Association of current *Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma mekongi* infection status and intensity with periportal fibrosis: a systematic review and meta-analysis

Adanna Ewuzie, Lauren Wilburn*, Dixa B Thakrar, Huike Cheng, Fabian Reitzug, Nia Roberts, Reem Malouf, Goylette F Chami*

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*Joint first authors

Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford, UK (A Ewuzie MSc, L Wilburn PhD, D B Thakrar MRCS, H Cheng MSc, F Reitzug MSc, R Malouf MD, G F Chami PhD); **Health Care Libraries, Bodleian Libraries, University of Oxford, Oxford, UK** (N Roberts PhD)

Correspondence to: Dr Goylette F Chami, Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, UK **goylette.chami@ndph.ox.ac.uk**

Summary

Background Periportal fibrosis is a severe morbidity caused by both current and past exposure to intestinal schistosomes. We aimed to assess the association between current infection status and intensity of *Schistosoma mansoni*, *Schistosoma japonicum*, or *Schistosoma mekongi* with periportal fibrosis.

Methods In this systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, Embase, Global Health, Global Index Medicus, and MEDLINE from database inception to June 18, 2024. We applied methodological filters to limit our search to randomised controlled trials or observational studies, including before-and-after study designs. Animal studies were excluded, and no date or language limits were applied. We excluded reviews, editorials, personal opinions, and case reports. Self-reported infection status was an ineligible exposure. Two reviewers independently screened abstracts and full-text reports for eligibility. A third reviewer was consulted in cases of disagreement. The outcome of periportal fibrosis was recorded as reported by study authors to investigate variation in liver fibrosis definitions. For the key exposure of current infection, data were extracted for *Schistosoma* species, diagnostics, and author-provided infection status and intensity definitions. A meta-analysis was conducted for current schistosome infection status and intensity against author-defined current periportal fibrosis. Pooled effect sizes were derived using inverse-variance weighted random effects. Subgroup analyses included study characteristics and quality. The modified National Institute of Health risk of bias tool was used for assessing study quality. The protocol adhered to PRISMA reporting standards and was prospectively registered on PROSPERO, CRD42022333919.

Findings Our electronic search retrieved 2853 records, of which 1036 were duplicates. Nine records were identified in bibliographies of eligible full-text reports. We screened 1826 titles and abstracts to find 282 articles that met our inclusion criteria for full-text review. 41 studies were eligible for systematic review, 33 studies were eligible for infection status meta-analysis, and seven studies were eligible for infection intensity meta-analysis. Periportal fibrosis was heterogeneously defined with the Niamey ultrasound protocol most used. When findings were pooled, current schistosome infection status was associated with a higher likelihood of periportal fibrosis compared with no current infection (odds ratio [OR] 2·65, 95% CI 1·79–3·92; p<0·0001). Heterogeneity was high (I^2=95·81%). In sub-Saharan Africa, before the widespread introduction of mass drug administration in 2003 there was a significant association between current infection status and periportal fibrosis (OR 5·38, 95% CI 2·03–14·25) but this association was no longer present after 2003 (1·19, 0·82–1·74). No association of current infection status was observed with periportal fibrosis in studies that used the Niamey protocol (1·57, 95% CI 0·95–2·59). Associations depended on moderate to high risk of bias studies. No significant differences in pooled effect sizes were observed between infection intensity categories and periportal fibrosis.

Interpretation WHO guidelines use current schistosome infection intensity as a proxy for schistosomiasis-related morbidity. Our findings support that current infection status is only tenuously associated with periportal fibrosis. Guidelines are needed to better monitor schistosomiasis-related morbidities.

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Introduction

Periportal fibrosis is a severe but common complication of intestinal forms of the parasitic disease schistosomiasis. Periportal fibrosis disproportionately affects the lowest-income communities in Africa.[1] Transmission of the causative trematodes *Schistosoma mansoni*, *Schistosoma japonicum*, or *Schistosoma mekongi* requires human contact with freshwater that is contaminated with parasite eggs, in addition to the presence of competent snail species as the intermediate host.[2] Once individuals

Research in context

Evidence before this study

Periportal fibrosis is a severe consequence of intestinal schistosomiasis. We searched the Cochrane Central Register of Controlled Trials, Embase, Global Health, Global Index Medicus, and MEDLINE from database inception to June 18, 2024. The broad search terms were "Schistosoma", "fibrosis" AND "liver". There were no date or language restrictions on the search. Three reviews were detected by the search string that examined human genetic influence on liver fibrosis, non-invasive methods for periportal fibrosis diagnosis in patients with schistosomiasis, and human–host regulation of liver fibrosis during schistosome infection. Outside this search string, reviews were identified that explored the effect of co-infections (hepatitis B or C and malaria) on liver morbidity, validation of ultrasonography protocols for liver fibrosis, and the effect of preventive chemotherapy on liver fibrosis. No review assessed the influence of current intestinal schistosome infection status or intensity on periportal fibrosis.

Added value of this study

We provide quantitative evidence for the effect of (or lack thereof) current *Schistosoma mansoni, Schistosoma japonicum,* and *Schistosoma mekongi* infection status and intensity on periportal fibrosis, while assessing the quality (risk of bias [ROB]) of the available literature. By synthesising data ranging from 1988 to 2024, which encompassed 20 817 participants across all age ranges, we found that individuals with current schistosome infection were over twice as likely to have periportal fibrosis compared with individuals who were not currently infected. The association with current schistosome infection status was tenuous, determined solely by unadjusted studies that ignored confounders and were done before mass drug administration (MDA). The association was observed only in studies with a moderate to high ROB and not present in studies with a low ROB. Heterogeneity was high across studies and was not reduced when studies with a moderate or high ROB were excluded. Studies in South America, studies implemented after widespread MDA in sub-Saharan Africa, applying case–control designs, using an unmodified Niamey protocol, or defining periportal fibrosis as the mean of three periportal tract measurements showed at least a 10% absolute reduction in heterogeneity. By contrast, subgroup analyses by species or studies using Niamey image patterns C–F did not substantially reduce overall heterogeneity. We found no significant association between WHO categories of current schistosome intensity and periportal fibrosis, with few studies available on current infection intensity.

Our meta-analysis provides evidence that individuals currently infected with schistosomes had an increased likelihood of having periportal fibrosis, but only when infection status was considered rather than infection intensity. The Niamey protocol is the current WHO-recommended ultrasound protocol for assessing periportal fibrosis. The unexplained high heterogeneity found among studies presented here suggests the need for standardisation of periportal fibrosis diagnosis to accurately estimate the global burden of this disease. Our findings showed that in the current context of widespread, repeated MDA, infection proxy indicators were poor estimates of severe morbidity related to schistosomal liver fibrosis.

