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ABO blood group antigens may be associated with increased susceptibility to schistosomiasis: a systematic review and meta-analysis

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Research Paper

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Abstract

Schistosomiasis or bilharzia is a widespread parasitic disease caused by blood flukes of the genus *Schistosoma*. Some factors have been investigated previously regarding their effect on the pathophysiological mechanism of human schistosomiasis, but the possible influence of the ABO blood group on the severity of *Schistosoma* infection has been the most promising. Hence, we performed a systematic review and meta-analysis to further investigate the association of the ABO blood group with schistosomiasis susceptibility. Selected publications were retrieved from PubMed up to 21 August 2018, for related studies written in English. Number of cases (with schistosomiasis) and controls (without schistosomiasis) were extracted across all ABO blood types. Odds ratios (OR) and 95% confidence intervals (CI) were computed, pooled and interpreted. Subgroup analysis by the species of *Schistosoma* infecting the population and the participants' ethnicity was also performed. The overall analysis revealed heterogeneity in the outcomes, which warranted the identification of the cause using the Galbraith plot. Post-outlier outcomes of the pooled ORs show that individuals who are not blood type O are more susceptible (OR: 1.40; 95% CI: 1.17–1.67; $P^A < 0.001$) to schistosomiasis than those who are blood type O (OR: 0.71; 95% CI: 0.60–0.85; $P^A < 0.001$). Subgroup analysis yielded the same observations regardless of the species of schistosome and the ethnicity of the participants. Results of this meta-analysis suggest that individuals who are blood type B and A are more susceptible to schistosomiasis than those who are blood type O. However, more studies are needed to confirm our claims.

Introduction

As one of the neglected tropical diseases identified by the World Health Organization, schistosomiasis or bilharzia is a widespread parasitic disease caused by blood flukes of the genus *Schistosoma* (World Health Organization, 2015). Among the species of *Schistosoma*, *S. japonicum*, *S. mansoni* and *S. haematobium* inflict most infections in humans, with minimal cases caused by *S. intercalatum* and *S. mekongi* (Addisu and Tekeste, 2016). The disease is commonly seen among agricultural and fishing populations due to exposure to infested water (World Health Organization, 2015). The parasite is said to affect more than 240 million people worldwide in 78 countries, mostly in Africa, the Middle East and some endemic areas in the Americas and South-east Asia, with mortality rates as high as 200,000 per year in Africa alone (Colley *et al.*, 2014; World Health Organization, 2016; Gomes Casavechia *et al.*, 2018). Of all the cases of schistosomiasis needing medical intervention, 91.4% are from sub-Saharan Africa, which is endemic for both *S. mansoni* and *S. haematobium* (World Health Organization, 2016).

A number of factors have been investigated previously regarding their effect on the pathophysiological mechanism of human schistosomiasis, such as parasite egg intensity, organs or tissues affected, immunoregulatory mechanism of the host against the parasite, and even the presence of specific blood group and host antigens (Pearce and MacDonald, 2002; Alemu *et al.*, 2011). Among the suggested factors, the possible effect of the ABO blood group on the susceptibility and severity of schistosomiasis has been the most promising. It has been studied as early as 1979 (Pereira *et al.*, 1979; Trangle *et al.*, 1979), but its pathophysiologic mechanism in the disease is not yet well understood. A number of studies have shown that the incidence of schistosomiasis due to *S. mansoni* and *S. haematobium* among people with

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blood type O is less than among those with other blood types, suggesting that ABO blood group antigens may affect the severity of infection (Deribew *et al.*, 2012; Igbeneghu and Olisekodiaka, 2014; Degarege *et al.*, 2015; Addisu and Tekeste, 2016). Reports on the association of the ABO blood group with schistosomiasis susceptibility are limited, and their results are inconsistent. Hence, we performed a systematic review and meta-analysis to obtain more precise estimates by pooling the results of the individual studies available.

Materials and methods

Search strategy and study selection

An online search for relevant literature was initially carried out in PubMed up to 21 August 2018 using the MeSH (medical subject heading) terms "ABO blood group" and "schistosomiasis". Titles and abstracts of each of the studies returned in the search were screened manually by the authors (RET and NAP). Only studies with available abstracts were included in the initial screening. After removal of duplicates and irrelevant studies, the full text of the resulting articles was checked manually to determine their relevance. The following inclusion criteria were used: (1) studies that contain the incidence of schistosomiasis among cases and controls; (2) studies that grouped their participants depending on their ABO blood type; (3) studies that used microscopic examination in the identification of schistosomiasis; and (4) studies that are written in English. References cited in the selected studies were also checked for additional eligible articles. All studies identified were investigated for eligibility independently by RET and NAP.

Data extraction

Two of the authors (RET and NAP) independently extracted data and reached a consensus on all the items. For each study included, the following information was obtained: (1) the first author's last name; (2) year of publication; (3) country of the participants; (4) species of *Schistosoma* infecting the study population; (5) specimen used for schistosomiasis identification; (6) sources of controls; (7) total number of participants included; (8) total number of participants per ABO blood type; (9) total number of participants with schistosomiasis; and (10) total number of participants with schistosomiasis per ABO blood type.

Methodological quality assessment of the included studies

The Newcastle–Ottawa Scale (NOS) was used in assessing the methodological quality of the retrieved studies. All included articles were rated based on three perspectives: selection (maximum of 4 points), comparability (maximum of 2 points), and exposure (maximum of 3 points). The total scoring system used has ratings ranging from 0 to 9, i.e. from worst to best, respectively. An accumulated score of ≤ 4 points indicates low-quality studies, 5–6 points indicates moderate-quality studies, and ≥ 7 points indicates high-quality studies (Wells *et al.*, 2013).

Meta-analysis protocol

Statistical analysis for this study was carried out using Review Manager 5.3 (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014) and Meta-Essentials (Erasmus Research Institute of Management, 2017) (Suurmond *et al.*, 2017). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using either the fixed- (absence of heterogeneity) or random-effects model (presence of heterogeneity) (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986). Heterogeneity among the studies was determined using a $\chi 2$-based Q test (Lau *et al.*, 1997), and its degree was measured using I^2 statistics (Higgins *et al.*, 2003). Due to the low power of the test, the *P*-value (P^H) for heterogeneity testing was set at < 0.10 (Higgins and Thompson, 2002), whereas the *P*-value (P^A) for association was two-sided, with the significance threshold set at < 0.05. Subgroup analysis was also performed and was based on the species of *Schistosoma* and the ethnicity of the participants.

Other analysis

Robustness of the overall summary effects was determined using sensitivity analysis. In this test, the impact of the individual studies on the pooled ORs was examined by systematic removal of one study at a time. A study was considered robust if *P*-values for association and heterogeneity remained the same throughout. Publication bias was no longer estimated, given the low sensitivity of the test when the number of studies is < 10 (Ioannidis and Trikalinos, 2007).

