ABO blood group system and the coronary artery disease: an updated systematic review and meta-analysis

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ABO blood group system, a well-known genetic risk factor, has clinically been demonstrated to be linked with thrombotic vascular diseases. However, the relationship between ABO blood group and coronary artery disease (CAD) is still controversial. We here performed an updated meta-analysis of the related studies and tried to elucidate the potential role of ABO blood group as a risk factor for CAD. All detectable case-control and cohort studies comparing the risk of CAD in different ABO blood groups were collected for this analysis through searching PubMed, Embase, and the Cochrane Library. Ultimately, 17 studies covering 225,810 participants were included. The combined results showed that the risk of CAD was significantly higher in blood group A (OR = 1.14, 95% CI = 1.03 to 1.26, p = 0.01) and lower in blood group O (OR = 0.85, 95% CI = 0.78 to 0.94, p = 0.0008). Even when studies merely about myocardial infarction (MI) were removed, the risk of CAD was still significantly higher in blood group A (OR = 1.05, 95% CI = 1.00 to 1.10, p = 0.03) and lower in blood group O (OR = 0.89, 95% CI = 0.85 to 0.93, p < 0.00001). This updated systematic review and meta-analysis indicated that both blood group A and non-O were the risk factors of CAD.

In 1901, Karl Landsteiner, a Viennese MD and pathologist, discovered ABO blood group system which was the first human blood group1. From then on, studies on relation of ABO blood group system to various diseases have never been interrupted for a century, even in the popular era of gene detection, as ABO blood group is inherent in human's body and easily to be tested.

It has been reported that ABO blood group system is associated with cognitive impairment2, preeclampsia3, bleeding, neoplastic diseases4, and even longevity5. Among all of those studies, the mechanism of relationship between ABO blood group and venous thrombosis is elucidated6, and its major determinants are von Willebrand factor (vWF) and coagulation factor VIII7 which result in thrombosis. This interesting finding makes a theoretical hypothesis that ABO blood group may also be related to risk of coronary artery disease (CAD) and myocardial infarction (MI). Unfortunately, results of previous relevant studies are currently not convincing due to inconsistent conclusions. And previous studies including original observations and meta-analysis8–10 mainly paid attention to the blood group non-O and O, ignoring the blood group A and other blood types. Moreover, in those studies, links of ABO blood group with MI was often focused on; however, the relation between risk of CAD and ABO blood group was carelessly overlooked. Therefore, this updated systematic review and meta-analysis aims to evaluate the relationship between CAD and each type of ABO blood group.

Results

Description of included studies. Two hundred and thirty-one studies (231 from Pubmed and 0 from the Cochrane Library) were identified from two databases. Among them, 10 records were removed on account

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of duplicates. By screening titles and abstracts, we excluded 147 records on account of animal experiments, traditional reviews, improper or lack of comparison, or other blood group classification systems rather than ABO blood type. By browsing full-text articles, we excluded 58 records because of improper or lack of comparison, other confounding factors, irrelevant to the outcomes of this study and unavailable outcomes. At last, a total of 16 articles11–26 which met inclusion criteria were included into this systematic review. A flow-chart of study selection was generated according to the PRISMA requirements (Fig. 1).

Study characteristics. One15 of these 16 articles contained 2 studies. All the 17 studies were published in English from 1961 to 2014. Eleven articles11,13,14,16,17,19,21–23,25,26 were case-control studies, 2 articles12,15 were prospective cohort studies and 3 articles18,20,24 were retrospective cohort studies. Finally, a total of 225,810 patients were included. All studies described race and characteristic of the two groups. Nine studies 12,16,17,19–24 merely mentioned MI. Two studies12,17 only differentiated blood group non-O from blood group O. The remaining studies described all blood types. (Basic characteristics of included studies were presented in Table 1 and blood types distribution and outcome definitions of included studies were presented in Table 2, and Newcastle-Ottawa Scale (NOS) table was shown in Table 3).

