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ABO blood group as a risk factor for tuberculosis: A network meta-analysis

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ABSTRACT

Background: Despite numerous studies on ABO blood group and risk of tuberculosis, no consensus has been reached.
Methods: We conducted a systematic review following the Meta-Analysis of Observational Studies in Epidemiology group statement. English language articles providing odds ratio data regarding tuberculosis risk among ABO groups were eligible. Least-squares approach random-model network and random-model pairwise meta-analyses were conducted. The protocol-specified primary outcome was tuberculosis risk among ABO groups in the form of odds ratios calculated via a network meta-analysis.
Results: We identified 28 studies with 30 populations comprising 15,664 patients with tuberculosis and 254,610 controls. Subjects with AB blood type had a higher risk of becoming infected with tuberculosis than those with blood type O (odds ratio (OR) = 1.26, 95% confidence interval (CI): 1.14–1.38), A (OR = 1.25, 95% CI: 1.14–1.38), and B (OR = 1.22, 95% CI: 1.11–1.34). Pairwise comparison revealed that AB blood type was a risk factor for tuberculosis with OR = 1.23 (95% CI: 1.02–1.48) compared to other blood types. Region-based subgroup analyses suggested that the AB blood group was a substantial risk in Africa (OR = 1.78, 95% CI: 1.39–2.28) and India (OR = 1.48, 95% CI: 1.14–1.92).
Conclusions: AB blood group is a risk factor for tuberculosis of a substantial magnitude in Africa and India.

Key points

Our systematic review and meta-analysis included 30 populations comprising 15,664 patients with tuberculosis and 254,610 controls and showed that AB blood group was a risk factor for tuberculosis.

Introduction

Tuberculosis is a communicable disease caused by *Mycobacterium tuberculosis*, which spreads from person to person through the air. Globally, an estimated 1.5 million people died, with 10 million new tuberculosis cases in 2019 (World Health Organization, 2019). Well-established risk factors for tuberculosis disease include human immunodeficiency virus infection, malnutrition, diabetes, alcohol abuse, use of immunosuppressive drugs, and exposure to tobacco smoke (Narasimhan et al., 2013).

The ABO blood grouping system was originally discovered to improve the safety of blood transfusions in the early 20th century. Each of the two alleles carries antigen A, B, or neither. The combination of these alleles determines the blood type phenotype of an individual, which may be O, A, B, or AB. Since its discovery, there has been an ongoing interest in the potential role of the ABO blood group system in modulating infectious disease risk (Cooling, 2015). People with a specific blood group may have an increased or decreased risk of contracting infectious diseases. For example, persons with blood type O appeared to be more susceptible to norovirus infection (Liao et al., 2020a), and individuals who did not have blood type O were more susceptible to schistosomiasis (Tiongco et al., 2018). Individuals with B or AB blood groups are reportedly less likely to be infected with *Helicobacter pylori* (Chakrani et al., 2018). A recent genome-wide association study

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demonstrated a potential link between blood groups and the risk of contracting coronavirus disease-19 (Ellinghaus et al., 2020). Similarly, numerous studies have been conducted to elucidate the influence of ABO blood groups on the risk of tuberculosis since the 1920s (Raphael et al., 1927). However, no consensus could be reached because of inconsistent results among studies and insufficient statistical power in each study.

Here, we performed a systematic review and meta-analysis to assess the association between ABO blood group and the risk of tuberculosis using data from various regions in the world.

Methods

Overview

This study was designed according to the Meta-Analysis of Observational Studies in Epidemiology group statement and was registered on the University Hospital Medical Information Network (ID: UMIN000039721, e-Table 1) (Cooperative organization for national medical schools in Japan, 2020; Stroup et al., 2000). The requirement for Institutional Review Board approval was waived as this was a systematic review.

Study search

Four major databases (Medline, Cochrane, Web of Science, and Embase) were searched on March 5, 2020 to identify candidate articles using the strategy shown in e-Table 2. HC and NH independently performed the search and data extraction, and subsequently built a consensus. A hand search was conducted by three review authors (HC, HM, and NH) by checking the reference list of included studies. When the data in an article were questionable, review authors attempted to contact the authors.

Study selection, study design and publication type

We included cross-sectional and case-control studies that provided data required to calculate odds ratios (ORs). Non-English reports were excluded as old non-English articles were often not accessible. Short article and conference abstracts were included.

