Review Article

Morbidity Associated with Chronic *Strongyloides stercoralis* Infection: A Systematic Review and Meta-Analysis

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Abstract. *Strongyloides stercoralis*, a worldwide-distributed soil-transmitted helminth, causes chronic infection which may be life threatening. Limitations of diagnostic tests and nonspecificity of symptoms have hampered the estimation of the global morbidity due to strongyloidiasis. This work aimed at assessing *S. stercoralis*-associated morbidity through a systematic review and meta-analysis of the available literature. MEDLINE, Embase, CENTRAL, LILACS, and trial registries (WHO portal) were searched. The study quality was assessed using the Newcastle–Ottawa scale. Odds ratios (ORs) of the association between symptoms and infection status and frequency of infection-associated symptoms were calculated. Six articles from five countries, including 6,014 individuals, were included in the meta-analysis—three were of low quality, one of high quality, and two of very high quality. Abdominal pain (OR 1.74 [CI 1.07–2.94]), diarrhea (OR 1.66 [CI 1.09–2.55]), and urticaria (OR 1.73 [CI 1.22–2.44]) were associated with infection. In 17 eligible studies, these symptoms were reported by a large proportion of the individuals with strongyloidiasis—abdominal pain by 53.1% individuals, diarrhea by 41.6%, and urticaria by 27.8%. After removing the low-quality studies, urticaria remained the only symptom significantly associated with *S. stercoralis* infection (OR 1.42 [CI 1.24–1.61]). Limitations of evidence included the low number and quality of studies. Our findings especially highlight the appalling knowledge gap about clinical manifestations of this common yet neglected soil-transmitted helminthiasis. Further studies focusing on morbidity and risk factors for dissemination and mortality due to strongyloidiasis are absolutely needed to quantify the burden of *S. stercoralis* infection and inform public health policies.

INTRODUCTION

Strongyloides stercoralis is a soil-transmitted helminth (STH) affecting 100–370 million people worldwide, mostly in tropical and subtropical regions.¹ After penetration of the intact skin of the human host, the infective larvae (L3) migrate through the body tissues and molt. This acute phase of the infection is often completely asymptomatic or goes unnoticed. The adult female nematode settles in the intestine and produces eggs that hatch in the last part of the bowel, so that the first-stage larvae of the parasite (L1) and not the eggs are shed with feces. Some larvae molt to L3 before excretion and can reinfect the host by penetrating through the perianal skin or the rectal mucosa. This peculiar “autoinfective” cycle allows the perpetuation of the infection through the years, in the absence of further exposure to contaminated soil, contrary to what happens with the other STH infections.² Thus, strongyloidiasis is a chronic infection, which may persist lifelong even in the absence of reinfection. Another peculiarity of *S. stercoralis* is its capacity to cause a life-threatening syndrome, as a result of accelerated parasite replication and larval dissemination to organs where migration usually does not occur. This condition occurs in individuals with certain types of immunosuppression, such as due to corticosteroid intake, but other risk factors for dissemination are still poorly known.² Although the treatment with ivermectin is highly effective in the chronic phase of infection, it often fails in the case of hyperinfection/dissemination.³ Clinically, chronic infection with

S. stercoralis presents with nonspecific symptoms involving the skin (itching and urticaria), the gastrointestinal tract (diarrhea and abdominal pain/distention), and the respiratory tract (asthma-like symptoms and dyspnea).² However, the strength of the association between the infection status and these nonspecific symptoms commonly presented by infected individuals has been poorly defined. From the public health perspective, the issues related to this nonspecificity and uncertain association with infection of clinical symptoms, with the possible exception of *larva currens*,² together with the inaccuracy of the diagnostic tests for strongyloidiasis,^{4,5} have had important consequences, such as 1) underestimation of the global prevalence of strongyloidiasis with previous estimates having been questioned only in recent years¹ and 2) difficulty in evaluating the impact of the infection in terms of morbidity and mortality on populations living in endemic areas. As a result, the burden of strongyloidiasis is still unclear, and this has hampered the appraisal and implementation of specific control strategies in endemic areas. Indeed, *S. stercoralis* has not yet been included in the WHO programs for the control of STHs, despite the potentially fatal syndrome it may cause.