Main, subgroup and sensitivity analysis. All the 17 studies were included in this meta-analysis. Because of unnegligible heterogeneity in them, we conducted a subgroup analysis according to the research types (case-control study, prospective or retrospective cohort study) and used random-effect model27. Risk of CAD was significantly increased in patients with blood group A compared with blood group non-A (odds ratio (OR) = 1.14, 95% confidence intervals (CI) = 1.03 to 1.26, p = 0.01). Subjects in blood group A had a statistical increase in CAD incidence in case-control studies (OR = 1.14, 95% CI = 1.04 to 1.26, p = 0.005) with moderate heterogeneity (I² = 45%), while there was no statistical difference between blood group A and non-A in cohort studies (Fig. 2). Besides, risk of CAD had no statistical significant difference in patients with blood group B, AB compared with non-B, non-AB, respectively (Figs 3 and 4). Whereas, in contrast to the result of blood group A, blood group O was proved to be a protective factor in our analysis, presenting a decrease of CAD risk (OR = 0.86, 95% CI = 0.86 to 0.99, p = 0.04) in spite of high heterogeneity (F² = 78%), which is similar to prospective cohort studies (OR = 0.94, 95% CI = 0.89 to 0.98, p = 0.009) with no heterogeneity (I² = 0). However, there was no statistical significant difference in CAD incidence in retrospective cohort studies (OR = 0.58, 95% CI = 0.35 to 0.97, p = 0.04) with high heterogeneity (F² = 70%) (Fig. 5). In the
| Study year, study type | Reference | Total number of subjects | Age | Gender | Race | Patients with events | Controls |
|-----------------------|-----------|--------------------------|-----|--------|------|----------------------|---------|
| 2014                  | Chen      | 6242                     | 64.11 ± 11.42 | Chinese | consecutive patients undergoing diagnostic or interventional coronary angiography, who were finally diagnosed CAD or MI | consecutive patients undergoing diagnostic or interventional coronary angiography, who were not diagnosed CAD or MI |
| 2013                  | Gong      | 3806                     | 53.9 ± 9.9 | male (71%) | Chinese | angiographically documented CAD or diagnosed as MI | the patients without CAD or MI |
| 2013                  | Biswas    | 500                      | cases (mean: 54.71 years) and controls (mean: 54.49 years) (P > 0.05) | females constituted 18.4% of the cases and 16.8% of the controls and males constituted 81.6% of cases and 83.2% of the controls (P > 0.05) | Indian Bengali adults | Patients having typical angina and evidence of ischemia or infarction after electrocardiographic study, treadmill test, stress echo and echocardiographic study | the general population of Copenhagen without diagnoses of MI and IHD |
| 2013                  | Sode      | two prospective cohort studies | the Copenhagen general population study (25,900) + the Copenhagen city heart study (40,097) = 65,997 | aged 20–100 years | women (36,562); men (29,439) | white and of Danish descent | the patients with myocardial infarction (defined as ICD-8 code 410 and ICD-10 codes I21–I22) |
| 2013                  | Franchini  | 6151                     | mean age: 77 years in the CHD group; 34 years in the control group | females: 34.9% in the CHD group; 46.7% in the control group | Italians | the patients with coronary heart disease (CHD) | the healthy general population |
| 2012                  | He        | two prospective cohort studies | [NHS]2073 | aged 30–55 years | women | American (different ethnicities) | incident cases of CAD | patients in the same cohort who did not occur coronary heart disease |
| 2008                  | Sari      | case-control study | [HPFS]2742 | aged 40 to 75 years | male | American (different ethnicities) | incident cases of CAD | patients in the same cohort who did not occur coronary heart disease |
| 2006                  | Tanis     | case-control study | 826 | between 18 and 49 yr of age | women | Netherlands | the patients suffered from MI | women contacted by random-digit dialing, stratified for age, index year for MI, and area of residence |
| 2006                  | Amirzadeh | case-control study | 2026 | a mean age of 59 years | 1512 males (75.4%) and 494 females (24.6%) | Iranian | the patients with premature CAD defined as development of CAD under 45 years old | the patients without premature CAD defined as development of CAD under 45 years old |
| 2003                  | Nydegger  | case-control study | 266 | median age 57.0 years; range 32–72 years | 87.6% men in patients, 88.8% men in controls | Caucasian | survivors of an acute myocardial infarction that had occurred at least 2 months before inclusion in the study | healthy Caucasian without a history of thromboembolic events or tendency to bleed, were frequency-matched to the cases by age (50–55 years) and sex |
| 1985                  | Platt     | case-control study | 450 | 66/450 (age < 65 years) 384/450 (age ≥ 65 years) | 139/450 (male) | German | the patients with cardiac infarction | sample of the German population |
| 1973                  | Saha      | case-control study | 26186 | age ≥ 20 years | NR | Chinese | the patients with myocardial Infarction | the healthy individuals (matched for race and sex) |
| 1968                  | Allan     | case-control study | 7294 | NR | the ABO blood group distribution is almost exactly the same for men and women. | British | the patients with myocardial infarction | consecutively-registered blood donors |
| 1963                  | Gjorup    | case-control study | 15,150 | NR | 610/846 (Male) 236/846 (women) in case group | Danes | the patients with coronary occlusion | blood donors from the same area |
| 1961                  | Pell      | retrospective cohort study | 471 | from 17 through 64 years | NR | American | the medical records of the 438 employees (coronary patients) who had a first coronary attack of coronary thrombosis and or myocardial infarction during 1957 and 1958 | the records of the 438 matched controls (the controls were drawn at random from a complete listing of company employees with the aid of a table of random numbers, and were matched to each case in our study by age, sex, payroll classification, and geographical location) were reviewed to compare the occurrence of certain chronic diseases in the two groups |