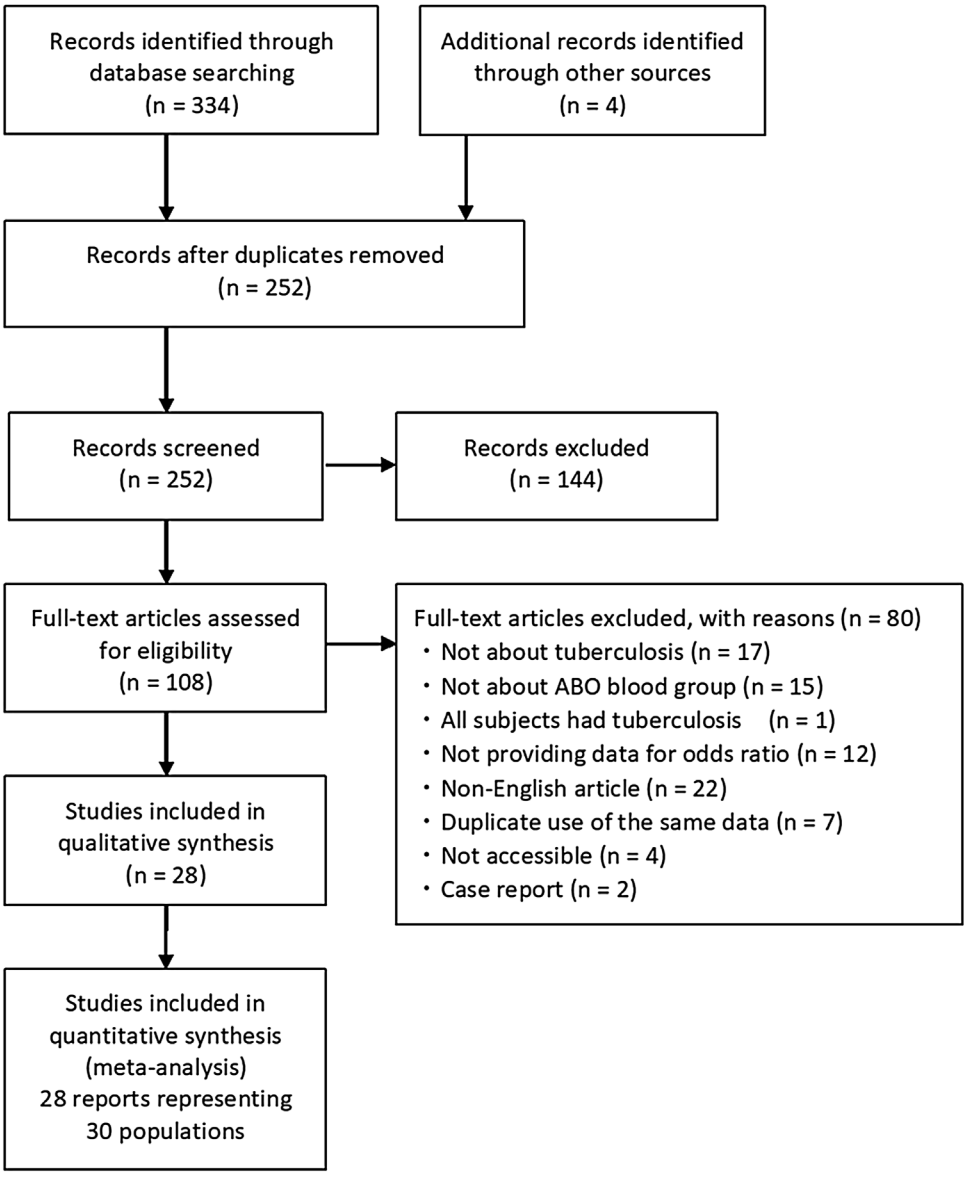

Figure 1. PRISMA flow chart.

