.22, 95%CI: 1.12-1.33, $P < 0.001$). Blood

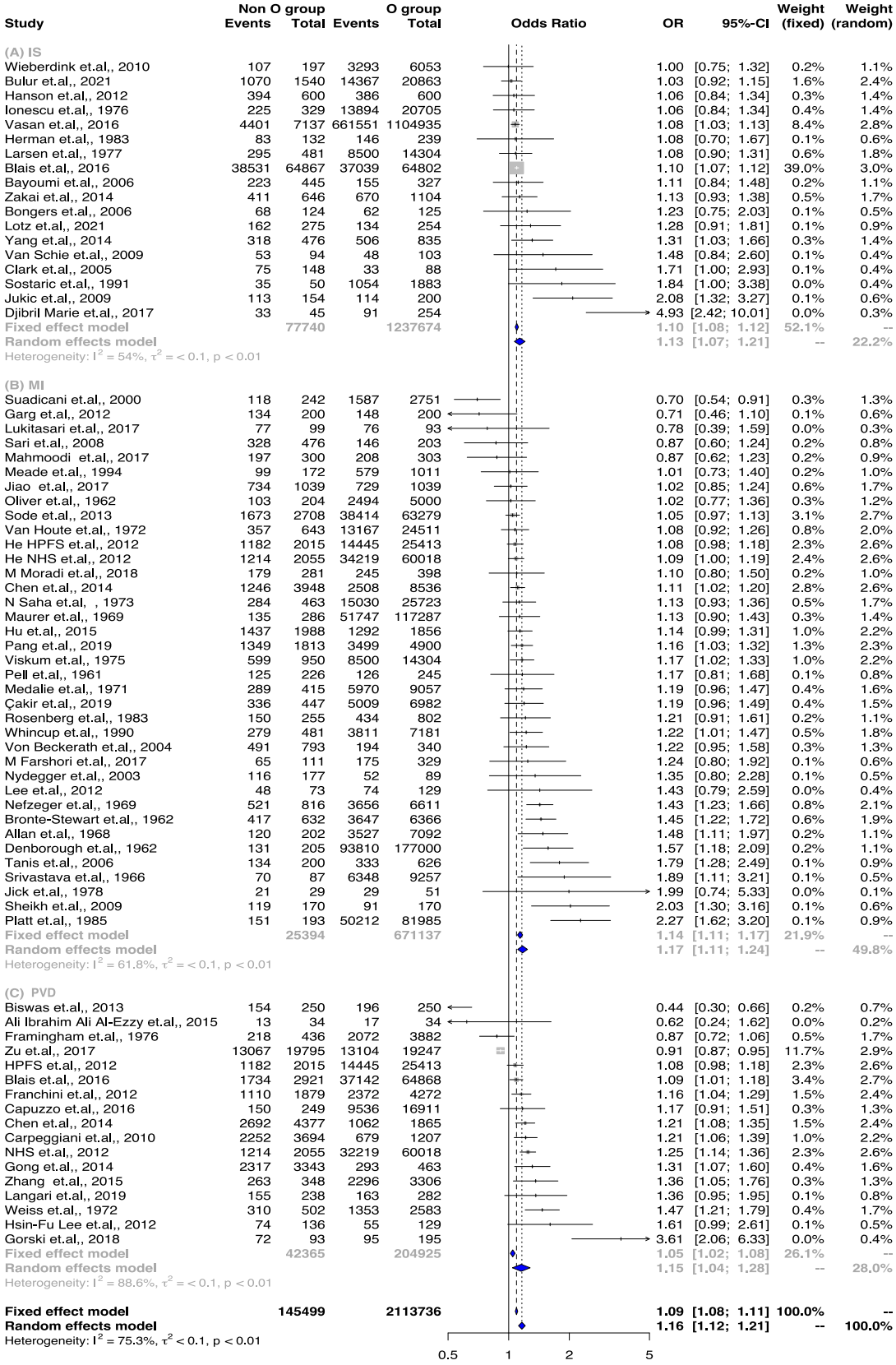

Fig. 2. *The association between blood group-O relative to non-O for (2A) IS, (2B) MI and (2C) PVD. CI, Confidence Interval; df, degrees of freedom;* P, *probability.*