Results

Search results

Figure 1 summarizes the study selection process utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2015). The initial search yielded a total of 43 studies that were thoroughly checked. After omitting duplicates and irrelevant studies following the set inclusion criteria, a total of 10 articles were included in this systematic review and meta-analysis (Pereira *et al.*, 1979; Trangle *et al.*, 1979; Kassim and Ejezie, 1982; Deribew *et al.*, 2012; Degarege *et al.*, 2014, 2015, 2017; Igbeneghu and Olisekodiaka, 2014; Addisu and Tekeste, 2016; Igbeneghu *et al.*, 2018).

Characteristics of the included studies

Table 1 summarizes the characteristics of the included studies. Year of publication ranged from 1979 to 2018. Overall, the total sample size from the 10 publications covered is 6472, with a wide range of total sample sizes across all the studies (200 to 2310). Subjects in nine of the articles were predominantly of sub-Saharan African origin (Trangle *et al.*, 1979; Kassim and Ejezie, 1982; Deribew *et al.*, 2012; Degarege *et al.*, 2014, 2015, 2017; Igbeneghu and Olisekodiaka, 2014; Addisu and Tekeste, 2016; Igbeneghu *et al.*, 2018), whereas one was of Western origin (Pereira *et al.*, 1979). As for the method of *Schistosoma* identification, four studies performed stool microscopy (Degarege *et al.*, 2014, 2015, 2017; Addisu and Tekeste, 2016), another four performed urine microscopy (Kassim and Ejezie, 1982; Deribew *et al.*, 2012; Igbeneghu and Olisekodiaka, 2014; Igbeneghu *et al.*, 2018), one performed both stool and urine microscopy (Trangle *et al.*, 1979), and another performed tissue biopsy (Pereira *et al.*, 1979). The majority (9 out of 10 studies) of the participants in the study were recruited from a population-based setting (Trangle *et al.*, 1979; Kassim and Ejezie, 1982; Deribew *et al.*, 2012; Degarege *et al.*, 2014, 2015, 2017; Igbeneghu and

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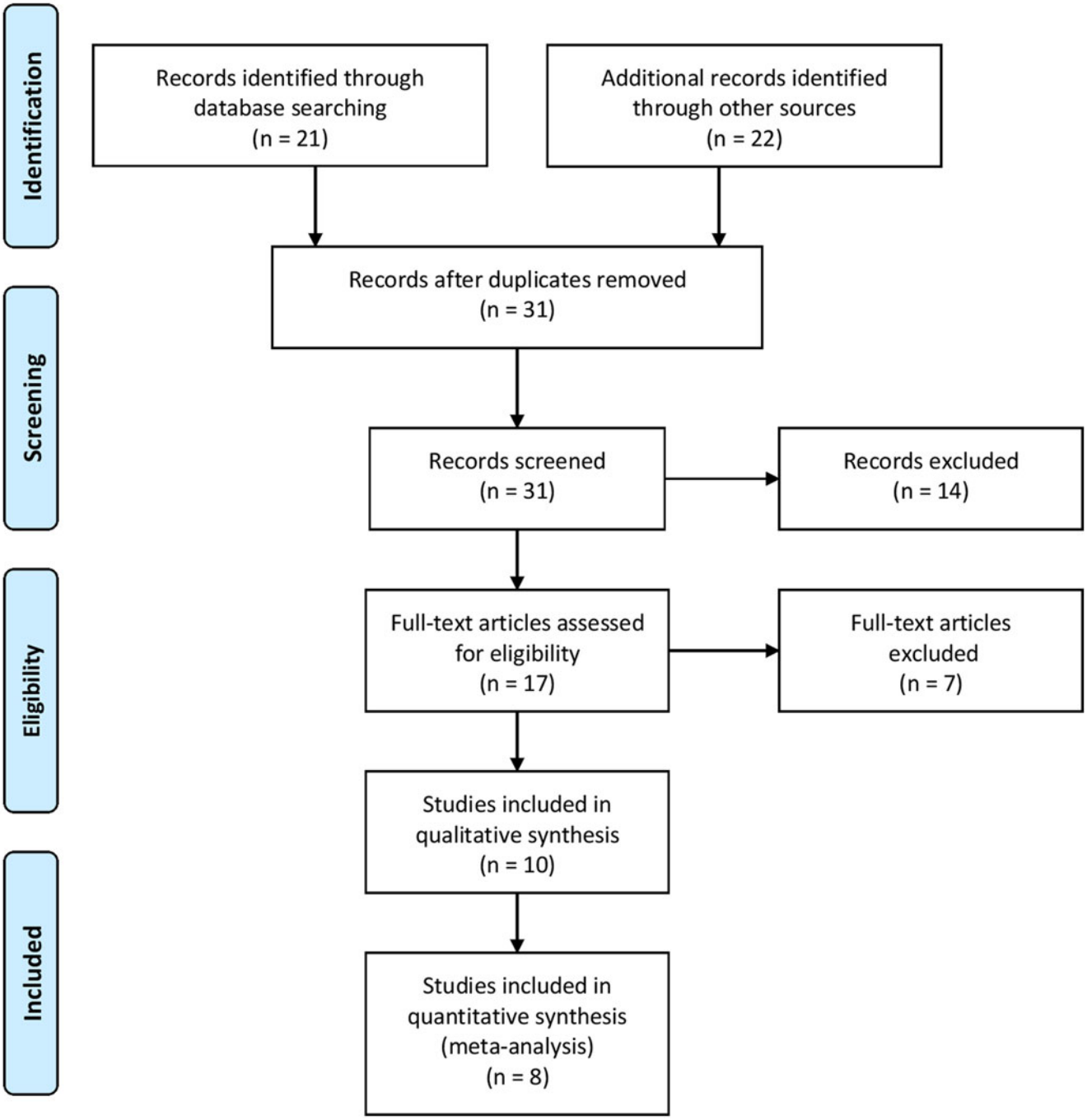

Fig. 1. Literature search summary following the PRISMA guideline.

Olisekodiaka, 2014; Addisu and Tekeste, 2016; Igbeneghu *et al.*, 2018). NOS scoring showed the mean and standard deviation to be 5.5 ± 0.5, with a median of 6, indicating that the included studies were of moderate quality.

Overall analysis for the association of non-O blood type and type O with schistosomiasis

Summary of overall effects

A total of 10 studies were included in the overall analysis for the relationship of non-O blood type with schistosomiasis susceptibility. The random-effects model (fig. 2a) showed significant associations (OR: 1.39; 95% CI: 1.02–1.91; $P^A = 0.04$), with a high degree of heterogeneity ($I^2 = 81\%$, $P^H < 0.001$). Based on the resulting pooled ORs, individuals with non-O blood type are more susceptible to schistosomiasis. On the other hand, the relationship of blood type O with schistosomiasis susceptibility was also tested using the random-effects model (fig. 2b) and also showed a significant association (OR: 0.72; 95% CI: 0.52–0.98; $P^A = 0.04$), with a high degree of heterogeneity ($I^2 = 81\%$, $P^H < 0.001$). The resulting pooled ORs for this comparison suggest that individuals with blood type O are less susceptible to schistosomiasis.