Table 1
Background characteristics of the included 28 studies

Author (year)	Country	Region	Population	Pt age (year)	TB type	TB test	ABO test	Control	NOS
Raphael (1927)	USA	Michigan	88% European		97% PTB		Cross-agglutination	American workers	5
Weinberger (1943)	UK	Papworth village			TB		Agglutination (forward)	Healthy control	5
Sen (1952)	India	Calcutta	Mostly Bengalee Hindus		surgical PTB		Glass slide agglutination	Race/location matched blood bank donor	5
Campbell (1956)	UK	Glasgow		15-	TB			Blood donor	4
Kooptzoff (1957)	Australia	Sydney	Australian		PTB		Agglutination (forward)	White Australian	5
Buckwalter (1961)	South Africa		Bantu, Indian		75% PTB		Isohemoagglutination	Prepartum woman, blood donor, friends, relative	5
Lewis (1961)	UK	London	Caucasian					London resident, historical cohort	4
Shenoy (1962)	India	Bombay			PTB		Agglutination (reverse)	blood donor	5
Kothare (1964)	India	Bombay Sewri	Marathi		PTB		Agglutination (reverse)	Community resident	5
Nand (1964)	India				Osteo-articular TB				4
Gupta (1966)	India	Gwalior			PTB	Sputum positive	Dacie's methods	normal individual, historical control,	6
Saha (1968)	Singapore		Malays, Indian		PTB	Clinical, sputum exam, Xray	Agglutination (reverse)	Historical control	6
Jain (1970)	India	Jaipur			PTB	Sputum exam, X-ray		Apparently healthy individuals	5
Saha (1973)	Singapore		Chinese		PTB	Clinical, sputum exam. Xray	Agglutination (reverse)	Blood donor, Historical control	6
Persson (1974)	Greenland	Greenland	Eskimos		PTB			All Eskimos in the area	4
Viskum (1975)	Denmark	Copenhagen			PTB			Blood donor, Historical control	4
Bhosale (1977)	India	Pune	Marathas		TB				4
Overfield (1980)	USA	Alaska	Eskimos	20-	TB	Skin test, clinical finding	Genetic loci	Resident in TB-epidemic lesion	8
Shankar (1986)	India	Ranchi		20–55	PTB inpatients	sputum, clinical		Healthy person	5
Reddy (1990)	India	Warangal		10–60	smear + male PTB	Clinical, radiological, laboratory test	Slid agglutination	Healthy male in blood bank	6
Knox-Macaulay (1993)	Nigeria	Kaduna	Predominantly Hausa-Fulani	16–60	TB			Medical student and historical cohort	4
Lakshmi (1993)	India	Visakhapatnam		14–60	PTB	Radiology, bacteriology	Agglutination	Age/sex matched healthy control	8
Cvjeticanin (2005)	Serbia	Belgrade		child	TB			Shool children of same age)	5
Ukaejiofo (2006)	Nigeria	Enugu Urban		25–60	HIV-TB		Standard technique	Age/sex matched blood donor	6
Gondaliya (2012)	India	Surendranagar			sputum + PTB		Agglutination (forward + reverse)	Blood bank donor	4
Rao (2012)	India	Andhra Pradesh			PTB	Sputum culture, radiology	Slide agglutination	Student, college worker	6
Ganguly (2016)	India	West Bengal	Hindu Caste	18–80	TB	Clinical diagnosis	Serological assay	Healthy adult	5
Pradhan (2016)	India	Odisha			PTB inpatients	Microscopy	Tube agglutination reaction	Blood bank donor	5

All were full original articles except for Lewis (1961, notes), Nand (1964, abstract), Knox-Macaulay (1993, short communication), and Lakshmi (1993, communication).
Overfield (1980) adopted cross-sectional design while the other studies used case-control methodology.
NOS: Newcastle-Ottawa Scale score. The score ranges from 0 (the worst) to 9 (the best).
TB: tuberculosis. PTB: pulmonary tuberculosis.

Patients

Subjects in each report were required to be clearly divided into those with and without tuberculosis. Patients with any type of tuberculosis were included, regardless of the organ involved, sputum smear status, human immunodeficiency virus co-infection, or drug-resistance status. We did not limit the diagnostic criteria for tuberculosis. Because control subjects should be healthy, subjects with comorbidities such as respiratory diseases were not used as controls in this analysis. No limitation was set for participant age.

Subjects were also classified into O, A, B, or AB blood type. Any method used to assess blood type, including genetic tests and forward/reverse agglutination tests, was accepted. Blood groups I, II, III, and IV based on Jansky's system were classified as blood groups O, A, B, and AB, respectively. Moss's blood types I, II, III, and IV were translated to AB, A, B, and O types, respectively (Bradbury, 1934).