Implications of all the available evidence

Current WHO guidelines focus on reducing schistosomiasis-related morbidity as approximated by community prevalence cutoffs based on only current schistosome infection intensity. WHO guidelines for approximating severe schistosomal morbidity were not supported by evidence from pooled analyses of the published literature. International guidelines or draft regional recommendations are needed from WHO or WHO Regional Office for Africa to assist endemic countries with directly monitoring schistosomiasis-related morbidities as opposed to monitoring current infections. Considerations for morbidity surveillance should factor in available local resources and health system constraints.

become infected, the flukes migrate to the liver and mature male and female flukes pair, eventually migrating to reside in mesenteric venules. Here, female flukes will produce 100–3000 eggs per day, depending on the species.[3] Not all eggs are excreted, and some can be swept back into the liver and spleen where granulomatous inflammation ensues, which can lead to periportal fibrosis. Periportal fibrosis is a type of fibrosis distinguished by distinct patterns adjacent to the hepatic portal tracts and portal area of the liver.[2,4] Ongoing fibrosis causes damage and eventual blockages of the liver vasculature, forcing local restructuring.[5] Left untreated, the disease can cause portal hypertension, upper gastrointestinal bleeding, and, ultimately, premature death.[2]

Mass drug administration (MDA) of praziquantel is recommended by WHO to control schistosomiasis infection and morbidity.[6] The availability of MDA has successfully led to widescale, substantial reductions in *Schistosoma* infection prevalence and intensity.[6] Yet, periportal fibrosis and related morbidities remain in treated communities despite repeated rounds of MDA.[7] Current WHO guidelines recommend administering praziquantel annually to individuals older than 2 years in communities with an infection prevalence greater than 10%.[6] However, estimated infection prevalence is heavily skewed by school-aged children, who typically have the highest prevalence and intensity of infection but low levels of periportal fibrosis.[8]

Periportal fibrosis is associated with chronic exposure to schistosomes, and the time taken from initial infection to development of severe fibrosis can range from 5 years to 15 years.[2] The time lag for periportal fibrosis development results in scenarios where treatment guidelines might not align with morbidity prevalence by age group.[7]

When coupled with the risk of reinfection, the contribution of ongoing chronic or inactive historical infections, and confounders of other co-infections or alcohol use, it remains unclear how current infection status relates to periportal fibrosis.[2] In the context of repeated MDA, individuals can have varying treatment histories; therefore, heterogeneity might be introduced into what is known about the relationship between current schistosome infection and periportal fibrosis.[9] Despite this uncertainty, WHO guidelines suggest that less than 1% prevalence of heavy infection intensities (>400 eggs per g of stool) in school-aged children approximates elimination of morbidity as a public health problem for schistosomiasis.[6]

In this systematic review and meta-analysis, we aimed to quantify the pooled effect size for current schistosome infection status and intensity with a severe, specific morbidity—periportal fibrosis—for schistosomiasis in endemic regions.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, Embase, Global Health, Global Index Medicus, and MEDLINE from database inception to June 18, 2024. The broad search terms covered title, abstract, author keywords, and subject headings for "Schistosom*", "fibrosis" AND "liver", with no exclusion criteria applied to the type of liver fibrosis. The full search strategy and keywords are described in appendix 1 (pp 6–12). The study protocol was prospectively registered on PROSPERO, CRD42022333919, on May 19, 2022, and was reported according to the PRISMA framework (appendix 1 pp 2–5).[10]

We applied methodological filters to limit our search to randomised controlled trials or observational studies, including before-and-after study designs.[11,12] Animal studies were excluded, and no date or language limits were applied. References were exported to Covidence (Veritas Health Innovation; Melbourne, VIC, Australia) for screening and deduplication.[13] When there were multiple publications on the same study population within the same study site and timepoint, the publication with the largest sample was used in the analysis. We excluded non-human studies, reviews, editorials, personal opinions, and case reports. Self-reported infection status was an ineligible exposure. Full inclusion and exclusion criteria are described in detail in appendix 1 (pp 13–14).

Two reviewers (AE and DBT) independently screened abstracts and full-text reports for eligibility. A third reviewer (RM) was consulted in cases of disagreement. AE and LW extracted the data independently (appendix 2). DBT then extracted data from 20% of the studies, without seeing the extracted data from AE and LW to quality check the extractions. Summary estimates were sought from the literature independently. Separate reviewers screened and extracted articles in Mandarin (HC) and French (FR). References of eligible full-text reports were searched, and any further articles found were screened with the same eligibility criteria.

The primary outcome of periportal fibrosis was recorded as reported by study authors to investigate variation in liver fibrosis definitions. For the key exposure of current infection, data were extracted for *Schistosoma* species, diagnostics, and author-provided infection status and intensity definitions. Additional information, such as study design, year, setting, age and sex of participants, and ultrasound protocol, was recorded (appendix 1 p 15). If effect sizes were not provided by study authors, odds ratios (ORs) were reconstructed where available from in-text information or as provided by authors when contacted for more information.

Data analysis

The primary outcome was periportal fibrosis as assessed by ultrasound and as defined by the study authors. The secondary outcomes were periportal fibrosis as defined by type of protocol and as differentiated by image patterns versus portal tract measurements. In the original PROSPERO protocol, we proposed to look at severity but this information was not available from published studies.

We used random-effects models using the generic inverse variance method to calculate pooled effect measures (ORs with 95% CIs) in Stata MP version 17. Overall heterogeneity was calculated using Higgin's I^2 statistic to explain between-study variation.[14] Subgroup analyses were done when at least three studies were available, resulting in subgroup analyses for continent, *Schistosoma* species, setting, study design, before versus after MDA in sub-Saharan Africa, ultrasound protocol, periportal fibrosis outcome definitions, Niamey modifications, and study quality (appendix 1 p 16). The quality of studies was assessed by assigning risk of bias (ROB) using a modified National Institute of Health Risk of Bias Tool from the National Heart, Lung, and Blood Institute (appendix 1 pp 17–19). Publication bias was evaluated using funnel plots and Egger's regression.[15,16]

See Online for appendix 1

Sensitivity analyses were done to assess pooled effect sizes broken down by risk of bias (low *vs* medium *vs* high) and pooling the low and medium risk of bias studies together (separating out the high risk studies). All analyses also were rerun to exclude the outliers (OR>30 with wide CI) and there were no significant differences to the pooled or subgroup findings.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

See Online for appendix 2

Results

Our electronic search retrieved 2853 records, of which 1036 were duplicates (figure 1). Nine records were identified in bibliographies of eligible full-text reports.