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Table 1. Characteristics of the included studies.

First author	Year	Country	*Schistosoma* sp.	Specimen	Source of control	No. of cases	Total no. of participants	Newcastle–Ottawa Scale
Igbeneghu	2018	Nigeria	*S. haematobium*	Urine	Population	132	285	7
Degarage	2017	Ethiopia	*S. mansoni*	Stool	Population	99	403	7
Addisu	2016	Ethiopia	*S. mansoni*	Stool	Population	299	410	6
Degarage	2015	Ethiopia	*S. mansoni*	Stool	Population	128	383	7
Degarage	2014	Ethiopia	*S. mansoni*	Stool	Population	61	480	6
Igbeneghu	2014	Nigeria	*S. haematobium*	Urine	Population	100	200	5
Deribew	2012	Ethiopia	*S. haematobium*	Urine	Population	95	370	6
Kassim	1982	Nigeria	*S. haematobium*	Urine	Population	97	681	4
Pereira	1979	Brazil	*S. mansoni*	Tissue biopsy	Hospital	280	2310	3
Trangle	1979	Swaziland	*S. mansoni*	Stool	Population	28	425	4
Trangle	1979	Swaziland	*S. haematobium*	Urine	Population	229	425	4

Outlier analysis outcomes

Significant heterogeneity was discovered among the two comparisons ($I^2 = 81–82\%$, $P^H < 0.001$), which warranted an investigation into its cause. The source of inconsistency was determined using the Galbraith plot (fig. 3), which identified three outlier studies. A significant loss in the level of heterogeneity was observed when the studies of Pereira *et al.* (1979), Kassim and Ejezie (1982), and one of the data from the study of Trangle *et al.* (1979) were omitted from the overall analysis. The reduction in the I^2 value to 0% (homogeneity) in the overall analysis after their omission indicates that these studies are responsible for the heterogeneity. According to the fixed-effects model (fig. 4a, b), the resulting pooled ORs after outlier analysis still indicate that individuals with non-O blood type are more susceptible to schistosomiasis (OR: 1.40; 95% CI: 1.17–1.67; $P^A < 0.001$) than those who are type O (OR: 0.71; 95% CI: 0.60–0.85; $P^A < 0.001$). Outcomes from this comparison were found to be robust, indicating the stability of our findings (data not shown).

Post-outlier subgroup analysis

Subgroup analysis was also performed by stratifying the studies based on the species of *Schistosoma* (*S. mansoni* and *S. haematobium*) and ethnicity (sub-Saharan African) of the participants. Based on the results of the post-outlier outcomes (table 2a), stratification showed the odds of acquiring schistosomiasis are high (OR: 1.38–1.44; CI: 1.08–1.92; $P^A < 0.01$) for individuals with non-O blood type, and low for those with blood type O (OR: 0.69–0.73; CI: 0.55–0.93; $P^A < 0.01$) regardless of the species of schistosome infecting the individual or the participant's ethnicity.

Post-outlier analysis for the association of other ABO blood types with schistosomiasis

A total of eight studies were included in the post-outlier analysis for this comparison (table 2b). The fixed-effects model showed a significant association between blood type A and schistosomiasis susceptibility, based on the resulting pooled ORs (OR: 1.32; 95% CI: 1.07–1.63; $P^A < 0.01$). For the subgroup analysis, significant findings were observed for those infected with *S. haematobium* rather than those infected with *S. mansoni*. Subgroup analysis by sub-Saharan African ethnicity also yielded significant associations (OR: 1.32; 95% CI: 1.07–1.63; $P^A < 0.01$). These findings suggest that individuals with blood type A are more susceptible to schistosomiasis than those with blood type O.

The resulting pooled ORs using the fixed-effects model also showed significant associations between blood type B and schistosomiasis susceptibility (OR: 1.52; 95% CI: 1.20–1.89; $P^A < 0.001$). Subgroup analysis, on the other hand, showed significant findings for the *S. mansoni* comparison (OR: 1.57; 95% CI: 1.19–2.06; $P^A < 0.01$) than the *S. haematobium* comparison. Subgrouping by sub-Saharan African ethnicity also yielded significant results (OR: 1.51; 95% CI: 1.20–1.89; $P^A < 0.001$). These findings indicate that increased susceptibility to schistosomiasis is also observed for those who are blood type B.

On the other hand, no significant associations were observed for individuals with blood type AB when compared to individuals with blood type O.

Discussion

Summary and interpretation of findings

The present meta-analysis summarizes the result of eight studies, involving 3056 participants, although 10 studies were included in the systematic review. By pooling all the ORs and 95% CIs from the individual articles, we showed that ABO blood group antigens are associated with increased susceptibility to schistosomiasis. Overall, increased susceptibility to the disease is observed among those who have ABO antigens on their red cell surface (blood types A and B) (OR: 1.40; 95% CI: 1.17–1.67; $P^A < 0.001$) compared to those individuals who do not have red cell surface antigens (blood type O) (OR: 0.71; 95% CI: 0.60–0.85; $P^A < 0.001$). Subgroup analysis indicated homogeneity ($I^2 = 0\%$, $P^H = 0.81$) across all the strata, indicating that the association is the same regardless of the species of *Schistosoma* infecting the individual and the participant's ethnicity. Significant associations ($P^A < 0.01$) were also noted for both comparisons.

The significant findings observed provide strong evidence of the possible role of ABO blood group antigens in the pathophysiology of schistosomiasis. This is supported by the homogeneity of