If an article independently described data of two or more races or ethnicities, these populations were analyzed separately.

Outcomes

The protocol-specified primary outcome was tuberculosis risk among ABO groups in the form of ORs calculated via a network meta-analysis. While calculating this, we noticed that subjects with blood group AB had higher tuberculosis risk and people who had the other blood types had lower risk. Besides, the risk was nearly identical among O, A, and B blood groups. Therefore, pairwise comparisons between the AB and non-AB groups were also performed.

Quality assessment

The Newcastle-Ottawa Scale was used to evaluate the quality of observational studies (Stang, 2010).

Statistics

The numbers of subjects with and without tuberculosis were compared among the blood groups. When one or more cells were null, 0.5 was added for continuity correction. Preceding meta-analyses, the ORs and accompanying confidence intervals were log-transformed to yield estimates of log(OR) and the variance thereof as input for standard least-squares meta-analysis. A least-squares approach random-model network meta-analysis (netmeta command, netmeta package for R projects, Gerta Rücker) (Rücker, 2016) and a random-model pairwise meta-analysis (RevMan, Cochrane, London, UK) were performed. The statistical significance threshold was set to 0.05. The I^2 statistic for heterogeneity was interpreted as follows: 0%: no heterogeneity; 0%-30%: weak heterogeneity; 30%-50%: moderate heterogeneity; 50%-75%: substantial heterogeneity; and 75%-100%: considerable heterogeneity (Higgins and Thomas, 2019). Publication bias was assessed via visual inspection and the Begg-Mazumdar test with Kendall's tau (Begg and Mazumdar, 1994).

For the region-based subgroup analysis, populations were divided into seven continents. India was regarded as an independent region from Asia because 16 of 30 populations in this analysis were from India and because specific *Mycobacterium tuberculosis* linages are prevalent in India and East Asia.

Results

Study search

Twenty-four research articles from the database search and four additional articles from the manual search were identified (Figure 1). Of these 28 articles, two comprised data from two independent populations each. Therefore, our analysis eventually included 30 populations comprising 15,664 tuberculosis-positive patients and 254,610 tuberculosis-negative subjects.

Characteristics of the studies included

The 28 articles selected were published between 1927 and 2016 (median 1974), suggesting that this topic has been of interest for nearly 100 years (Table 1). Studies were conducted in India (N = 14), UK (N = 3), Nigeria (N = 2), the United States of America (N = 2), Singapore (N = 2), and other countries (N = 1 for each). An article from South Africa reported separate results from the Bantu population, a large ethnic group in Africa, and an Indian population. Another article from Singapore independently described Indian and Malay populations. Seven studies assessed adults only, or adults and adolescents aged >14 years. One study recruited participants aged 10–60 years. Another focused on pediatric participants. The other 19 studies did not mention patient age. Thirteen studies only recruited patients with pulmonary tuberculosis. In two other studies, 75% and 97% of cases had pulmonary tuberculosis. One study each focused on human immunodeficiency virus-coinfected tuberculosis, surgical pulmonary tuberculosis, and osteoarticular tuberculosis, while the other studies did not specify the tuberculosis type. There was one cross-sectional study; the others were case-control studies. Historical cohorts from the literature (N = 6) and blood donors (N = 9) were frequently used as data sources for controls, probably because these approaches maximize the number of controls.

Among 270,274 subjects, blood group O (n = 118,531, 43.9%) was the most prevalent, followed by group A (n = 98,436, 36.4%), B (n = 41,532, 15.4%), and AB (n = 11775, 4.4%) (e-Table 3).

The median Newcastle-Ottawa Scale score was five points (Table 1), suggesting that the quality of most studies was acceptable.

Network meta-analysis

Because studies selected included the numbers of cases and controls with O, A, B, or AB blood groups, ORs could be calculated for any pair of blood groups in every population. The network plot suggested that four blood groups were well compared (e-Figure 1).