The aim of this systematic review and meta-analysis was to assess the morbidity due to *S. stercoralis* infection, through identification of symptoms associated with the infection status (primary outcome) and by estimating the proportion of infected people reporting those symptoms. This was conceived as a first step toward estimating the clinical burden caused by strongyloidiasis to support public health stakeholders in evaluating the need of implementing specific control programs. Although the burden of disease estimates should also be based on severe morbidity and mortality caused by the disseminated infection, it is extremely difficult

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to quantify these conditions because of the impossibility of performing prospective controlled trials without intervention on infected people and the difficulty in obtaining good quality data with other study designs.³ For this reason, severe morbidity and mortality were not addressed in the present review.

METHODS

Search strategy. The protocol of the review was published in the PROSPERO international prospective registry of systematic reviews⁶ (registration no. CRD42018088225). The following databases were searched: MEDLINE (PubMed), Embase, CENTRAL (Cochrane Library), and LILACS (Bireme). In addition, we searched trial registries via the WHO portal. The search was performed, in all the database sources, on October 31, 2017. Databases were searched using the keywords:

“strongyloidiasis”, “*Strongyloides stercoralis*”, “soil transmitted helminths”, “anguillulose”, and “anguillulosis”. The detailed strategy is available in Supplemental Table 1. The search results were combined and duplicates removed before screening for relevance. The reference lists of all included studies were searched for other potentially relevant articles. No restriction was applied regarding language, publication date, or publication status. The work is presented according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.⁷

Population, inclusion and exclusion criteria, study design, and outcomes. Original studies reporting symptoms presented by individuals, of all ages and both sexes, infected with *S. stercoralis* were included in this review. No restriction was applied regarding publication type (e.g., research article or conference report) or setting (endemic or non-endemic area

FIGURE 1. Flow diagram for search and selection of included studies.

and field or clinical setting). We included cross-sectional, case-control, and interventional studies. Cross-sectional and case-control studies, including a control group not infected with *S. stercoralis*, were used for the meta-analysis to evaluate the association of infection with symptoms; interventional studies were also included to determine the proportion of *S. stercoralis*-infected individuals with symptoms. Case reports and case series, as well as review articles, were excluded. Among studies with eligible design, those focusing on a subset of infected patients (e.g., patients with *S. stercoralis* larval counts above a designated threshold) were excluded. Only studies where *S. stercoralis* infection was diagnosed by Baermann method or stool culture were included; other copromicroscopic methods (e.g., direct fecal smear examination, Kato-Katz, and formol-ether concentration) and serology were excluded because of low sensitivity and specificity, respectively, which would have implied the misclassification of a high proportion of individuals. In the reviewed studies, self-reported symptoms were assessed by questionnaires.

Study selection and data extraction. Two authors (F. T. and E. M.) reviewed titles and abstracts of publications identified by the search to identify all studies that potentially met the inclusion criteria. After having obtained the full text of the potentially eligible articles, the two authors independently assessed whether or not each study met the inclusion criteria using an eligibility form. Potentially eligible studies were excluded if 1) the full text and abstract were both unavailable or only the abstract was available but did not convey the needed data, 2) symptoms were not described, 3) symptoms were indicated but the needed data were not extractable, 4) symptoms were described for a subgroup of infected individuals only, 5) the diagnostic method was not mentioned or not eligible, 6) *S. stercoralis* was not investigated, and 7) the study was duplicated. When F. T. and E. M. did not reach a consensus, a third review team member (D. B.) made the final decision. Two authors (F. T. and S. S.) independently performed the data extraction using a predesigned data extraction form (Excel file). Any disagreement regarding the data extraction was resolved by discussion between the two

authors. When necessary, a third author (D. B.) facilitated the discussion until a consensus was reached. The following data were extracted: 1) study design, 2) study methodology (diagnostic method and recall time frame of symptoms), 3) study population (number of individuals examined and setting [village-based or selected data set]), and 4) target symptoms (symptoms investigated and number of individuals reporting symptoms). Among reported symptoms, the following were included in our analysis, based on the results of self-reported symptoms extracted by eligible articles: gastrointestinal (specifically abdominal pain and diarrhea), respiratory (specifically cough), and dermatological (specifically diffuse itching and pruritic rash/urticaria), as reported in each study.

Statistical analysis and data synthesis. Odds ratios (ORs) of the association between symptoms and infection status for each study were calculated, together with their corresponding 95% CI. The Mantel-Haenszel method with fixed effect and random effects models was then used to obtain a pooled estimate of the effect of each symptom. The I^2 and the DerSimonian-Laird estimator for τ^2 were also calculated as measures of heterogeneity. Forest plots were used to illustrate the point estimate with 95% CI. The frequency of symptoms significantly associated with the infection was calculated as the proportion of the total number of infected individuals with each self-reported symptom over the total number of infected individuals in all eligible studies; for interventional studies, the number of infected individuals with symptoms pretreatment was extracted. The meta-analysis was performed using R version 3.4.3,⁸ package "meta," command "metabin." A P -value ≤ 0.05 was considered statistically significant.