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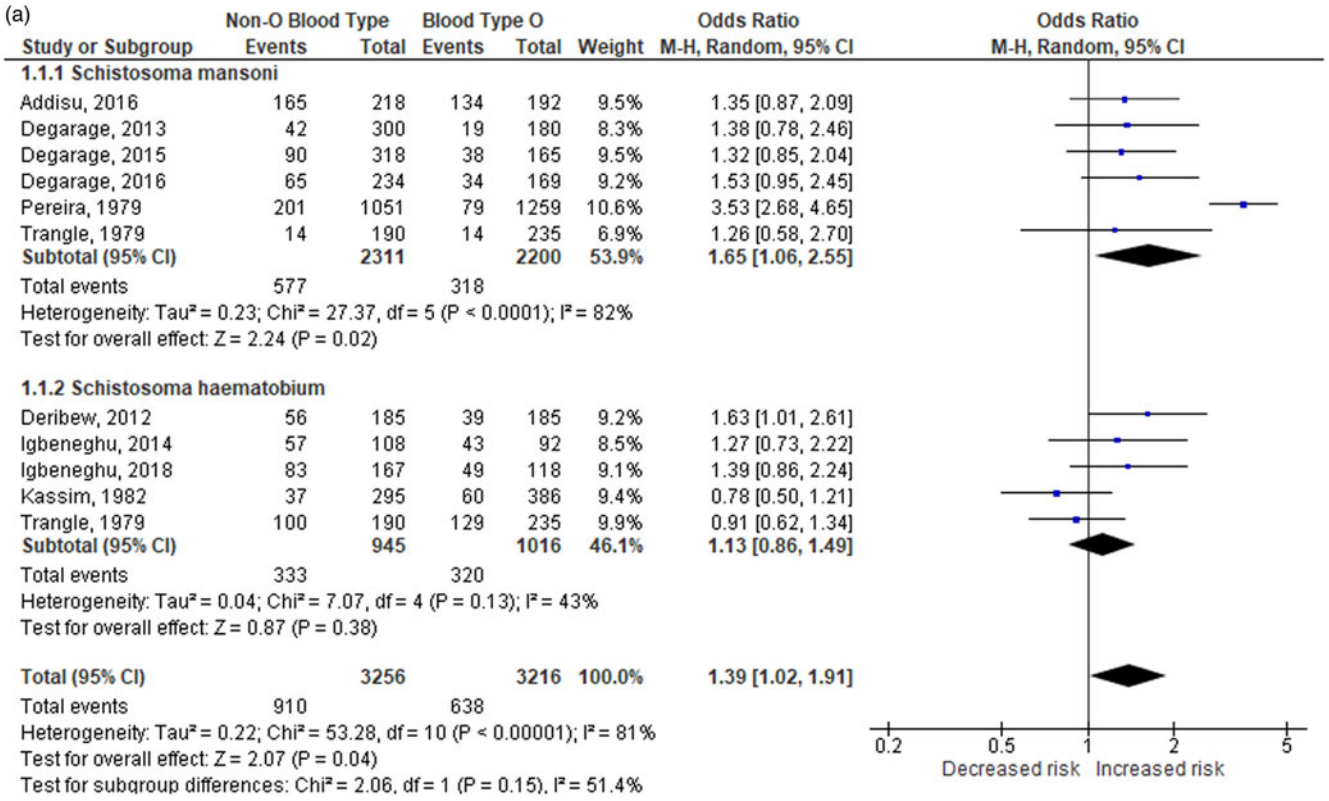

Fig. 2a. Overall and subgroup analysis of the association of non-O blood type with schistosomiasis. CI: confidence interval; df: degrees of freedom.

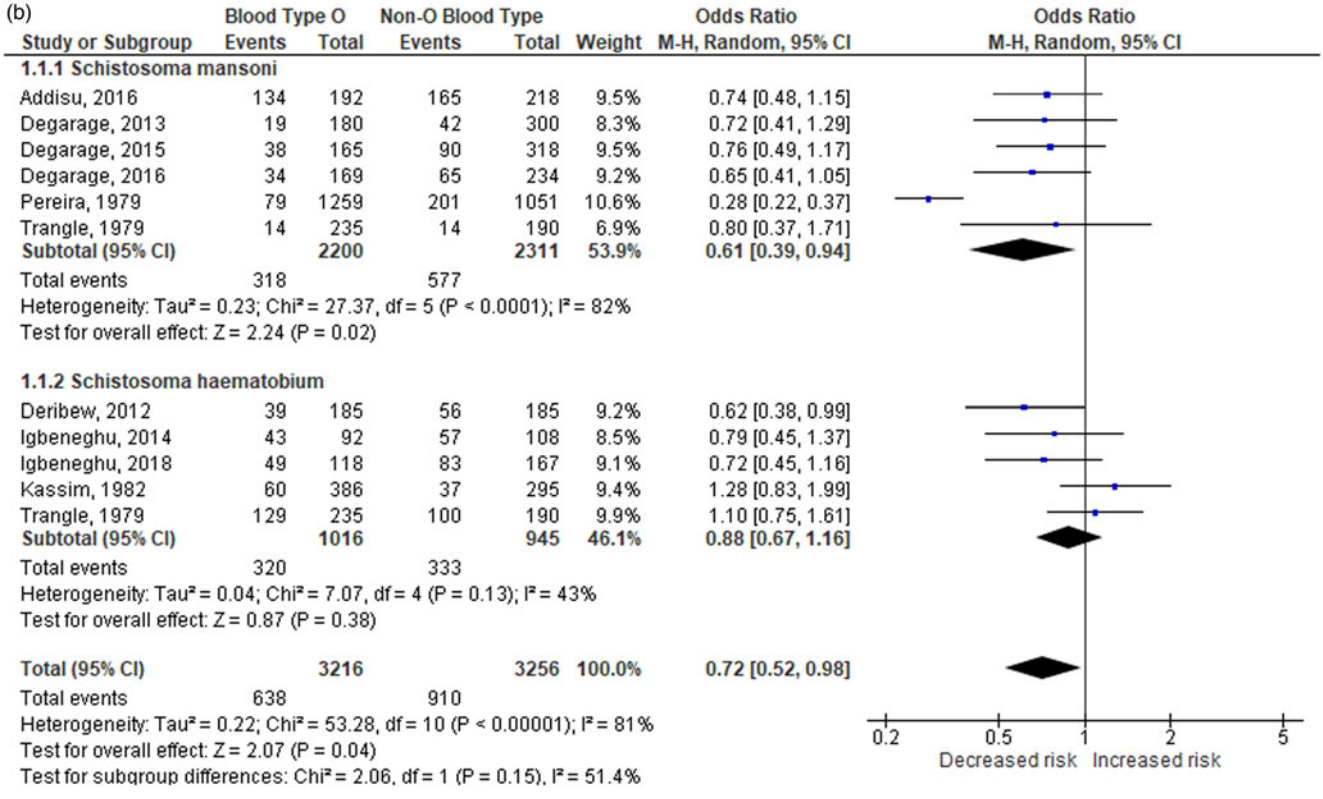

Fig. 2b. Overall and subgroup analysis of the association of blood type O with schistosomiasis. CI: confidence interval; df: degrees of freedom.