According to the least-squares random-model network meta-analysis, subjects with blood type AB had a higher risk of becoming infected with tuberculosis than those with O (OR = 1.26, 95% confidence interval (CI): 1.14-1.38, P < 0.001), A (OR = 1.25, 95% CI: 1.14-1.38, P < 0.001), or B (OR = 1.22, 95% CI: 1.11-1.34, P < 0.001) blood type (Figure 2, e-Table 4). No significant difference was noted between O and A (compared to A, OR = 1.00, 95% CI: 0.92-1.08, P = 0.922), between A and B (compared to B, OR = 0.97, 95% CI: 0.89-1.06, P = 0.508), and between B and O (compared to O, OR = 1.03, 95% CI: 0.95-1.12, P = 0.441) blood groups (Figure 2A, e-Table 4). An I^2 statistic of 67.8% indicated there was substantial heterogeneity in this model. No heterogeneity was observed between direct and indirect comparisons (P = 0.9997).

Pairwise meta-analysis comparing blood groups AB and non-AB

Blood types O, A, and B were collectively categorized as "non-AB," as no meaningful risk difference was identified among these three groups. According to the random-model meta-analysis, the risk of tuberculosis was higher in persons with blood type AB than in those with other blood types (OR = 1.23, 95% CI: 1.02-1.48, P = 0.03; I^2 = 78%, P for heterogeneity < 0.001, Figure 3). The fixed-model meta-analysis yielded similar results (OR = 1.32, 95% CI: 1.22-1.42, P < 0.001, e-Figure 2). Visual inspection of the

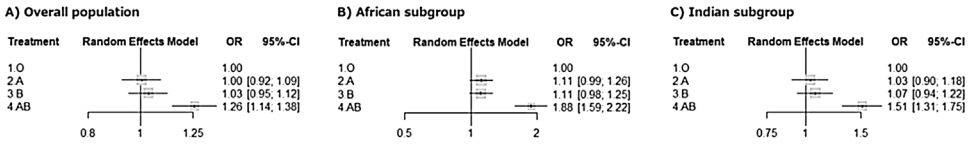

Figure 2. Forest plot for the network meta-analysis
OR: odds ratio.
95%-CI: 95% confidence interval.
Blood type O was the reference.