Table 1. Characteristics of included studies. NR: not report. CAD: coronary artery disease. MI: myocardial infarction.
| Study year, reference | A, non-A | B, non-B | AB, non-AB | O, non-O | Outcome definitions |
|----------------------|---------|---------|------------|---------|---------------------|
| Chen 2014            | 1227/1692, 3150/4550 | 1142/1611, 3235/4631 | 323/451, 4054/5791 | 1685/2488, 2692/3754 | CAD: Significant CAD indicated by >50% stenosis in ≥1 coronary artery in angiography. |
| Gong 2014            | 909/1026, 2434/2780 | 1106/1241, 2237/2565 | 367/410, 2976/3396 | 961/1129, 2382/2677 | significant angiographically documented CAD as having >50% diameters stenosis in ≥1 major coronary artery |
| Biswas 2013          | 60/114, 190/386 | 77/158, 173/342 | 17/78, 233/422 | 96/150, 154/350 | CAD: typical angina and evidence of ischemia or infarction |
| Sode 2013            | 856/2604, 1023/3547 | 179/617, 1700/5534 | 75/261, 1804/5890 | 769/2669, 1110/3482 | coronary artery disease (CHD) |
| Franchini 2013       | 723/22358, 1332/39715 | 296/8263, 1759/53810 | 195/4812, 1860/57261 | 841/26640, 1214/35433 | coronary artery disease (CHD) |
| He 2012 [NHS]        | 723/22358, 1332/39715 | 296/8263, 1759/53810 | 195/4812, 1860/57261 | 841/26640, 1214/35433 | coronary artery disease (CHD) |
| He 2012 [HPFS]       | 737/10213, 1272/17215 | 246/3365, 1769/24063 | 199/2049, 1816/25379 | 833/11801, 1182/15627 | coronary artery disease (CHD) |
| Lee 2012             | 54/85, 82/180 | 36/71, 100/194 | 5/13, 131/252 | 41/96, 95/169 | presence of CAD was defined as >50% stenosis in at least 1 major coronary branch, on coronary angiography. |
| Sari 2008            | 205/295, 271/384 | 72/103, 4054/576 | 51/76, 425/603 | 148/205, 326/474 | MI: based on typical chest pain for at least 30 min, ST elevation of 0.2 mV or more in at least 2 contiguous electrocardiogram leads and confirmatory elevations of at least two-fold in serum creatine kinase-MB isoenzyme levels |
| Tanis 2006           | 25/127, 325/4550 | 15/24, 300/4550 | 5/9, 184/412 | 34/145, 317/535 | acute MI |
| Amirzadegan 2006     | 60/650, 148/1376 | 59/503, 149/1523 | 8/153, 200/1873 | 8/153, 127/1306 | premature CAD defined as development of CAD under 45 years old |
| Nydegger 2003        | 87/133, 90/133 | 21/25, 156/241 | 8/10, 169/256 | 61/98, 116/168 | acute myocardial infarction |
| Platt 1985           | 137/253, 56/197 | 9/38, 184/412 | 5/14, 188/436 | 42/145, 151/305 | cardiac infarction: NR |
| Saha 1973            | 119/6506, 344/19680 | 120/7210, 343/18976 | 45/1598, 418/24588 | 179/10872, 284/15314 | myocardial Infarction: all cases of myocardial infarction as confirmed by clinical, electrocardiographic, and biochemical investigations |
| Allan 1968           | 92/2607, 110/4687 | 774/795, 178/6499 | 4/245, 198/7049 | 82/3647, 120/3647 | myocardial Infarction: unequivocal electrocardiographic evidence of recent infarction, or if appropriate rises in serum transaminase levels occurred where myocardial changes were masked, as, for example, by a bundle-branch-block pattern |
| Gjørup 1963          | 372/6671, 474/8479 | 93/1650, 753/13500 | 36/680, 810/14470 | 345/6149, 501/9001 | coronary occlusion: typical ECG abnormalities combined with characteristic pains |
| Pell 1961            | 98/192, 128/279 | 21/46, 205/425 | 6/13, 220/458 | 101/220, 125/251 | MI/NR |