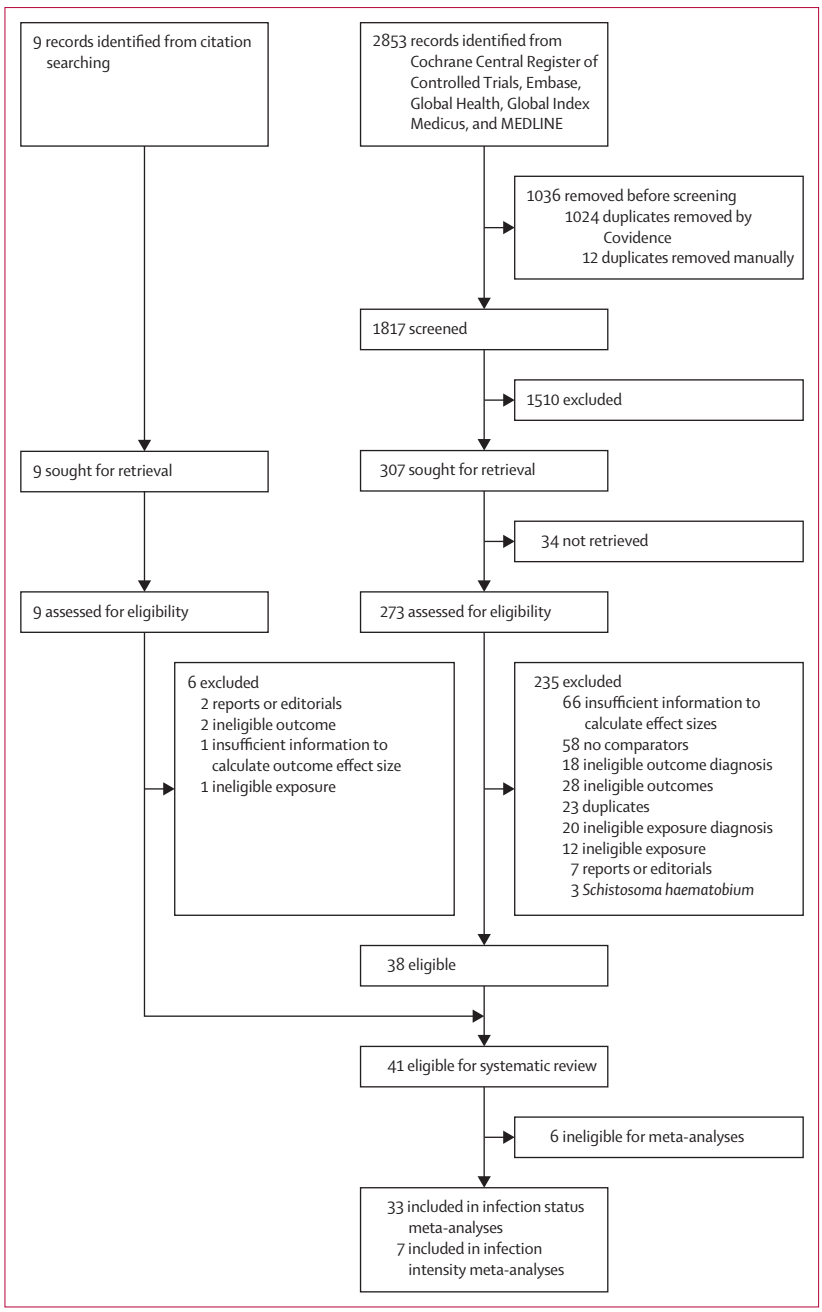

Figure 1: **Study selection**

We screened 1826 titles and abstracts to find 282 articles that met our inclusion criteria for full-text review (appendix 1 pp 20–29). 41 studies were eligible for systematic review,[7,17–56] 33 studies were eligible for infection status meta-analysis,[7,17–28,30–32,36–41,43–45,47,48,50–54,56] and seven studies were eligible for infection intensity meta-analysis.[7,25,26,36,39,49,55] Six studies were ineligible for meta-analyses due to the unique presentation of exposures or outcomes, which could not be combined with at least two similar studies (appendix 1 p 30).[29,33–35,42,46]

32 records from Cochrane were identified by our search string, but most were excluded as the studies did not have an uninfected or low-infection comparator group for schistosome exposure. For the 66 studies excluded due to insufficient information to calculate outcome effect sizes, 14 were from Brazil, eight were from China, nine were from Egypt, eight were from Tanzania, five were from Sudan, three were from the Philippines, 16 were from sub-Saharan African countries other than those listed, one was from a non-endemic country (Italy), one was a multi-country study, and for one study the country was unclear. For the 58 studies excluded due to having no comparator, 29 were from Brazil, 13 were from China, nine were from Egypt, three were from sub-Saharan African countries other than those listed, three were from southeast Asian countries, and one was from Venezuela. Among these 58 studies, in 35 (60%) all individuals were infected with schistosomes and in 23 (40%) all infected individuals had periportal fibrosis. For the 18 studies excluded due to ineligible outcome measurements, eight studies were from Egypt, five were in China, two were in Sudan, one was in Brazil, one was in Madagascar, and one was a multi-country study. For the 20 studies excluded due to ineligible exposure diagnosis, six were from Brazil, six were from China, six were from Egypt, one was from South Africa, and one was from Zambia.

We included 32 334 participants across 41 studies (appendix 1 pp 31–40). Egypt was the most frequently studied country (figure 2; eight [20%] of 41 studies).[17,20,21,28,34,38,43,44] Seven studies were included in the infection intensity review that are not shown in figure 2 (Uganda: two studies; Kenya: one study; Tanzania: two studies; Zimbabwe: one study; and one study across Mali, Niger, Tanzania, and Uganda).