(A) IS

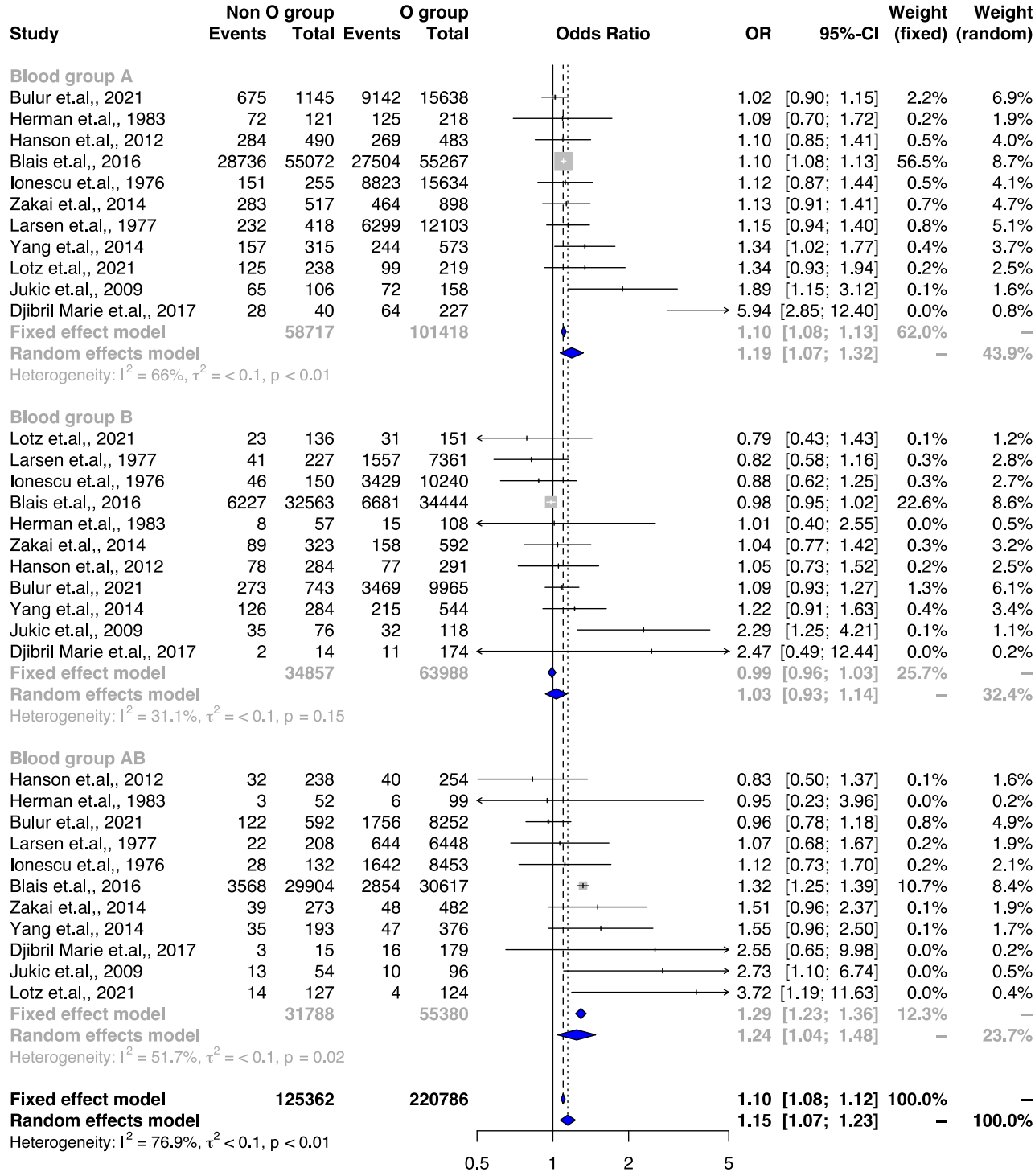

Fig. 3. *The association between blood group-O relative to A, B, and ABO for (3A) IS, (3B) MI and (3C) PVD. CI, Confidence Interval; df, degrees of freedom;* P, *probability.*