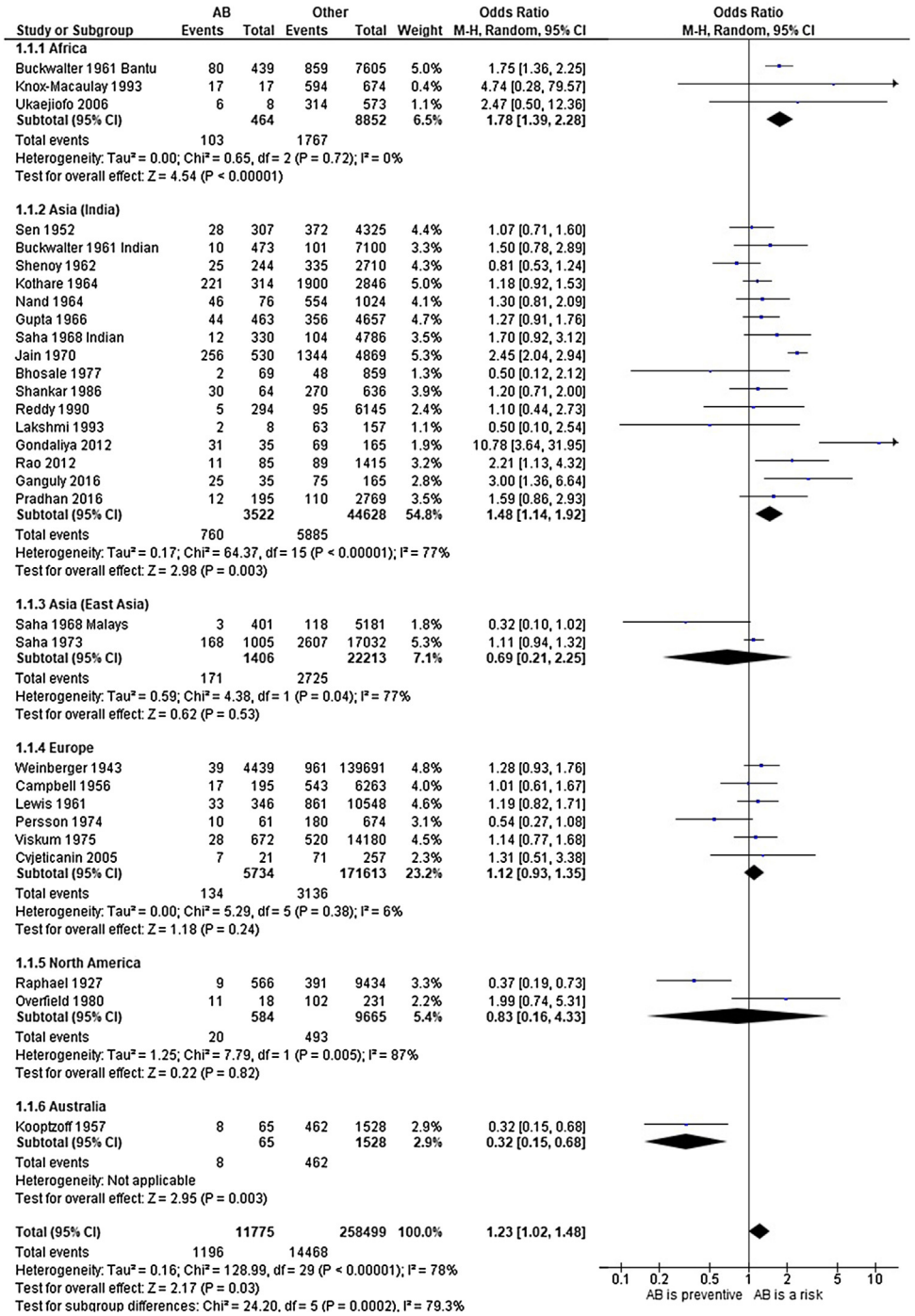

Figure 3. Forest plot for the pairwise random-model meta-analysis comparing blood group AB and non-AB
M-H: Mantel-Haenszel
95% CI: 95% confidence interval

symmetrical funnel plot showed no publication bias (e-Fig. 3). The Begg-Kendall test also did not reveal any publication bias (tau = 0.012, P = 0.929, e-Fig. 3).

Region-based subgroup analysis

In an exploratory subgroup analysis that stratified studies by regions and continents, blood type AB was the strongest risk factor in Africa (three populations, n = 9,316, OR = 1.78, 95% CI: 1.39–2.28, P < 0.001, I^2 = 0%, P for heterogeneity = 0.83, Figure 3) followed by India (16 studies, n = 48150, OR = 1.48, 95% CI: 1.14–1.92, P = 0.003, I^2 = 78%, P for heterogeneity <0.001, Figure 3).

According to network meta-analyses using only data from Africa or India, blood group AB was a clear risk factor for the tuberculosis (Figure 2B and C). In addition, blood groups A and B were very weak risk factors compared to group O in these two regions.

Discussion

This meta-analysis included 30 populations comprising 15,664 patients with tuberculosis and 254,610 non-tuberculosis controls and demonstrated that the AB blood group is a weak but significant risk for tuberculosis disease. We believe our results are robust and may end this century-long clinical controversy. Strengths of this study include solid methodology in accordance with the Meta-Analysis of Observational Studies in Epidemiology group statement, statistical power ensured by the inclusion of more than 270,000 subjects, lack of publication bias, and consistent results obtained using network and pairwise meta-analyses.

Although we included 30 populations from 28 articles, data from only four populations showed that the AB blood group was a significant risk factor for tuberculosis (Figure 3). Most studies did not have sufficient statistical power to compare group AB with other blood types. In our analysis, only 10,579 of 254,610 controls (4.2%) had AB blood type and the median number of patients with tuberculosis in each study was 17 (e-Table 3). As a result, most studies included lacked the statistical power to reveal the influence of AB blood group on the risk of tuberculosis. Pooling the data in a meta-analysis is therefore a reasonable strategy to summarize the data when individual studies lack the statistical power.

Epidemiological studies cannot explain why subjects with AB blood type are at a high risk of contracting tuberculosis. Unlike other Gram-positive bacteria, *M. tuberculosis* contains a periplasmic layer and a polysaccharide called lipo-arabino-mannan comprising arabinogalactan and other components. Arabinogalactan is a polysaccharide consisting of arabinose and galactose. On the other hand, ABO antigenicity is defined by the diversity of glycolipids and glycoprotein structures expressed on the surface of erythrocytes, body fluids, and mucosal secretions (Stoop et al., 2013). Polysaccharide in *M. tuberculosis* and ABO antigens may therefore share certain similarities. People with type AB do not have anti-A and B antibodies in their serum and may therefore not be able to attack *M. tuberculosis* polysaccharide. In our subgroup analysis, blood type AB was associated with a stronger risk of tuberculosis, especially in Africa and India. African and African-Indian lineages are the dominant *M. tuberculosis* strains in these areas and these linages may have lipo-arabino-mannan structures that are similar to human A and B blood type antigens (Wirth et al., 2008).