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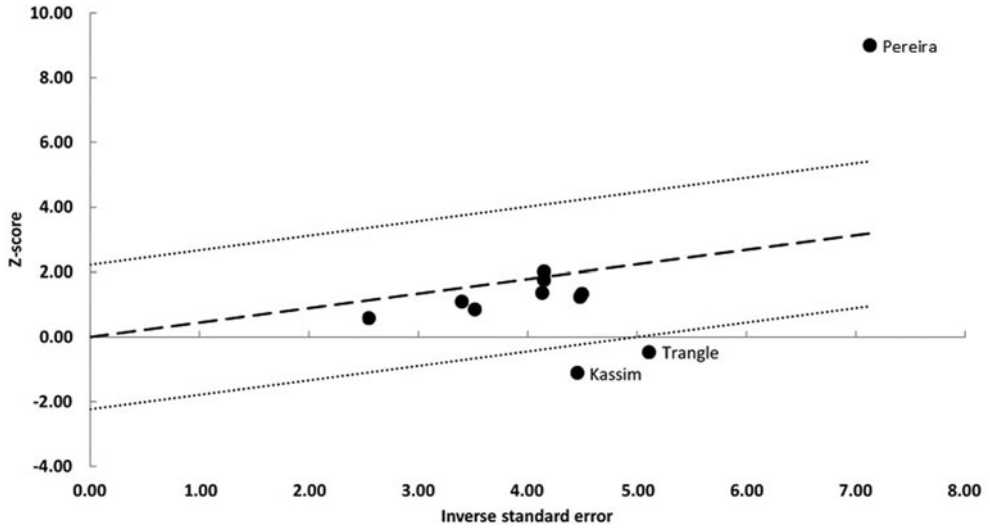

Fig. 3. Identification of outlier studies using the Galbraith plot.

the post-outlier results indicating combinability of the individual studies. Moreover, a high degree of significance, the consistent precision of effects, and the robustness of the post-outlier outcomes enhance the level of evidence presented in this meta-analysis.

Comparison with other studies

The findings of this meta-analysis are similar to the results of previous studies (Degarege *et al.*, 2015, 2017; Addisu and Tekeste, 2016). According to Degarege *et al.*, the odds of being infected with *S. mansoni* are higher among school-aged children with non-O blood type compared to those with blood type O. Also, significant associations were observed between non-O blood type individuals and egg intensity when compared to children with blood type O (Degarege *et al.*, 2017). In another study by Degarege *et al.* they noted that severity of *S. mansoni* infection was significantly higher among individuals with blood type A than those with blood type O. Also, the odds of *S. mansoni* infection were comparable to those with blood types B and AB (Degarege *et al.*, 2015), which is similar to the findings of another study (Trangle *et al.*, 1979). In terms of the degree of infection, Addisu and Tekeste showed that lighter schistosomiasis infections are more likely to be seen among those with blood type O than those with non-O blood type. Interestingly, those with a moderate to high degree of schistosomiasis were about twice as likely to have non-O blood type (Addisu and Tekeste, 2016). Results are still variable regarding which specific blood type is more associated with schistosomiasis. Two of the studies (Degarege *et al.*, 2015; Addisu and Tekeste, 2016) showed that schistosomiasis is more associated with individuals with blood type A than those with blood type B, whereas in another study (Degarege *et al.*, 2017) the opposite was observed, which is consistent with our findings.

Association of human blood groups with infection and host susceptibility

The relationship of different blood groups with pathologic processes in the human body has been studied for a long time. Several studies have noted the association of different blood groups with susceptibility to various conditions, such as cardiovascular disease (Dentali *et al.*, 2012; Franchini and Mannucci, 2014) and even cancer (Franchini *et al.*, 2012; Liumbruno and Franchini, 2014). Aside from that, the association of different blood groups with infectious disease has also been noted. Blood group antigens may play an essential role in various infectious processes by serving as receptors and co-receptors for different microorganisms and parasites (Cooling, 2015). These blood group antigens also facilitate various invasion mechanisms, such as intracellular uptake of pathogens (Amano and Oshima, 1999; Marionneau *et al.*, 2002), signal transduction (Gupta and Surolia, 2010; Pontier and Schweisguth, 2012; Nakayama *et al.*, 2013), and adhesion to different cells (Bensing *et al.*, 2004; Yang *et al.*, 2014). Aside from those mentioned, blood group antigens can also modify the innate immune system response to the invading microorganism, as seen in the case of *Schistosoma* (Sell and Dean, 1972; Goldring *et al.*, 1976).

Acquisition of human blood group antigens by Schistosoma

Years before this meta-analysis was conducted, studies investigated the possible acquisition of human blood group antigens by *Schistosoma* (Clegg *et al.*, 1971; Dean, 1974; Goldring *et al.*, 1976). The first investigation started in 1971, wherein after being cultured in human blood of various specificities, schistosomes showed specificity for anti-A or anti-B upon testing. This preliminary experiment suggested that the schistosomula acquired human blood group antigens during culture (Clegg *et al.*, 1971). Similarly, both the studies of Dean and Goldring *et al.* demonstrated that the schistosomula of *S. mansoni* acquired ABO blood group antigens A and B from the host after being cultivated in human blood (Dean, 1974; Goldring *et al.*, 1976). Therefore, these findings led to the hypothesis that the schistosomula can passively adsorb ABO blood group antigens and possibly even other host antigens. The exact mechanism by which ABO blood group antigens attach to the surface of the schistosome is still unknown, but Gardas and Koscielak (1973) were able to shed some light regarding the matter. In their view, glycolipids in the plasma, such as the A, B and H antigens, have the unique

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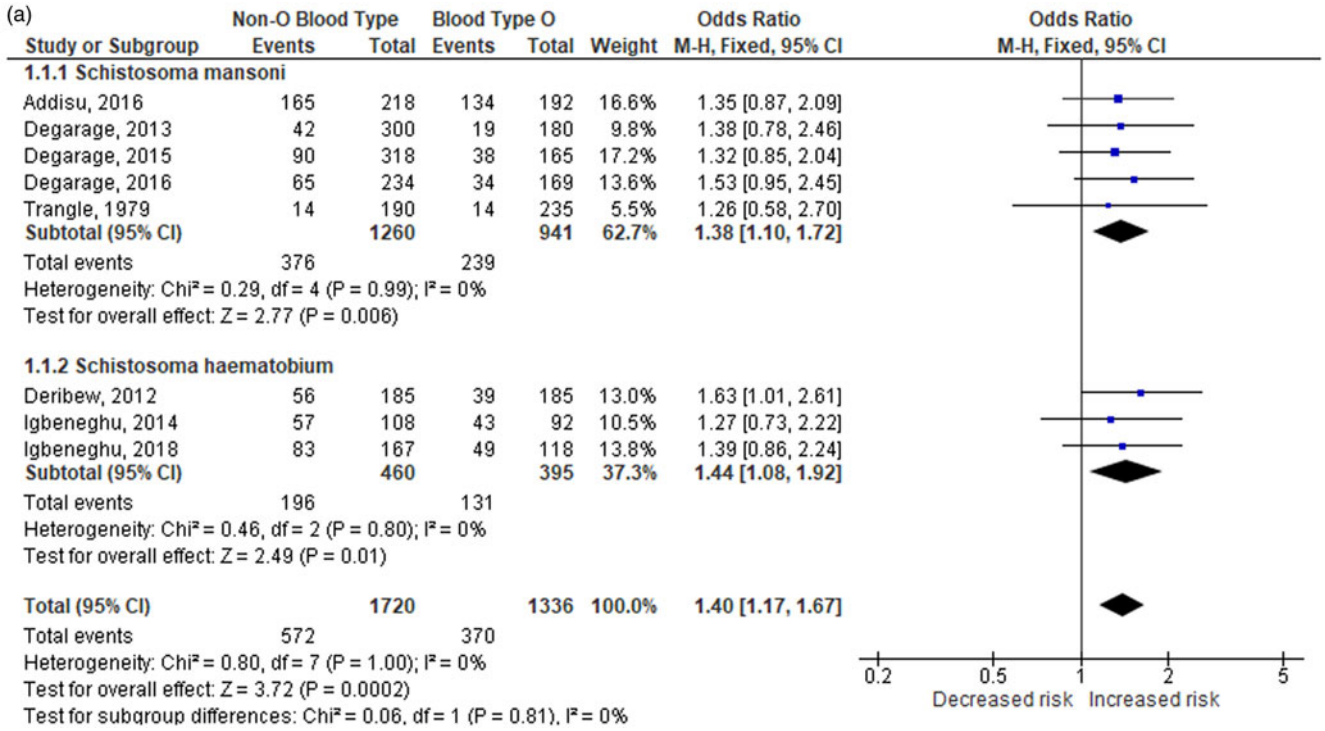