Table 2. Blood types distribution and outcome definitions of included studies. NR: not report. CAD: coronary artery disease. MI: myocardial infarction.

Sensitivity analysis, exclusion of any single study did not substantively alter the overall result in blood group A, B, AB and O. In order to exclude the effect of established positive relationship between ABO blood group and MI, we removed the studies\(^2,16,17,19-24\) which only paid attention to MI patients and found the similar relationship between ABO blood group and CAD as before, namely, A (OR = 1.05, 95% CI = 1.00 to 1.10, p = 0.03) and O (OR = 0.89, 95% CI = 0.85 to 0.93, p < 0.00001).

Furthermore, risk of MI was significantly higher in blood group A (OR = 1.24, 95% CI = 0.97 to 1.59, p = 0.08) compared with non-A group. Nevertheless, patients with blood group B or AB compared to non-B or non-AB, respectively, had no statistical differences in MI incidence (OR = 0.94, 95% CI = 0.74 to 1.18, p = 0.59; OR = 1.11, 95% CI = 0.91 to 1.35, p = 0.31). However, an overall effect was detected to be statistically different when comparing blood group O with non-O for the risk of MI (OR = 0.81, 95% CI = 0.69 to 0.94, p = 0.007).

Publication bias. We generated a funnel plot to assess publication bias. Exploration for the funnel plot of the blood group O in CAD suggested no asymmetry. No obvious evidence of publication bias was present in the comparison of blood group O (Fig. 6).

Discussion

Previous systematic reviews and meta-analysis paid more attention to the relationship between MI and ABO blood group, but the link of ABO blood group system to CAD was rarely evaluated. Besides, almost all available studies principally focused on blood type non-O and O. Hence, the relation between ABO blood group and risk of CAD is worthy to be assessed scientifically and strictly.
Our meta-analysis involved 16 articles (17 studies) covering 225,810 individuals. It was suggested that the risk of CAD in blood group A was mildly increased compared with that in blood group non-A ($OR = 1.14$). Meanwhile, we investigated the relationship of blood group B, AB compared with non-B, non-AB, respectively, but failed to confirm statistical difference. Moreover, our results indicated that the risk of CAD in blood group O was significantly lower than that in non-O groups ($OR = 0.85$), which is similar to previous studies.28

To our knowledge, this is the first meta-analysis involved the relationship between the risk of CAD and blood group A and non-A. Several clinical studies have provided direct evidence with different results. Whincup et al.28 found that the incidence of ischaemic CAD was higher in those with blood group A than that with blood group non-A ($OR = 1.21, 95\% CI = 1.01$ to $1.46$). A study from Wazirali et al.29 suggested that blood group A was associated with a substantially increased risk of CAD, which is independent of conventional cardiovascular risk factors. Whereas, another research did not support this association and indicated that the risk of CAD in blood group A was lower than that in other blood groups.30 As we known, meta-analyses provide advance over traditional single studies. That is a reason why we performed a meta-analysis for further evaluating the relation of blood group A to the risk of CAD. In our study, we affirmed blood group A was a risk factor, which is more convincing and reliable. Similar evidence was more robust in the analysis for MI incidence ($OR = 1.24$).