(B) MI

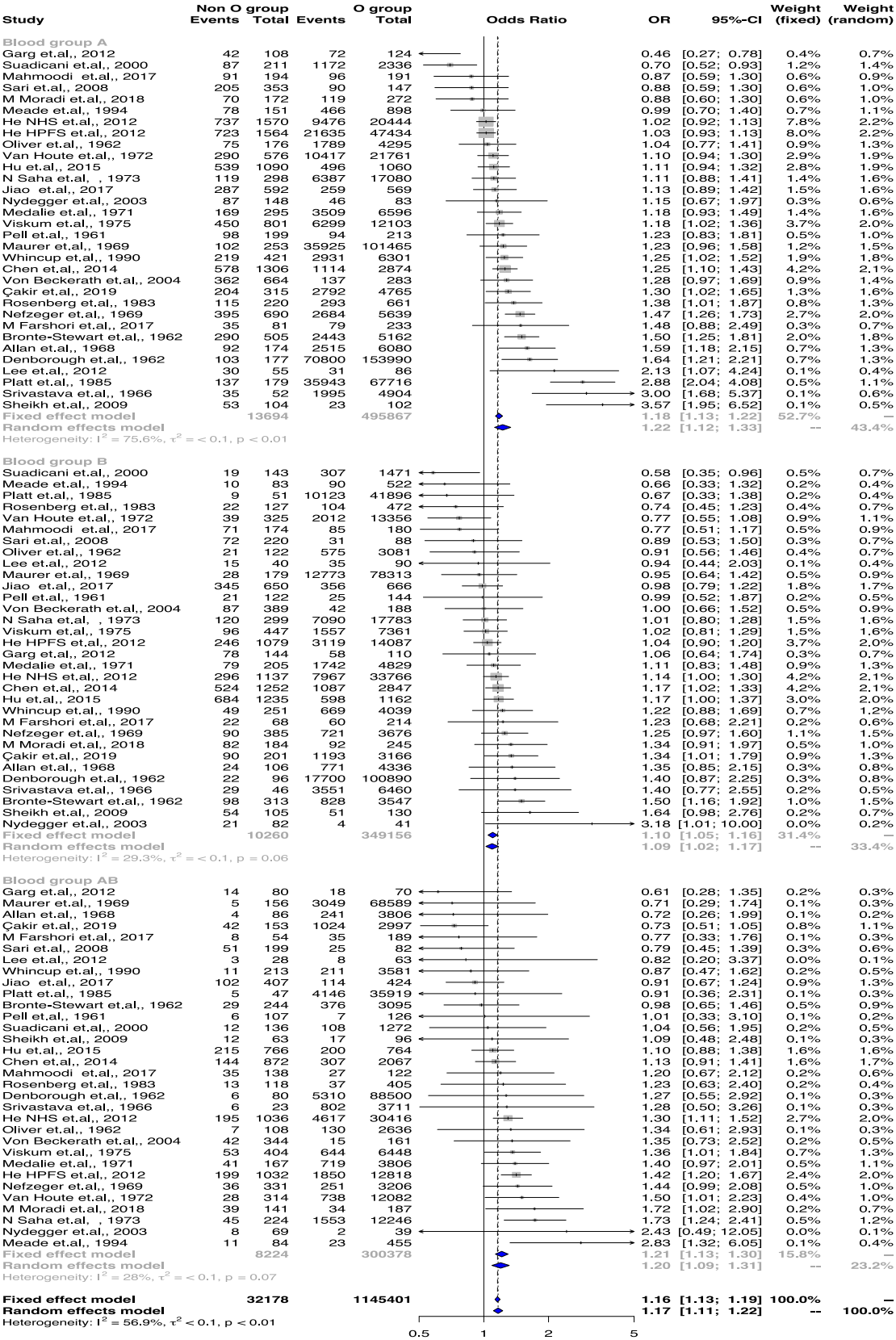

Fig. 3. *Continued*

(C) PVD

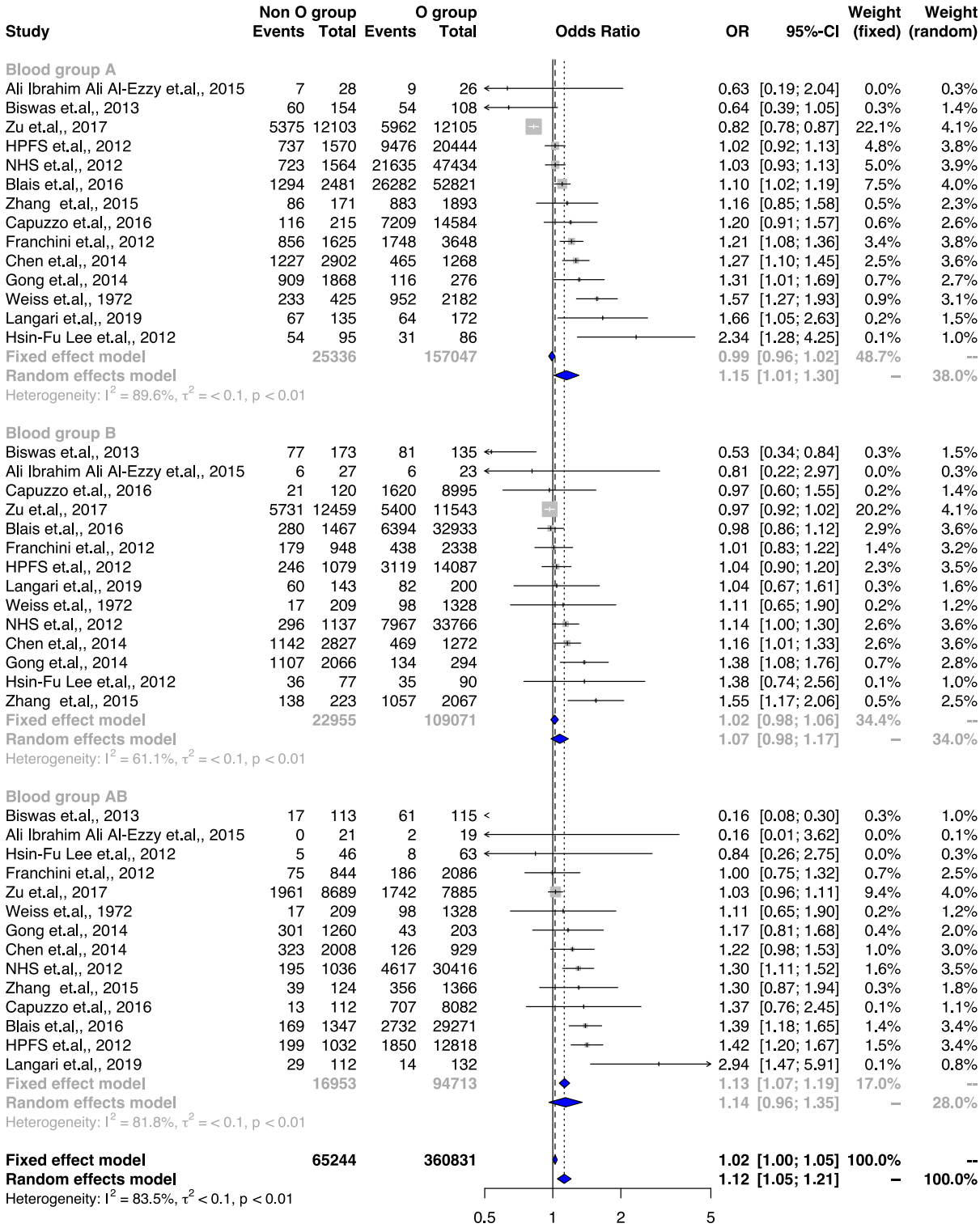

Fig. 3. *Continued*

group-AB had a statistically significant increase in MI compared with blood group-O (OR=1.20, 95%CI: 1.09-1.31, $P < 0.001$). In addition, there was statistically significant difference in MI between blood groups-B or O (OR=1.09, 95%CI: 1.02-1.17, P=0.01).