Most studies included both men and women (40 [98%] of 41 studies).[7,17–40,42–56] The most used study designs were cross-sectional (30 [73%] of 41 studies)[17–25,27,30–37,39,41–45,47,48,51–54] and case–control (seven [17%] of 41 studies).[26,28,38,40,50,56] One randomised controlled trial was eligible for inclusion.[49] Most studies were done in the community (29 [70%] of 41 studies)[17–19,21–23,27,28,30,31,33–37,39,40,42–44,46–51,54,56] and a small number in schools[26,32,38,52,55] or health centres (five [12%] studies each).[20,24,25,29,45] Community-based studies tended to cover all age groups (14 [48%] of 29 studies)[17,18,21–23,30,33,35,37,39,43,44,46,50] or were restricted to adolescents and adults (aged ≥15 years) and school-aged children (aged 5–14 years; nine [31%] of 29 studies).[7,27,28,31,34,42,47,48,54] Few studies were restricted to only adolescents and adults (two [7%] of 29 studies),[36,56] only school-aged children (one [3%] study),[19] or only preschool-aged children (aged 0–4 years; one [3%] study).[49]

Most studies defined periportal fibrosis according to Niamey protocol patterns C–F (15 [37%] of 41 studies),[7,19,24,25,32–34,36,37,39,45,47,48,52,55] with the next most common definition being the mean of three periportal tract measurements (eight [20%] of 41 studies).[17,21,23,27,38,43,44,51] Network (interseptal) fibrosis was reported in three (7%) of

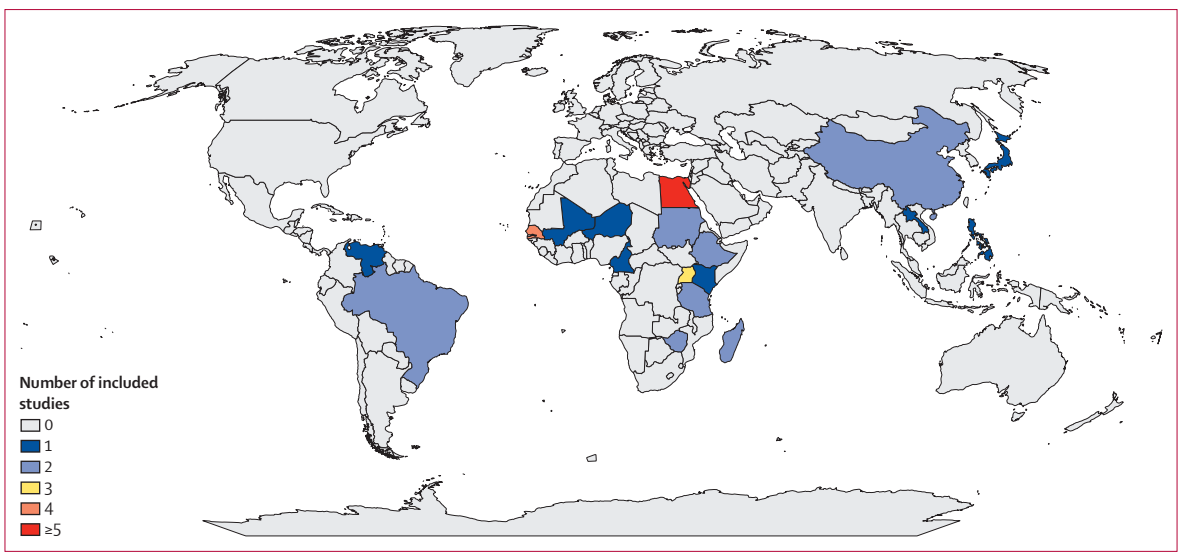

Figure 2: **Geographical focus of studies on current infection and periportal fibrosis**

41 studies.[29,35,56] Most studies diagnosed schistosome infection solely by Kato-Katz microscopy (34 [83%] of 41 studies),[17–22,24–27,30–48,50,52–56] with two (5%) studies using only serology or antigen-based tests[29,45] and five (12%) studies using a combination of microscopy, serology, and antigen tests.[7,23,28,49,51] 18 (44%) of 41 studies[7,18,19,24,25,32–34,36,37,39,40,42,45,48,49,52,55] used the Niamey protocol and 12 (29%) of 41 studies used the Cairo protocol.[17,20,21,23,27,35,38,43,44,46,51,56] Eight (20%) of 41 studies used alternative ultrasound protocols[26,28–31,41,47,54] and three (7%) studies did not report the ultrasound protocol that was used.[22,50,53]

All studies included in the systematic review were evaluated for quality (ROB; appendix 1 pp 41–53). Ten (24%) of 41 studies had a high ROB,[24,26,28,29,38,42,47,51,53,56] 24 (59%) had a moderate ROB,[17,19–23,27,30–33,35,37,40,41,43–46,48,54,55] and seven (17%) had a low ROB.[7,18,25,36,39,49,52] Common reasons for being categorised with moderate or high ROB were provision of data in an unadjusted model or only presenting descriptive statistics (31 [76%] of 41 studies).[17–21,24,26–34,38,40–48,50,51,53,54,56] Further breakdowns of summary statistics are reported for studies analysed only in infection status or infection intensity meta-analyses (table 1). Current schistosome infection status and effects on periportal fibrosis were mostly extracted from unadjusted analyses, without consideration of confounding variables.

33 studies, involving 20 817 participants, were eligible for inclusion in the meta-analysis (table 1). Eight studies were not included in the infection status meta-analysis (appendix 1 p 30).[29,33–35,42,46,49,55] When findings were pooled, current schistosome infection status was associated with a higher likelihood of periportal fibrosis compared with no current infection (OR 2·65, 95% CI 1·79–3·92; p<0·0001; figure 3). Heterogeneity was high (I^2=95·81%).

Studies within Asia (OR 8·83, 95% CI 2·00–39·06) or Africa (2·32, 1·57–3·41) showed an association between current infection status and periportal fibrosis, but there was no association for South America (1·32, 0·60–2·92; table 2). *S japonicum* (8·22, 1·06–99·62) had a greater pooled effect size but much higher variability compared with studies of *S mansoni* (2·18, 1·53–3·11). Within community-based studies (2·48, 1·53–4·03), a positive association was observed but no association was present within school-based studies (3·39, 0·81–14·13) or health centres (1·86, 0·81–4·31). Case–control studies (18·91, 7·65–46·73) presented stronger associations of current infection status with periportal fibrosis compared with cross-sectional studies (1·84, 1·36–2·47). High-quality study designs with a low ROxwed no associations between current infection status and periportal fibrosis (1·51, 0·82–2·78), but a significant association was found for moderate ROB studies (2·27, 1·41–3·52) and high ROB studies (7·40, 2·33–23·52).