Fig. 4a. Overall and subgroup analysis of the association of non-O blood type with schistosomiasis without the outlier. CI: confidence interval; df: degrees of freedom.

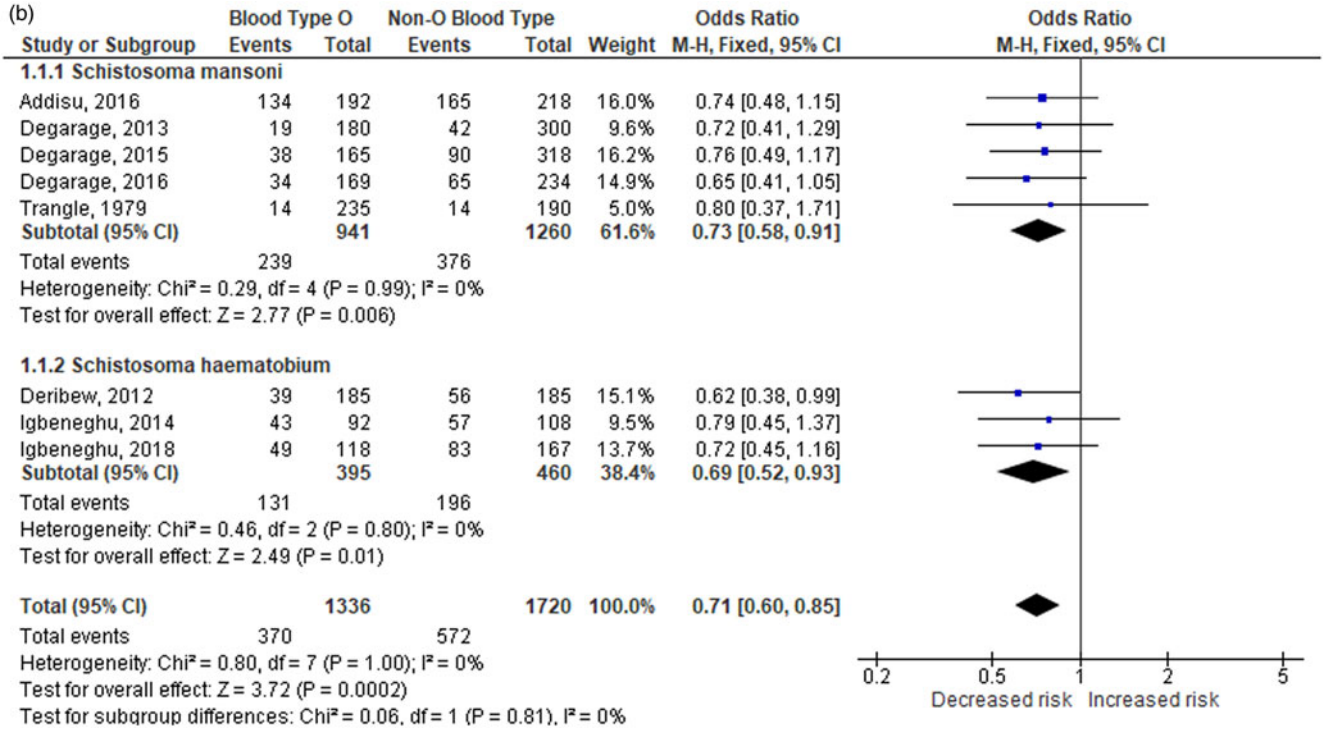

Fig. 4b. Overall and subgroup analysis of the association of blood type O with schistosomiasis without the outlier. CI: confidence interval; df: degrees of freedom.

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Table 2a. Overall and subgroup analysis of the association of blood type O with schistosomiasis.

			Association		Heterogeneity		
Comparison	Overall/Subgroup	N	OR (95% CI)	P^A	I^2	P^H	AM
Non-O type *vs* Type O	Overall	10	1.39 (1.02, 1.91)	0.04*	81%	< 0.001**	R
	Overall w/o outlier	8	1.40 (1.17, 1.67)	< 0.001*	0%	1.00	F
	S. mansoni	6	1.65 (1.06, 2.55)	0.02*	82%	< 0.001**	R
	S. mansoni w/o outlier	5	1.38 (1.10, 1.72)	< 0.01*	0%	0.99	F
	S. haematobium	5	1.13 (0.86, 1.49)	0.38	43%	0.13	R
	S. haematobium w/o outlier	3	1.44 (1.08, 1.92)	0.01*	0%	0.80	F
	African ethnicity	9	1.22 (1.05, 1.42)	< 0.01*	3%	0.41**	F
	African ethnicity w/o outlier	8	1.40 (1.17, 1.67)	< 0.001*	0%	1.00	F
Type O *vs* Non-O type	Overall	10	0.72 (0.52, 0.98)	0.04*	81%	< 0.001**	R
	Overall w/o outlier	8	0.71 (0.60, 0.85)	< 0.001*	0%	1.00	F
	S. mansoni	6	0.61 (0.39, 0.94)	0.02*	82%	< 0.001**	R
	S. mansoni w/o outlier	5	0.73 (0.58, 0.91)	< 0.01*	0%	0.99	F
	S. haematobium	5	0.88 (0.67, 1.16)	0.38	43%	0.13	R
	S. haematobium w/o outlier	3	0.69 (0.55, 0.93)	0.01*	0%	0.80	F
	African ethnicity	9	0.82 (0.70, 0.95)	< 0.01*	3%	0.41	F
	African ethnicity w/o outlier	8	0.71 (0.60, 0.85)	< 0.001*	0%	1.00	F

N: number of studies included; OR: odds ratio; CI: confidence interval; AM: analysis model; R: random-effects; F: fixed-effects
**P*-value significant at < 0.05
***P*-value significant at < 0.10

property of combining with cells and conferring upon them appropriate specificity (Gardas and Koscielak, 1973). The attachment of these antigens in the schistosome surface is made possible by the presence of at least two types of O-linked oligosaccharides, which can interact with different glycolipids (Nyame *et al.*, 1987). There is also evidence that the presence of the poly-N-acetyllactosamine-containing oligosaccharides synthesized by the schistosomes contributes to host–pathogen interactions. A good example of this is observed in the interaction of *Mycoplasma pneumoniae* with human erythrocytes containing poly-N-acetyllactosamine chains of Ii antigen type (Makaaru *et al.*, 1992).