A symmetrical funnel plot suggested no significant publication bias (supplementary Fig. S2B). The risk of bias for the cohort and cross-sectional studies (Supplementary Fig. S2B.1) was lower than the case-control studies (Supplementary Fig. S2B.2). A few studies had unclear risk of bias due to lack of information or unsuitability of the control cohort or insufficient length of follow-up.

Blood type and PVD

A total of 17 studies comprising 9 case-control[59,61,65–71] (7,758 PVD cases & 26,521 controls), 8 cohort[25,54,68,72–75] (34,607 PVD cases & 178,404 controls) met our inclusion criteria (Fig. 1). Mean age of PVD cases and controls ranged between 18 and 90 years. All 18 studies were published in English from 1972 to 2019 totalling of 42,365 patients and 204,925 controls. The risk of PVD was significantly increased in patients with non-O blood group compared with blood group-O (OR=1.15, 95%CI: 1.04-1.28, P=0.005) (Fig. 2C), with high inter-study heterogeneity ($I^2 = 88.6\%$, $P < 0.01$).

A subgroup analysis to determine any statistically significant difference between the subtypes was undertaken in the 9 case-control and 8 cohort studies (supplementary Fig. S1C). Subject in blood group non-O had a statistically associated with PVD compared with blood group-O among case-control studies (OR=1.22, 95%CI: 1.00-1.49, P=0.05). In comparison to the case-control studies, there was a lower (but still statistically significant) incidence of non-O phenotype compared with blood group-O in the cases than in the controls resulting in a lower pooled OR of 1.11 (95%CI: 0.99-1.25, P=0.07) among cohort studies.

A subgroup analysis by individual blood groups (Fig. 3C) show that those with blood group-A had a statistically significant increase in PVD compared with blood group-O (OR=1.15, 95%CI: 1.01-1.30, P=0.03). However, there was no statistically significant difference in PVD between blood groups-B or AB and blood group-O (OR=1.07, 95%CI: 0.98-1.17, P=0.12; OR=1.14, 95%CI: 0.96-1.35, P=0.13, respectively).

A symmetrical funnel plot suggested no significant publication bias (Supplementary Fig. S2C). The risk of bias for the case-control studies (Supplementary Fig. S2C.1) showed high risk in six out of the nine studies, with bias observed for comparability in three of those studies. All the studies had adequate case definitions and ascertainment of exposure, thus were considered low risk. Three study designs[65,68,69] showed no risk of bias in any of the criteria, while the remaining studies did not exceed more than two criteria with a high risk of bias. Cohort studies (Supplementary Fig. S2C.2) had high-risk criteria for three of the eight studies. No study exceeded more than two high-risk parameters in the study design. The remaining five studies showed no risk of bias in any criteria.

Geographical variations

Data for individual ethnicity was not available to determine whether ancestry contributed to blood group variation and cardiovascular disease. However, in a surrogate attempt to address this question the analysis between blood group-O relative to non-O for IS, MI and PVD was stratified by geographical locations of Europe, Asian, North American or Africa. The risk of IS was significantly increased in patients with non-O blood group compared with blood group-O among Europe and North American population (OR=1.10, 95%CI: 1.03-1.19, $P < 0.001$; OR=1.10, 95%CI: 1.07-1.12, $P < 0.001$), respectively: the risk of MI was significantly increased in patients with non-O blood group compared with blood group-O among Europe, Asian, and North American population (OR=1.17, 95%CI: 1.05-1.30, $P < 0.001$; OR=1.13, 95%CI: 1.04-1.22, $P < 0.001$; OR=1.18, 95%CI: 1.05-1.32, $P < 0.001$), respectively: and, the risk of PVD was significantly increased in patients with non-O blood group compared with blood group-O among Europe and North American population (OR=1.33, 95%CI: 1.07-1.65, $P < 0.001$; OR=1.13, 95%CI: 1.01-1.27, $P < 0.001$), respectively. Unfortunately, there was insufficient data to analyse for the Africa population. A subgroup analysis by individual blood groups had no effect on the results, but some of the sample sizes were too small for analysis.