Figure 2. Forest plot of blood group A.

| Experimental | Control | Odds Ratio | | | | | | | | |
|--------------|---------|------------|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Weight | M-H. Random. 95\% CI | | | | | | |
| case-control studies | | | | | | | | | | |
| Allan 1968 | 92 | 2607 | 110 | 4687 | 6.1\% | 1.52 [1.15, 2.02] | | | |
| Biowas 2013 | 60 | 114 | 190 | 366 | 4.0\% | 1.15 [0.75, 1.74] | | | |
| Chen 2014 | 1227 | 1692 | 3150 | 4850 | 9.6\% | 1.17 [1.04, 1.33] | | | |
| Franchini 2013 | 856 | 2604 | 1023 | 3947 | 9.9\% | 1.21 [1.08, 1.35] | | | |
| GjáRúP 1963 | 372 | 6671 | 474 | 8479 | 9.3\% | 1.00 [0.87, 1.15] | | | |
| Gong 2014 | 909 | 1026 | 2434 | 2780 | 7.4\% | 1.10 [0.88, 1.38] | | | |
| Lee 2012 | 54 | 65 | 82 | 160 | 2.8\% | 2.08 [1.23, 3.54] | | | |
| Nydegger 2003 | 87 | 133 | 90 | 133 | 3.0\% | 0.90 [0.54, 1.50] | | | |
| Saha 1973 | 119 | 6506 | 344 | 19680 | 7.7\% | 1.05 [0.85, 1.29] | | | |
| Sari 2008 | 205 | 255 | 271 | 384 | 5.2\% | 0.95 [0.68, 1.32] | | | |
| Subtotal (95\% CI) | 21733 | 44806 | 65.1\% | 1.14 [1.04, 1.26] | | | | | |
| Total events | 3981 | 8168 | | | | | | | |
| Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 16.48$, df = 9 ($P = 0.06$); $I^2 = 45\%$ | | | | | |
test for overall effect: $Z = 2.79$ ($P = 0.005$) | | | | | |

| prospective cohort studies | | | | | | | | | | |
| He 2012 (HPFS) | 733 | 192687 | 1272 | 324625 | 10.3\% | 0.98 [0.89, 1.07] | | | |
| He 2012 (NHIS) | 723 | 564896 | 1332 | 1022248 | 10.3\% | 0.96 [0.88, 1.05] | | | |
| Subtotal (95\% CI) | 757583 | 1326873 | 20.6\% | 0.97 [0.91, 1.03] | | | | | |
| Total events | 1460 | 2694 | | | | | | | |
| Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.04$, df = 1 ($P = 0.84$); $I^2 = 0\%$ | | | | | |
test for overall effect: $Z = 0.95$ ($P = 0.34$) | | | | | |

| retrospective cohort studies | | | | | | | | | | |
| Amiranadegan 2006 | 60 | 650 | 148 | 1376 | 5.5\% | 0.84 [0.62, 1.16] | | | |
| Fell 1981 | 98 | 192 | 128 | 279 | 4.6\% | 1.23 [0.85, 1.78] | | | |
| Platt 1985 | 137 | 253 | 56 | 197 | 4.2\% | 2.97 [2.00, 4.42] | | | |
| Subtotal (95\% CI) | 1096 | 1852 | 14.4\% | 1.44 [0.71, 2.96] | | | | | |
| Total events | 295 | 332 | | | | | | | |
| Heterogeneity: $\tau^2 = 0.37$; $\chi^2 = 24.00$, df = 2 ($P < 0.00001$); $I^2 = 92\%$ | | | | | |
test for overall effect: $Z = 1.01$ ($P = 0.31$) | | | | | |

| Total (95\% CI) | 780411 | 1373531 | 100.0\% | 1.14 [1.03, 1.26] | | | | | |
| Total events | 5736 | 11104 | | | | | | | |
| Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 58.46$, df = 14 ($P < 0.00001$); $I^2 = 76\%$ | | | | | |
test for overall effect: $Z = 2.46$ ($P = 0.01$) | | | | | |
test for submean differences: $\chi^2 = 8.95$, df = 2 ($P = 0.01$); $I^2 = 77.7\%$ | | | | | |
MI and angina in 2008. In their study, taking group O as index, group A and non-O were related to an increase in MI risk (OR = 1.29, 95% CI = 1.16 to 1.45, p < 0.00001, OR = 1.25, 95% CI = 1.14 to 1.36, p < 0.00001), while no similar effect was found in the risk of angina. Furthermore, a meta-analysis by Dentali et al. found that patients with blood group non-O presented a higher prevalence of MI than that with blood group O (OR = 1.28, 95% CI = 1.17 to 1.40, p < 0.001). Takagi et al. enrolled 10 studies with a total of 174,945 participants and demonstrated a 14% increase in CAD incidence in individuals with blood group non-O compared to that in blood group O (OR = 1.14, 95% CI = 1.04 to 1.25, p < 0.006). All in all, the quantitative results from these meta-analyses and our one provided plenty of evidence on the close relationship between risk of CAD and blood group non-O.