In sub-Saharan Africa, before the introduction of MDA in 2003 there was a significant association between current infection status and periportal fibrosis (OR 5·38, 95% CI 2·03–14·25) but this association was no longer present after the introduction of MDA in 2003 (1·19, 0·82–1·74). No association of current infection status was observed with periportal fibrosis in studies that used the Niamey protocol (1·57, 95% CI 0·95–2·59). The Cairo protocol (2·77, 1·53–5·04) or alternative protocols including Homeida, Managil, Doehring-Schwerdtfeger, and Abdel-Wahab (4·19, 1·33–13·23) found diagnoses of periportal fibrosis that were strongly associated with current infection status. Studies that defined periportal fibrosis based on Niamey protocol patterns C–F showed no association of infection status with periportal fibrosis (1·26,0·77–2·04). The absence of association remained when only studies that did not modify the Niamey protocol were considered as a subgroup (1·17, 0·79–1·72). Periportal fibrosis when defined as the mean of three periportal tracts (1·84, 1·44–2·36) or other

	Systematic review synthesis (n=41)		Infection status meta-analyses (n=33)		Infection intensity meta-analyses (n=7)	
	Participants (n)	Studies	Participants (n)	Studies	Participants (n)	Studies
Study aims						
Prevalence of schistosome infection and morbidity	11 901	12 (29%)	7597	9 (27%)	0	0
Use of ultrasound in the diagnosis of fibrosis	4231	11 (27%)	4231	11 (33%)	930	1 (14%)
Association of schistosome infection and periportal fibrosis	5882	7 (17%)	5760	6 (18%)	3430	2 (29%)
Immunology, genetics, or hormones and periportal fibrosis	3454	4 (10%)	1868	2 (6%)	1868	2 (29%)
Effect of praziquantel on schistosomiasis morbidity	5943	4 (10%)	785	3 (9%)	5158	1 (14%)
Risk factors in transmission	576	2 (5%)	576	2 (6%)	0	0
Influence of infection intensity on periportal fibrosis	347	1 (2%)	0	0	347	1 (14%)
Study region						
Sub-Saharan Africa	22 904	24 (59%)	11 919	19 (58%)	11 733	7 (100%)
North Africa or Middle East	7140	7 (17%)	7140	7 (21%)	0	0
South and Central America	717	4 (10%)	620	3 (9%)	0	0
Central Asia	1179	4 (10%)	744	2 (6%)	0	0
Southeast Asia	394	2 (5%)	394	2 (6%)	0	0
Study design						
Cross-sectional	20 125	30 (73%)	15 508	26 (79%)	2798	3 (43%)
Case-control	2597	7 (17%)	2475	6 (18%)	596	1 (14%)
Cohort	9265	3 (7%)	2834	1 (3%)	7992	2 (29%)
Randomised controlled trial	347	1 (2%)	0	0	347	1 (14%)
Study setting						
Community	24 053	29 (71%)	17 816	23 (70%)	5782	4 (57%)
School	6774	5 (12%)	1616	4 (12%)	5754	2 (29%)
Health centre	829	5 (12%)	707	4 (12%)	197	1 (14%)
Workplace	435	1 (2%)	435	1 (3%)	0	0
Community and health centre	243	1 (2%)	243	1 (3%)	0	0
***Schistosoma* species**						
Schistosoma mansoni	30 761	35 (85%)	19 679	29 (88%)	11 733	7 (100%)
Schistosoma japonicum	1330	5 (12%)	895	3 (9%)	0	0
Schistosoma mekongi	243	1 (2%)	243	1 (3%)	0	0
Schistosome diagnostic tool						
Kato-Katz microscopy	27 794	34 (83%)	16 746	28 (85%)	8552	5 (71%)
Microscopy and serology	360	2 (5%)	360	2 (6%)	0	0
Microscopy and antigen	3181	2 (5%)	2834	1 (3%)	3181	2 (29%)
Antigen only	299	1 (2%)	299	1 (3%)	0	0
Microscopy and miracidial hatching	578	1 (2%)	578	1 (3%)	0	0
Serology only	122	1 (2%)	0	0	0	0
Ultrasound protocol						
Niamey	18 413	18 (44%)	8604	13 (39%)	11 137	6 (86%)
Cairo	9808	12 (29%)	8222	10 (30%)	0	0
Homeida	1302	3 (7%)	1302	3 (9%)	0	0
Abdel-Wahab	189	2 (5%)	189	2 (6%)	0	0
Managil	561	1 (2%)	561	1 (3%)	0	0
Doehring-Schwerdtfeger	596	1 (2%)	596	1 (3%)	596	1 (14%)
Uto	122	1 (2%)	0	0	0	0
Not reported	1343	3 (7%)	1343	3 (9%)	0	0

(Table 1 continues on next page)

definitions (7·01, 3·43–14·33) showed positive associations between schistosome status and periportal fibrosis. Subgroup analyses remained robust when studies showing outlier effect sizes of 30 or more were excluded, except for the low ROB subgroup (appendix 1 pp 54–55).

The pooled effect size for current infection status was constructed from studies with high heterogeneity

	Systematic review synthesis (n=41)		Infection status meta-analyses (n=33)		Infection intensity meta-analyses (n=7)	
	Participants (n)	Studies	Participants (n)	Studies	Participants (n)	Studies
(Continued from previous page)						
Author-defined periportal fibrosis definition						
Niamey protocol patterns C–F	17001	15 (37%)	7636	12 (36%)	10790	5 (71%)
Mean of three periportal tracts measurements	7915	8 (20%)	7915	8 (24%)	0	0
Portal vein thickness	1035	2 (5%)	1035	2 (6%)	0	0
Network (interseptal) fibrosis	601	3 (7%)	166	1 (3%)	0	0
Doehring-Schwerdtfeger scores	1869	2 (5%)	596	1 (3%)	0	0
Niamey pattern scores	490	2 (5%)	143	1 (3%)	596	1 (14%)
Unique definitions	3033	8 (20%)	2936	7 (21%)	347	1 (14%)
Not reported	390	1 (2%)	390	1 (3%)	0	0

Data are n (%), unless otherwise indicated. The table shows only the studies that were eligible for meta-analysis for either infection status or infection intensity exposure, excluding six studies that were only synthesised narratively (figure 1).

Table 1: **Summary of the characteristics of studies included in meta-analyses**

(I^2=95·81%). Removing outliers did not reduce heterogeneity (appendix 1 p 56). Heterogeneity was reduced in subgroup analyses by continent, setting, modified Niamey protocols, study design, fibrosis definition, and post-MDA (table 2). Absolute reductions in overall heterogeneity of at least 10% were found for South America (38·40%), health centres (35·52%), when an unmodified Niamey protocol for patterns C–F was followed (30·07%), in case–control designs (18·25%), with fibrosis defined based on the means of three periportal tract measurements (16·33%), and post-MDA (10·26%). Little (<10%) reduction in heterogeneity was found by focusing on a single species or low ROB studies. No clear indications of publication bias or small study effects were observed (appendix 1 p 58).