In our subpopulation analysis, the AB blood group was the strongest risk factor for tuberculosis in Africa. Natural selection affects the frequency of a certain blood trait in a region. Contagious diseases may drastically impact natural selection as these spread within a community in which people may have similar genetic backgrounds. For example, individuals with glucose-6-phosphate dehydrogenase deficiency, sickle cell diseases, and thalassemia are known to be resistant to malaria (Siniscalco et al., 1966). Therefore, these diseases are prevalent in malaria-endemic regions. Tuberculosis is a bacterium that originated in Africa 40,000-70,000 years ago (Wirth et al., 2008; Comas et al., 2013), and Africa remains a tuberculosis-endemic area to this day (World Health Organization, 2019). Thus, the African population has been widely exposed to tuberculosis for millennia. Currently, the prevalence of AB blood type is estimated to be 5.9% worldwide while those in African countries were 2.6-3.7% in Nigeria and 3.0% in South Africa (Anifowoshe et al., 2017; Anon, 2021) Over the last 10,000 years, the AB blood type, which carries a high risk for tuberculosis, may have been negatively selected and the frequency of AB types in Africa may have decreased.

Recently, many studies have investigated ABO blood types and their association with bacterial and viral infections. In 2020, a genome-wide association study analyzed 1,610 patients with coronavirus disease-2019 and 2,205 unaffected controls in Italy and Spain (Ellinghaus et al., 2020). After identifying the 9q34.2 locus, which determines ABO blood types, researchers performed a blood-group-based analysis. They concluded that blood group A was a risk factor for coronavirus disease-2019 with an OR of 1.45 (Ellinghaus et al., 2020). Meta-analyses may play a key role in evaluating the association between ABO blood groups and disease susceptibility. The potential role of ABO blood types in modulating the risk of *Helicobacter pylori* infection has been discussed since 1990. A random-effect model meta-analysis of 30 studies comprising 12,708 participants revealed that subjects with AB blood type had a lower risk of *H. pylori* infection (OR = 0.77, 95%CI 0.59-0.99, P = 0.043) (Chakrani et al., 2018). An observational study in 2002 first demonstrated that blood group B was a very strong preventive factor for Norwalk virus infection (OR = 0.09) (Hutson et al., 2002). However, many subsequent studies on this topic have presented conflicting data. In 2020, Liao et al. performed a systematic review and meta-analysis to investigate how ABO blood groups influenced the risk of norovirus infection. Data pooled from 17 studies concluded that having blood group B did not protect a subject from norovirus (Liao et al., 2020b). These studies were epidemiological or observational studies and did not directly investigate the biological mechanisms underlying the association of ABO blood groups with infectious risk. Nonetheless, these studies are important in demonstrating the association between ABO types and infectious diseases. We hope that geneticists would investigate how the region around 9q34.2 affects TB disease and other infectious disease susceptibility.

This study has limitations. We could not directly prove any causal relationships because this is a systematic review of observational studies. However, the blood group is genetically determined, and there are no plausible confounding factors linking blood types and the risk of tuberculosis. Therefore, we believe that our data indicate that having AB blood type makes an individual susceptible to tuberculosis, although what introduced population heterogeneity is still unclear.

In conclusion, our systematic review and meta-analysis included 30 populations comprising 15,664 patients with tuberculosis and 254,610 controls and showed that AB blood group was a risk factor for tuberculosis. Furthermore, a subgroup analysis suggested that the impact of the AB blood group was substantial in Africa and India.

Author contribution

HC worked for data acquisition and drafting manuscript. NH contributed to the study conception, data acquisition, analysis, interpretation, and drafting. HM and HN performed data acquisition, interpretation, and critical revision. YH, NK, AG, and TK

conducted the interpretation and critical revision. All the authors provided final approval and took full responsibility for the manuscript.

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Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.01.057.

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