The underlying mechanism of the relationship between blood group O and CAD has been clarified. ABO antigen may affect plasma levels of vWF and coagulation factor VIII, and blood group non-O has the lowest expression of O antigen and relatively higher levels of vWF and factor VIII. That blood group O is a potentially important genetic risk factor for bleeding, which also supports this mechanism theory. Another biologically plausible mechanism involves in glycotransferase-deficient enzyme which renders the ABO blood group to encode O phenotype, resulting in protection of subjects from MI risk. The latest study reveals that serum lipid mediates the effect of ABO blood group on CAD. In fact, blood group A is one of the risk factors of CAD mainly due to higher serum total cholesterol (TC) concentration in subjects. Our recent study also indicated that there is an association between blood group A and risk of CAD, and around 10.5% of the effect of blood group A on CAD is mediated by TC levels.

Figure 3. Forest plot of blood group B.
It was mentioned that there were several potential limitations in this study. Firstly, there was certain heterogeneity between various studies. Although we performed subgroup analyses, it was still different among the studies in blood testing methods and diagnostic criteria of CAD, race, life and eating habits, religious beliefs, socio-economic patterns, and concern of the disease, which might result in the heterogeneity. Secondly, we did not find unpublished studies, which may bring about publication bias.

In conclusion, this updated meta-analysis suggests that blood group A and non-O are associated with an increased risk of CAD. However, considering the heterogeneity of included studies and limited number of studies, more rigorous studies with high quality are needed to give high level of evidence to confirm this association.

**Methods**
This meta-analysis was performed according to the MOOSE group guidelines of observational meta-analyses.

**Data sources and searches.** Two reviewers (Zhuo Chen and Sheng-Hua Yang) searched Pubmed and the Cochrane Library from their inception to August 15, 2015 in order to identify all existing literature which assessed the association between ABO blood group and CAD. Mesh vocabulary and free text terms were used for each database with relevant key words such as blood grouping and cross-matching, ABO blood group system, blood group antigens, myocardial ischemia, myocardial infarction, acute coronary syndrome and angina pectoris. Language was limited to English. There was no limitation of country and publication date.
To ensure comprehensive acquisition of studies, the reference lists of the included articles were also manually screened to identify additional eligible studies. Manual searches were also performed on other databases, including Web of Science, and Google Scholar. Furthermore, databases of ongoing trials were also searched: Clinical Trials.gov (http://clinicaltrials.gov/) and Current Controlled Trials (http://www.controlled-trials.com/).

**Study selection.** Studies were independently identified by two reviewers (Zhuo Chen and Sheng-Hua Yang) according to inclusion criteria. Disagreements were resolved through discussion and decided by a third reviewer. Both case-control and cohort studies were included if they met all the following criteria: 1) patients with CAD or even MI; 2) separate data for patients with or without CAD were provided; 3) diseases were objectively diagnosed in line with the diagnosis level at the time; 4) a clear extractable ABO blood group typing. Patients included were regardless of age and race.

**Data extraction and quality assessment.** The retrieved papers were subjected to a rigorous extraction by two authors (Zhuo Chen and Sheng-Hua Yang) independently according to a predesigned form. Disagreements were resolved by consensus or consulted from the third author (Hao Xu). We did not try to contact authors to obtain unpublished data. The methodological quality of studies was assessed using the NOS.