11 (29%) of 41 studies reported a measure of intensity of schistosome infection against periportal fibrosis (appendix 1 p 58).[7,25,26,33–36,39,46,49,55] However, only seven (17%) studies provided similar measurements of current schistosome infection intensity to enable a meta-analysis.[7,25,26,36,39,49,55] Pooled effect sizes for unadjusted[7,25,26,36,39,49] and adjusted analyses considering at least age and sex are shown in figure 4.[7,25,36,55] No significant differences in pooled effect sizes were observed between infection intensity categories and periportal fibrosis.

Discussion

WHO guidelines use current infection intensity cutoffs of less than 5% prevalence or less than 1% prevalence of heavy infection intensities as proxy indicators of schistosomiasis-related morbidity to monitor control and elimination, respectively.[6] To assess these guidelines for periportal fibrosis, we synthesised 41 studies and did a meta-analysis of 33 of those studies for infection status and seven studies for infection intensity. The studies that were meta-analysed included 26 322 participants from 17 countries endemic for *S mansoni*, *S japonicum*, or *S mekongi*. Current schistosome infection status was shown to affect periportal fibrosis but was dependent on study design, moderate to high ROB, and studies done in sub-Saharan Africa before widespread MDA.

The irrelevance of infection intensity in our study either conveys important information on disease pathogenesis or simply shows the incompleteness of the existing literature. Current infection intensity might not be the best proxy measure of history of exposure that reflects chronic infection, reinfection, or current cumulative fluke burden—all of which are important to the long timelines needed for periportal fibrosis development.[7] Similarly, current infection intensity does not narrow down risk groups for periportal fibrosis given that the highest average intensities are found in school-aged children[57] rather than adults, who are more likely to have periportal fibrosis.[7] However, only seven eligible studies could be included in our meta-analysis for infection intensity and periportal fibrosis.[7,25,26,36,39,49,55] Additionally, most of these studies defined the comparator group as low infection intensity rather than uninfected participants. This meta-analysis showed that, at present, there is insufficient evidence to support using WHO guidelines to monitor periportal fibrosis.[36,39,55]

We found that individuals with current schistosome infection were more likely to have periportal fibrosis compared with uninfected individuals, supporting WHO guidelines designed for MDA implementation, which prioritise treatment for communities with a high schistosomiasis prevalence.[6] This pooled effect size was greater in magnitude than indicators of the history of exposure reported elsewhere, such as fishing occupations.[7] However, the effect size was similar in magnitude to suggested effect sizes for other co-infections or comorbidities causing liver fibrosis, including HIV or hepatitis B.[7,58] With only two studies[7,25] providing adjusted effect sizes eligible for meta-analysis and no subgroup analysis possible by studies adjusting for HIV or hepatitis B co-infections, our pooled effect might be an

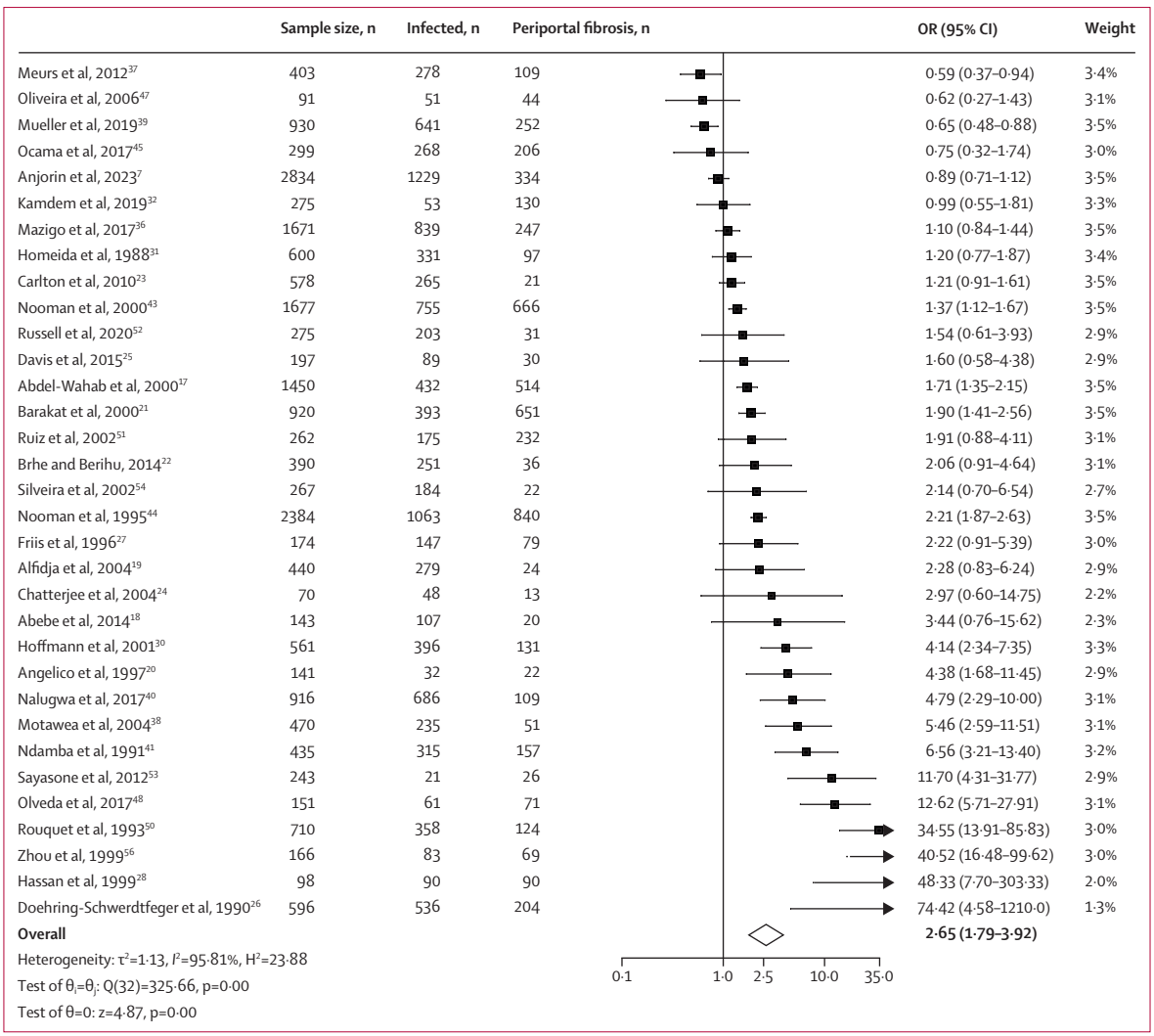

Figure 3: **Association of current schistosome infection status with periportal fibrosis**
Only unadjusted findings are shown. OR=odds ratio.

overestimation of the association of current infection status with periportal fibrosis. A lack of adjustment might be one reason for the high heterogeneity that remained despite investigation of several subgroups.