Discussion

Our comprehensive meta-analysis and systematic review shows that a non-O blood group is significantly associated with an increased risk for IS, MI, and PVD, with greater than 16% likelihood of increasing risk in each disease (Fig. 2). Our findings suggest that although non-O blood groups exhibit increased odds of IS, MI, and PVD, blood group-AB has the greatest risk associated with IS, and blood group-A has the greatest risk associated with MI and PVD in comparison to blood group-O. Blood group-B has the lowest risk associated with MI and no significant association with IS and PVD.

Data evaluating the association between ABO blood groups and IS is limited. However, a previous meta-analysis[4] on the association between IS and non-O blood groups in 6 studies revealed a pooled OR of 1.17. However, once this analysis was restricted to higher quality (cohort) studies, no association was seen, a result similar to our findings. Additionally, the relationship between non-O blood groups and IS has also been found by a study showing a reported pooled OR of 1.14, whilst another identified blood group AB as a major predictor of stroke severity[26,76]. The former is in line with our findings,

but we go on further to show that blood group-A was the (non-O) subgroup that most associated with IS.

This result was lower than the previous (smaller) meta-analyses by Wu et al.[76] which reported a pooled OR of 1.25 for non-O blood group with MI, while Dentali et al.[4] reported a similar pooled OR of 1.28. Furthermore, our analysis of prospective cohort studies[4] shows non-O group have an 8% increased risk associated with MI whilst previous studies have not demonstrate any association.[76] Blood group-A demonstrated the highest pooled OR of 1.22, followed by blood group-AB (OR 1.20), B (OR 1.09), and O respectively (A>AB>B>O).

Non-O blood groups (A, B and AB) individuals have regularly been found to demonstrate an increased prevalence of thrombosis whilst blood group-O individuals have a reduced predisposition. This higher risk is caused in part by the ABO blood group's influence on the plasma levels of vWF and haemostasis.[77,78] ABO blood groups are a key determinant of the wide variations observed in normal plasma vWF and FVIII levels with around 30% of the total plasma variation of vWF and 12% of FVIII explained by the ABO blood groups.[79] Moreover, blood group-O individuals are found to have 25% lower FVIII and vWF in their plasma than non-O individuals.[1,2] In addition to this, the AB blood phenotype is associated with the highest levels of vWF, followed by blood group B and then A.[2] Increased levels of vWF have also been associated with hypercholesterolemia, an additional risk factor for IS, MI and PVD.[80,81] Thus, the totality of evidence suggests that non-O blood groups are an important cardio- and cerebro-vascular predictive biomarker.[78]

Elevated levels of vWF/FVIII have been previously associated with the increased risk of IS, MI or PVD, it is plausible to assume that the increased association arising between blood group non-O and IS, MI or PVD could be down to the increased levels of vWF-FVIII which causes excessive blood clotting in non-O individuals leading to an ischemic stroke.[82–84] In addition to this, increased levels of vWF have also been associated with hypercholesterolemia, which is a major risk factor for ischemic stroke.[80,81] High cholesterol levels can lead to increased plaque formation which increases the likelihood of clot formation and IS, MI or PVD.