Immune evasion by Schistosoma

This elusive trait may enable the schistosome to mask some of its antigenic sites, rendering it unrecognized by the host (Sell and Dean, 1972), a highly effective disguise that contributes to the parasite's successful invasion. Moreover, the evasive ability of the schistosome may infer the high survivability of the adult fluke in human blood (Clegg *et al.*, 1971), as seen in some cases where the parasite can live up to 40 years inside its human host (Colley *et al.*, 2014). Vaccines against the very early schistosomula and/or stimulation of effector mechanisms, such as macrophages, which does not require recognition or interaction of the parasite surface antigens, may be an effective counter treatment for schistosomiasis, considering its evasive capability (Pearce and Sher, 1987). Therefore, it is vital to understand the nature of host antigen acquisition and the evasive mechanism of schistosomes in progress towards the development of the necessary vaccine and/or treatment in combatting this clinically important parasite.

Limitations of the study

Overall findings of this meta-analysis suggest the possible association of ABO blood group antigens with schistosomiasis susceptibility. However, interpreting these results warrants awareness of the study's limitations: (1) a wide range of year of publication and patient sample sizes across the individual studies; (2) only two species of *Schistosoma* (*S. mansoni* and *S. haematobium*) were emphasized; (3) lack of representation of *S. japonicum* in the study; (4) lack of representation of other areas where schistosomiasis is endemic; (5) no representation of the different ethnic groups present in the study population; and (6) failure to include other risk factors of schistosomiasis. Given these limitations, the findings of this meta-analysis should be treated with caution when applied clinically.

To our knowledge, this is the first meta-analysis that investigated the association of ABO blood group antigens and schistosomiasis susceptibility. With this approach, we hope we have contributed to a better understanding of the pathophysiology of schistosomiasis and the possible role of the ABO blood group in disease susceptibility, and to establishing new ways of treating and controlling schistosomiasis. Generally, based on the resulting pooled ORs, our findings suggest that individuals with blood type B or A are more likely to be infected with schistosomiasis than those with blood type O. Further studies regarding the interaction of *Schistosoma* spp. with the different ABO and other host

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Table 2b. Overall and subgroup analysis of the association of blood types A, B and AB with schistosomiasis.

			Association		Heterogeneity		
Comparison	Overall/Subgroup	N	OR (95% CI)	P^A	I^2	P^H	AM
Type A *vs* Type O	Overall	10	1.35 (0.91, 2.01)	0.14	84%	< 0.001**	R
	Overall w/o outlier	8	1.32 (1.07, 1.63)	< 0.01*	0%	0.73	F
	S. mansoni	6	1.44 (0.77, 2.71)	0.25	88%	< 0.001**	R
	S. mansoni w/o outlier	5	1.24 (0.95, 1.62)	0.12	0%	0.46	F
	S. haematobium	5	1.17 (0.92, 1.49)	0.19	2%	0.39	F
	S. haematobium w/o outlier	3	1.46 (1.05, 2.04)	0.02*	0%	0.85	F
	African ethnicity	9	1.21 (1.01, 1.45)	0.05	0%	0.55	F
	African ethnicity w/o outlier	8	1.32 (1.07, 1.63)	< 0.01*	0%	0.73	F
Type B *vs* Type O	Overall	10	1.40 (1.11, 1.77)	< 0.01*	38%	0.10	R
	Overall w/o outlier	8	1.51 (1.20, 1.89)	< 0.001*	1%	0.42	F
	S. mansoni	6	1.64 (1.29, 2.08)	< 0.001*	0%	0.42	F
	S. mansoni w/o outlier	5	1.57 (1.19, 2.06)	< 0.01*	17%	0.31	F
	S. haematobium	5	1.11 (0.76, 1.61)	0.59	41%	0.15	R
	S. haematobium w/o outlier	3	1.39 (0.94, 2.06)	0.10	1%	0.37	F
	African ethnicity	9	1.36 (1.05, 1.75)	0.02*	40%	0.09**	R
	African ethnicity w/o outlier	8	1.51 (1.20, 1.89)	< 0.001*	1%	0.42	F
Type AB *vs* Type O	Overall	10	1.37 (1.00, 1.89)	0.05	0%	0.68	F
	Overall w/o outlier	8	1.42 (0.95, 2.12)	0.09	0%	0.89	F
	S. mansoni	6	1.69 (1.12, 2.54)	0.01*	2%	0.40	F
	S. mansoni w/o outlier	5	1.41 (0.86, 2.31)	0.18	0%	0.61	F
	S. haematobium	5	1.04 (0.63, 1.71)	0.89	0%	0.68	F
	S. haematobium w/o outlier	3	1.45 (0.74, 2.84)	0.28	0%	0.89	F
	African ethnicity	9	1.20 (0.85, 1.71)	0.30	0%	0.79	F
	African ethnicity w/o outlier	8	1.42 (0.95, 2.12)	0.09	0%	0.89	F

N: number of studies included; OR: odds ratio; CI: confidence interval; AM: analysis model; R: random-effects; F: fixed-effects
*P-value significant at < 0.05
**P-value significant at < 0.10

antigens may help better understand their role in the pathophysiology of schistosomiasis and to develop a treatment against the disease.

Conflict of interest. None.

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References

Addisu A and Tekeste Z (2016) The association between ABO blood groups and intestinal schistosomiasis among Masero primary school children in Sanja, northwest Ethiopia. *Journal of Tropical Diseases* **4**, doi: 10.4172/2329-891X.1000196.

Alemu A *et al.* (2011) Soil transmitted helminths and *Schistosoma mansoni* infections among school children in Zarima town, northwest Ethiopia. *BMC Infectious Diseases* **11**, 189.

Amano J and Oshima M (1999) Expression of the H type 1 blood group antigen during enterocytic differentiation of Caco-2 cells. *Journal of Biological Chemistry* **274**, 21209–21216.