The effect of current infection status on periportal fibrosis was largely dependent on context and study design. A significant positive association was only observed in African and Asian regions and when participant sampling was directly from communities rather than schools or health centres. We suspect the significant effect in communities cannot be driven solely by older participants, as adults were included in health centre studies and community studies included preschool-aged children. The choice of overall study design affected the magnitude of the relationship between current infection status and periportal fibrosis. Case–control studies have the potential to highlight risk factors for uncommon disease outcomes, such as more severe stages of periportal fibrosis. However, no case–control studies used this aspect of design, choosing instead to match on infection exposure, age, and sex rather than disease outcomes, to retrospectively ascertain the relevance of a range of risk factors.[26,28,38,40,50,56] Hence, it is questionable whether the larger effect size in case–control designs represents the true effect size of infection status. Future studies should consider case–control designs that match on disease outcome, especially within existing resource constraints of health systems. For example, patients with prediagnosed, severe stages of liver fibrosis might be easily identified by observable complications arising from portal hypertension and matched with individuals without such complications.

We found that only before 2003—before widespread introduction of MDA in sub-Saharan Africa[59]—was a significant association observed between current infection status and periportal fibrosis. The loss of association between current infection status and periportal fibrosis

	Number of studies	Number of participants	Number of participants infected with schistosomes	Number of participants with periportal fibrosis	Odds ratio (95% CI)	I^2	Test of group differences
Continent	..	..	..	..	..	..	Q(2)=5·01; p<0·0001
Africa	26	19 059	10 054	5167	2·32 (1·57–3·41)	94·98%	..
Asia	4	1138	430	187	8·83 (2·00–39·06)	94·63%	..
South America	3	620	410	298	1·32 (0·60–2·92)	57·41%	..
Species*	..	..	..	..	..	..	Q(1)=1·57; p=0·21
Schistosoma mansoni	29	19 679	10 464	5465	2·18 (1·53–3·11)	94·12%	..
Schistosoma japonicum	3	895	409	161	8·22 (1·06–99·62)	94·12%	..
Study setting†	..	..	..	..	..	..	Q(2)=0·59; p=0·75
Community	23	17 816	9094	4782	2·48 (1·53–4·03)	97·16%	..
School	4	707	437	271	3·39 (0·81–14·13)	89·12%	..
Health centres	4	1616	1027	416	1·86 (0·81–4·31)	60·29%	..
Study design‡	..	..	..	..	..	..	Q(1)=23·02; p<0·0001
Cross-sectional	26	15 508	8048	4623	1·84 (1·36–2·47)	91·02%	..
Case-control	6	2475	1617	695	18·91 (7·65–46·73)	77·56%	..
Sub-Saharan Africa MDA§	..	..	..	..	..	..	Q(1)=8·00; p<0·0001
Pre-MDA (before 2003)	7	3146	2131	805	5·38 (2·03–14·25)	89·83%	..
Post-MDA (inclusive of 2003 or after)	11	8333	4644	1504	1·19 (0·82–1·74)	83·55%	..
Ultrasound protocol¶	..	..	..	..	..	..	Q(2)=3·52; p=0·17
Niamey	13	8604	4781	1576	1·57 (0·95–2·59)	91·28%	..
Cairo	10	8222	3580	3145	2·77 (1·53–5·04)	96·86%	..
Alternative	7	2648	1903	745	4·19 (1·33–13·23)	92·46%	..
Fibrosis definitions	..	..	..	..	..	..	Q(2)=15·62; p<0·0001
Niamey protocol patterns C–F	12	7636	4039	1501	1·26 (0·77–2·04)	90·61%	..
Mean of three periportal tract measurements	8	7915	3465	3054	1·84 (1·44–2·36)	79·48%	..
Other definitions	11	4280	26 603	867	7·01 (3·43–14·33)	87·71%	..
Niamey modification‖	..	..	..	..	..	..	Q(1)=0·01; p=0·94
Niamey	8	5164	2649	844	1·17 (0·79–1·72)	65.74%	..
Modifications to Niamey	4	3298	2071	671	1·21 (0·50–2·95)	91·58%	..
Risk of bias (granular)	..	..	..	..	..	..	Q(2) =5·70, p=0·058
Low	7	6485	3423	1071	1·51 (0·82–2·78)	92·24%	..
Medium	18	12 336	6232	3852	2·27 (1·47–3·52)	95·09%	..
High	8	1996	1239	729	7·40 (2·33–23·52)	89·38%	..
Risk of bias	..	..	..	..	..	..	Q(1)=4·36; p=0·037
Low or medium	25	18 821	9655	4933	2·04 (1·42–2·92)	94·81%	..
High	8	1996	1239	729	7·40 (2·33–23·52)	89·38%	..

MDA=mass drug administration. Q(1)=one degree of freedom. Q(2)=two degrees of freedom. *One study was not included for species *Schistosoma mekongi*. †Two studies were not included conducted in the workplace and both a health centre and community. ‡One cohort study was not included. §For MDA, 15 studies were not included—14 were not in sub-Saharan Africa and for one study it was unclear whether it took place before or after 2003. ¶Three studies were not included that did not report the protocol. ‖21 studies were not included as the outcome did not include Niamey patterns C–F.

Table 2: **Subgroup analyses**

after 2003 for studies within sub-Saharan Africa might be attributed to successful reduction in schistosome infection prevalence after repeated MDA, yet with residual morbidities remaining after treatment with praziquantel.[9] However, in this context only intestinal schistosomes were considered, and MDA has been shown to be more effective at reducing morbidity in urinary schistosomiasis.[60] Alternatively, MDA might have introduced heterogeneity into the known infection epidemiology in endemic populations due to systematically missing certain individuals across multiple rounds of MDA.[9] Our findings might reflect the treatment history of individuals through MDA. Heterogeneity between studies was reduced by over 10% after MDA compared with before MDA. Future studies are needed to track the same individuals or the same targeted populations over multiple years of MDA to