| Study or Subgroup | Experimental Events | Control Events | Total Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|---------------------|----------------|--------------|-------------------------------|
| case-control studies |                     |                |              |                               |
| Allan 1968        | 82                  | 3647           | 120          | 3647                          | 5.2% | 0.68 [0.51, 0.90] |
| Biswas 2013       | 96                  | 150            | 154          | 350                          | 3.6% | 2.26 [1.52, 3.38] |
| Chen 2014         | 1665                | 2488           | 2862         | 3754                         | 9.1% | 0.83 [0.74, 0.92] |
| Franchini 2013    | 769                 | 2699           | 1110         | 3482                         | 9.1% | 0.86 [0.77, 0.97] |
| GjERUP 1963       | 345                 | 6149           | 501          | 9001                         | 8.4% | 1.01 [0.88, 1.16] |
| Gong 2014         | 961                 | 1129           | 2382         | 2677                         | 6.9% | 0.71 [0.58, 0.87] |
| Lee 2012          | 41                  | 96             | 95           | 169                          | 2.5% | 0.58 [0.35, 0.96] |
| Nydegger 2003     | 61                  | 98             | 116          | 168                          | 2.4% | 0.74 [0.44, 1.25] |
| Saha 1973         | 179                 | 10872          | 284          | 15314                        | 7.3% | 0.89 [0.73, 1.07] |
| Sari 2008         | 148                 | 205            | 328          | 474                          | 4.0% | 1.16 [0.80, 1.66] |
| Tanis 2006        | 66                  | 359            | 134          | 467                          | 4.4% | 0.56 [0.40, 0.78] |
| Subtotal (95% CI) | 2785                | 39503          | 62.7%        | 0.86 [0.75, 0.99]            |
| Total events      | 4433                | 7916           |              |                               |

Heterogeneity: Tau² = 0.04; Ch² = 46.31, df = 10 (P < 0.00001); I² = 78%
Test for overall effect: Z = 2.07 (P = 0.04)

| prospective cohort studies |                     |                |              |                               |
|-----------------------------|---------------------|----------------|--------------|-------------------------------|
| He 2012 (HPFS)              | 833                 | 11801          | 1182         | 15627                         | 9.5% | 0.93 [0.85, 1.02] |
| He 2012 (NHS)               | 841                 | 26640          | 1214         | 35433                         | 9.5% | 0.92 [0.84, 1.00] |
| Sode 2013                   | 1035                | 25900          | 1673         | 40087                         | 9.7% | 0.96 [0.88, 1.03] |
| Subtotal (95% CI)           | 64341               | 91147          | 28.7%        | 0.94 [0.89, 0.98]            |
| Total events                | 2709                | 4069           |              |                               |

Heterogeneity: Tau² = 0.00; Ch² = 0.46, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)

| retrospective cohort studies |                     |                |              |                               |
|-----------------------------|---------------------|----------------|--------------|-------------------------------|
| Amirzadehag 2006            | 8                   | 153            | 127          | 1306                          | 1.4% | 0.51 [0.25, 1.07] |
| Pell 1961                   | 101                 | 220            | 125          | 251                           | 4.0% | 0.86 [0.60, 1.23] |
| Platt 1965                  | 42                  | 145            | 151          | 305                           | 3.2% | 0.42 [0.27, 0.63] |
| Subtotal (95% CI)           | 518                 | 1862           | 8.6%         | 0.58 [0.35, 0.97]            |
| Total events                | 151                 | 403            |              |                               |

Heterogeneity: Tau² = 0.14; Ch² = 6.71, df = 2 (P = 0.03); I² = 70%
Test for overall effect: Z = 2.09 (P = 0.04)

| Total (95% CI)              | 92721               | 132512         | 100.0%       | 0.85 [0.78, 0.94]            |
| Total events                | 7293                | 12388          |              |                               |

Heterogeneity: Tau² = 0.02; Ch² = 66.34, df = 16 (P < 0.00001); I² = 76%
Test for overall effect: Z = 3.36 (P = 0.0008)
Test for subgroup differences: Ch² = 4.41, df = 2 (P = 0.11). I² = 54.7%

Figure 5. Forest plot of blood group O.
We rated cohort studies a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for outcome assessment. The maximum score of case-control studies for selection, comparability, and exposure assessment was 4, 2, 3, respectively, too. The highest score is 9, and more stars meant better quality.

Data analysis and synthesis. Revman 5.2 software (The Cochrane Collaboration, Oxford, UK) was used for data analyses. We presented dichotomous data as OR and its 95% CI. Data were assessed by both random and fixed effect models, but only the random effect analyses were reported if the heterogeneity was significant evaluated by the I² statistic which assessed the appropriateness of pooling all studies. A funnel plot was used to assess publication bias.
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Author Contributions

J.-J.L. and H.X. conceived and designed the review and provided methodological perspectives; Z.C. and S.-H.Y. developed the search strategy and did the literature search, study selection, data extraction, data analyses and interpretation.

Additional Information

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