Bensing BA, Lopez JA and Sullam PM (2004) The *Streptococcus gordonii* surface proteins GspB and Hsa mediate binding to sialylated carbohydrate epitopes on the platelet membrane glycoprotein Ib. *Infection and Immunity* **72**, 6528–6537.

Clegg JA, Smithers SR and Terry RJ (1971) Acquisition of human antigens by *Schistosoma mansoni* during cultivation in vitro. *Nature* **232**, 653–654.

Colley DG *et al.* (2014) Human schistosomiasis. *The Lancet* **383**, 2253–2264.

Cooling L (2015) Blood groups in infection and host susceptibility. *Clinical Microbiology Reviews* **28**, 801–870.

Dean DA (1974) *Schistosoma mansoni*: adsorption of human blood group A and B antigens by schistosomula. *The Journal of Parasitology* **60**, 260.

Degarege A *et al.* (2014) The association between multiple intestinal helminth infections and blood group, anaemia and nutritional status in human populations from Dore Bafeno, southern Ethiopia. *Journal of Helminthology* **88**, 152–159.

Degarege A, Hailemeskel E and Erko B (2015) Age-related factors influencing the occurrence of undernutrition in northeastern Ethiopia. *BMC Public Health* **15**, 108.

Degarege A *et al.* (2017) The relationship between helminth infections and low haemoglobin levels in Ethiopian children with blood type A. *Journal of Helminthology* **91**, 278–283.

Dentali F *et al.* (2012) Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature. *Seminars in Thrombosis and Hemostasis* **38**, 535–548.

Deribew K, Tekeste Z and Petros B (2012) The association of ABO blood group and urinary schistosomiasis in the Middle Awash Valley, Ethiopia. *International Journal of Medicine and Medical Sciences* **2**, 232–235.

DerSimonian R and Laird N (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials* **7**, 177–188.

Franchini M and Mannucci PM (2014) ABO blood group and thrombotic vascular disease. *Thrombosis and Haemostasis* **112**, 1103–1109.

Franchini M *et al.* (2012) ABO blood group, hypercoagulability, and cardiovascular and cancer risk. *Critical Reviews in Clinical Laboratory Sciences* **49**, 137–149.

Gardas A and Koscielak J (1973) New form of A-, B-, and H-blood-group-active substances extracted from erythrocyte membranes. *European Journal of Biochemistry* **32**, 178–187.

Goldring OL *et al.* (1976) Acquisition of human blood group antigens by *Schistosoma mansoni*. *Clinical and Experimental Immunology* **26**, 181–187.

Gomes Casavechia MT *et al.* (2018) Systematic review and meta-analysis on *Schistosoma mansoni* infection prevalence, and associated risk factors in Brazil. *Parasitology* **145**, 1000–1014.

Gupta G and Surolia A (2010) Glycosphingolipids in microdomain formation and their spatial organization. *FEBS Letters* **584**, 1634–1641.

Higgins JPT and Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21**, 1539–1558.

Higgins JPT *et al.* (2003) Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560.

Igbeneghu C and Olisekodiaka JM (2014) Urinary schistosomiasis: association with ABO blood group and effect on some haematological parameters. *International Journal of Basic and Applied Medical Sciences* **4**, 378–382.

Igbeneghu C *et al.* (2018) Distribution of ABO and rhesus blood groups, haemoglobin variants, phenylthiocarbamide taste perception and secretor status in urogenital schistosomiasis. *International Journal of Basic and Applied Medical Sciences* **12**, 1–6.

Ioannidis JPA and Trikalinos TA (2007) The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* **176**, 1091–1096.

Kassim OO and Ejezie GC (1982) ABO blood groups in malaria and schistosomiasis haematobium. *Acta Tropica* **39**, 179–184.

Lau J, Ioannidis JPA and Schmid CH (1997) Quantitative synthesis in systematic reviews. *Annals of Internal Medicine* **127**, 820–826.

Liumbruno GM and Franchini M (2014) Hemostasis, cancer, and ABO blood group: the most recent evidence of association. *Journal of Thrombosis and Thrombolysis* **38**, 160–166.

Makaaru CK *et al.* (1992) The human blood fluke *Schistosoma mansoni* synthesizes a novel type of glycosphingolipid. *Journal of Biological Chemistry* **267**, 2251–2257.

Mantel N and Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* **22**, 719–748.

Marionneau S *et al.* (2002) Norwalk virus binds to histo-blood group antigens present on gastroduodenal epithelial cells of secretor individuals. *Gastroenterology* **122**, 1967–1977.

Moher D *et al.* (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* **4**, 1.

Nakayama H *et al.* (2013) GSL-enriched membrane microdomains in innate immune responses. *Archivum Immunologiae et Therapiae Experimentalis* **61**, 217–228.

Nyame K, Cummings RD and Damian RT (1987) *Schistosoma mansoni* synthesizes glycoproteins containing terminal O-linked N-acetylglucosamine residues. *Journal of Biological Chemistry* **262**, 7990–7995.

Pearce EJ and MacDonald AS (2002) The immunobiology of schistosomiasis. *Nature Reviews Immunology* **2**, 499–511.

Pearce EJ and Sher A (1987) Mechanisms of immune evasion in schistosomiasis. *Contributions to Microbiology and Immunology* **8**, 219–232.

Pereira FEL *et al.* (1979) A, B, O blood groups and hepatosplenic form of schistosomiasis mansoni (Symmer's fibrosis). *Transactions of the Royal Society of Tropical Medicine and Hygiene* **73**, 238.

Pontier SM and Schweisguth F (2012) Glycosphingolipids in signaling and development: from liposomes to model organisms. *Developmental Dynamics* **241**, 92–106.

Sell KW and Dean DA (1972) Surface antigens on schistosoma. *Clinical Experimental Immunology* **12**, 315–324.

Suurmond R, van Rhee H and Hak T (2017) Introduction, comparison, and validation of Meta-Essentials: a free and simple tool for meta-analysis. *Research Synthesis Methods* **8**, 537–553.

Trangle KL *et al.* (1979) Distribution of blood groups and secretor status in schistosomiasis. *Parasite Immunology* **1**, 133–140.

Wells GA *et al.* (2013) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. *The Ottawa Hospital Research Institute* **3**, 1–4.

World Health Organization (2015) Investing to overcome the global impact of neglected tropical diseases. Available at http://www.who.int/neglected_diseases/9789241564861/en/ (accessed 8 September 2018).

World Health Organization (2016) Schistosomiasis: fact sheet. Available at http://www.who.int/news-room/fact-sheets/detail/schistosomiasis (accessed 6 September 2018).

Yang Y-H *et al.* (2014) Structural insights into SraP-mediated *Staphylococcus aureus* adhesion to host cells. *PLoS Pathogens* **10**(6), e1004169.

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