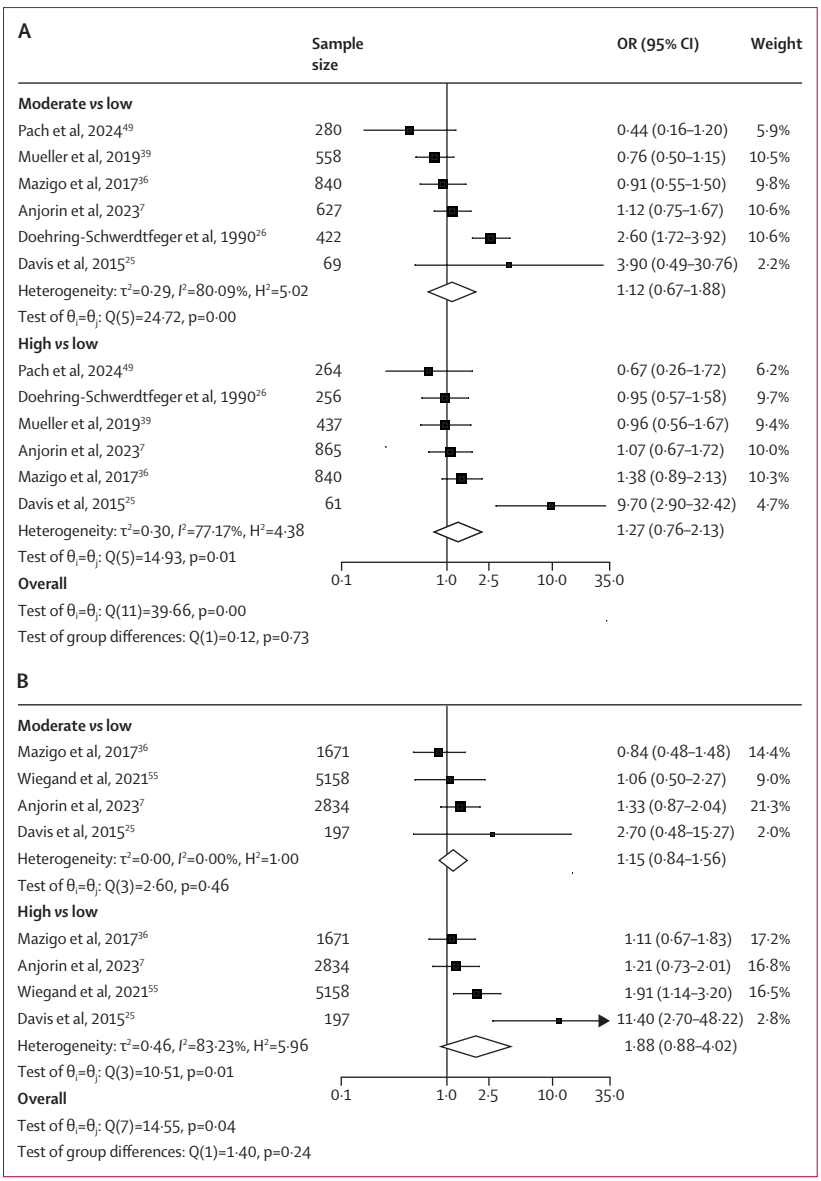

Figure 4: **Association between current schistosome infection intensity and periportal fibrosis**
(A) Meta-analyses with unadjusted findings. (B) Meta-analysis with adjusted findings where all models do not include uninfected people. All studies were minimally adjusted for at least age and sex. OR=odds ratio.

ascertain how MDA affects the onset or progression of periportal fibrosis.

Significant associations between infection status and periportal fibrosis were only found when periportal fibrosis was defined as the mean of three periportal tract measurements rather than Niamey image patterns C–F. This difference might be due to the Niamey image patterns encompassing a wide range of fibrosis types (periportal and portal) of varying levels of severity. There might also have been differences in distributions of C–F grades between studies. Although studies measuring periportal tracts initially showed less heterogeneity, when modifications to the Niamey protocol were considered heterogeneity between C–F image pattern studies adhering to the original protocol was lower than between studies measuring periportal tracts. A systematic review by Ockenden and colleagues[1] highlights challenges with the existing standardisation of the Niamey protocol, including insufficient ultrasound image acquisition guidance, selective subjective use of specific elements of the protocol, a range of personal interpretations of image patterns, and an absence of quality control and validation. Given most studies in this meta-analysis and the wider literature applied the current WHO-recommended Niamey protocol to diagnose periportal fibrosis, there is a need to revise this guidance to simplify image acquisition procedures, introduce clearer terminology for liver fibrosis outcomes, and distinguish outcomes by stage of severity where criteria are determined by expected clinical complications.[1,4]

There were many limitations of the existing literature. We applied a search string that was not limited to periportal fibrosis to capture all types of liver fibrosis. However, some studies used liver parenchymal fibrosis and periportal fibrosis interchangeably, introducing heterogeneity into definitions.[23,48] The likelihood of periportal fibrosis changes across the lifespan of an individual, increasing in adolescence, remaining stable in adulthood, and declining after age 55 years.[7] Age was poorly reported, without clear ranges, and no breakdowns of periportal fibrosis by age were provided, which remains an area for future study. Most studies were of high or moderate ROB, with adjusted analyses considering common confounders of age and sex rarely reported and insufficiently shared to calculate any adjusted pooled effect sizes. We focus here only on liver fibrosis. To confirm the generalisability of our findings beyond periportal fibrosis and intestinal schistosomiasis, our study design can be applied in future meta-analyses to evaluate WHO guidelines for other morbidities of varying severity across *Schistosoma* species.

In conclusion, current infection status with intestinal schistosomes was tenuously associated with periportal fibrosis, but no association was observed for WHO categories of current infection intensity. Further epidemiological studies that adjust for age and gender, and capture the influence of current, chronic, and historical schistosome infection on periportal fibrosis, are required. At present, there is no strong support for approximating periportal fibrosis using current schistosome infection intensity, and infection status appears irrelevant within the context of repeated MDA, which is now routine in areas endemic with schistosomiasis. Therefore, there is an urgent need to directly monitor periportal fibrosis-related morbidity in areas endemic for schistosomiasis and to develop strategies to enable such monitoring within already constrained health systems.

Contributors
Resources and supervision: GFC. Conceptualisation: GFC. Data curation: AE, LW, DBT, HC, and FR. Pre-registration protocol, data extraction tool, and risk of bias tool: AE, RM, and GFC. Data validation: LW, NR, and RM. Investigation and methodology: AE, LW, RM, and GFC. Formal analysis and visualisation: AE and LW. Writing—original

draft: AE, LW, and GFC. Writing—review and editing: all authors. Funding acquisition: GFC. LW, RM, and GFC had full access to the data and accept responsibility for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All data used for this study were extracted from publicly available sources. The data have been provided as a supplementary dataset in appendix 2.

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