The reason a decrease in association was seen in blood group-B as compared with blood groups A and AB could also be due to differences in the ABO genotype. As the B allele encodes for a different glycosyltransferase to blood group A, that adds d-galactose onto the H antigen, this structural difference between blood groups A and B could explain the different associations observed. Furthermore, previous research identified genotypes A/B, A/A and A/O to contain the most vWF/FVIII levels, with genotypes O/O and B/O containing lower amounts of vWF/FVIII.[85] The findings are in support of this, as lower, insignificant associations were seen in the combined, case-control and cohort studies assessing the association between blood group B and IS.[86] This may imply blood group-B in exhibiting similar protective effects to blood group-O against IS and clot formation due to lower vWF/FVIII levels.

Individuals with non-O blood type have higher levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL) and non-high-density lipoprotein cholesterol.[59] Around 10% of the varying concentrations of cholesterol in serum can be linked to ery-apoB, which was demonstrated to be two-fold higher in the O blood group compared to each non-O blood group.[59] In addition, studies showed that LDL-c, and TC have their highest concentrations in blood group A followed by, AB, and B, while the lowest concentration was in blood group O.[87] Since HDL-c levels were higher in the non-O blood groups, it may suggest that the atherogenic properties of LDL-c exceed that of the cholesterol removal facilitated by HDL-c. Varying concentrations of cholesterol in serum can be linked to ery-apoB, which was demonstrated to be two-fold higher in the O blood group compared to each non-O blood group.[88] Ery-apoB mediates the attachment of LDL molecules to the erythrocyte membrane. It is postulated, that the carbohydrate groups on the apoB molecule interact with components of the A, B, and H antigens, affecting its efficacy and expression.[89] Due to the aforementioned observations ery-apoB has been described to have an atheroprotective effect, through facilitating the removal of serum cholesterol before it can be deposited in vasculature.

As with any meta-analysis several limitations need to be considered. Comparisons between B vs O, and AB vs O comprised of fewer participants as compared with A and non-O, which could lead to potentially imprecise estimates of the effect, although the overall number of participants was large. As there are no randomised controlled trials reporting on the link between ABO blood groups and IS, MI, and PVD, our data could only include case-control and prospective/retrospective cohort studies. Cohort studies have a lower potential risk of bias than case-controls[90] and show fewer significant associations, which may imply that the extent of observed association between IS, MI, PVD and ABO blood groups might lessen with larger datasets. Finally, interpreting the threshold of heterogeneity (I^2) can be misleading because the importance of inconsistency depends on several factors[10] such as the size and direction of the effect and the strength of evidence from the chi-square test of the heterogeneity *P*-value, or the confidence interval of I^2[91].

Confounding variables must be taken into account when determining the relationship between ABO blood groups and IS, MI, and PVD. The major risk factors for IS, MI and PVD including atrial fibrillation, and cardiometabolic risk (diabetes mellitus, hypertension, dyslipidaemia, obesity, and body fat distribution) as well as ethnicity, socio-economic status, diet, and lifestyle factors. The socio-economic status, diet and lifestyle factors which may influence morbidity and mortality was not able to be

considered with specific blood type. However, these effects are likely to be equally represented in a non-differential bias across all blood groups and cardiovascular end points. We did not seek associations with specific subtypes of stroke (large artery atherosclerosis, small vessel occlusion, cardio-embolism) as datasets were either unavailable or too small for reliable analysis.

Our work provides a robust foundation for the involvement of blood group and cardiovascular disease. Future work on this association will need to determine a causal relationship (perhaps using mendelian randomization) leading to a reliable mechanistic understanding for its aetiological basis and novel targeted treatment approaches.

Conclusions

In this comprehensive meta-analysis, we show that blood groups A and AB have a strong statistically significant association to IS, MI and PVD. The potential for identifying people at risk with targeted treatment and lifestyle preventative interventions should be considered.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article.

Contributors

PS conceived the study. PS and TH designed the methodology with some modifications by GKD. The study was undertaken by ZL, FH, MR, JI and PS. Data analysis was undertaken by ZL, FH, MR, JI and GKD. Data interpretation was done by all authors. The first draft of the manuscript was written by ZL, FH, MR, JI and GKD, and revisions were made by GKD, TH and PS. The final version was agreed by all authors. PS accepts overall responsibility for the manuscript.

Declaration of Competing Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2023.107215.

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