Quality assessment. The quality of each study included in the meta-analysis was assessed using an adapted version of the Newcastle-Ottawa quality assessment scale,⁹ which consisted of three main domains: selection of studies, comparability, and outcome. Supplemental Table 2 summarizes the items included in each domain and the characteristics for the attribution of the "stars" (scoring system). Quality was assessed at study level and was expressed as low (in case a single or two stars were assigned to the study), high (three or four stars), or very high (five to six stars).

TABLE 1
Main characteristics of included articles

Study*	Design	Country	Age group	Diagnostic test	Ss infected individuals	Abdominal pain†	Diarrhea†	Cough	Itching	Urticaria†
Forrer et al. ^{11*}	cs	Cambodia	All ages	Stool culture + Baerman	853	y	y	y	y	y
Khieu et al. ^{13*}	cs	Cambodia	All ages	Stool culture + Baerman	601	y	y	y	y	y
Suputtamongkol et al. ²⁵	i	Thailand	Adults	Stool culture	90	y	y	n	n	n
Becker et al. ^{10*}	cc	Ivory Coast	All ages	Stool culture + Baerman	37	y	y	y	y	y
Herrera et al. ^{12*}	cc	Peru	All ages	Baermann	50	y	y	n	n	y
Marcos et al. ¹⁹	i	Peru	All ages	Baermann	33	n	n	n	n	y
Zaha et al. ²⁶	i	Japan	Adults	Stool culture	50	y	y	n	y	y
Rodriguez Calabuig et al. ^{15*}	cc	Spain	Adults	Stool culture + Baerman	47	n	n	y	y	n
Cremades Romero et al. ¹⁷	i	Spain	Adults	Stool culture	37	n	y	y	y	y
Marti et al. ²⁰	i	Tanzania	Children	Baermann	333	n	n	y	y	y
Shikiya et al. ²²	i	Japan	Adults	Stool culture	23	n	y	n	n	n
Zaha et al. ²⁷	i	Japan	Adults	Stool culture	299	y	y	n	y	y
Oyakawa et al. ²¹	i	Japan	Adults	Stool culture	161	y	y	n	y	y
Shikiya et al. ²⁴	i	Japan	Adults	Stool culture	54	y	y	n	y	y
Shikiya et al. ²³	i	Japan	Adults	Stool culture	59	y	y	n	y	y
Oliver et al. ^{14*}	cc	Tasmania	Adults	Stool culture	18	y	y	n	n	y
Grove ¹⁸	i	Australia	Adults	Stool culture	42	n	y	n	n	y

cc = case-control; cs = cross-sectional; i = interventional; n = no-symptom not reported in the article; Ss = *Strongyloides stercoralis*; y = yes-symptom reported in the article.

* Included in the meta-analysis.

† Symptoms associated with *Strongyloides stercoralis* infection as assessed by meta-analysis.

RESULTS

The search and selection of included studies is shown in Figure 1. The database search retrieved a total of 11,152 records. After duplicates were removed, 8,515 records were screened for potential eligibility by title and abstract, and 110 articles were selected for full text review. Of these, 93 were further excluded, leaving 17 articles for the evaluation of the frequency of *S. stercoralis*-associated symptoms in the infected population, and, among these, six^{10–15} were eligible for meta-analysis of the association between *S. stercoralis* infection and the selected symptoms (Table 1).

Among described symptoms, gastrointestinal (specifically abdominal pain and diarrhea), respiratory (specifically cough), and dermatological (specifically diffuse itching and itching rash/urticarial) were consistently reported by three or more

studies and were included in the meta-analysis. Other mentioned symptoms, such as asthma, loss of appetite/anorexia, tiredness, stunting, muscle pain, fever, constipation, and anemia, were not included.

***Strongyloides stercoralis* infection and association with gastrointestinal, respiratory, and cutaneous symptoms.**

Six studies reported the frequency of at least one of the five target symptoms in *S. stercoralis*-infected individuals and uninfected controls. In particular, three studies reported the frequency of all target symptoms, two studies reported the frequency of three target symptoms, and one study reported only the frequency of two of the target symptoms (Table 1). Of the six studies included, three were considered to be of low quality, one of high quality, and two of very high quality (Supplemental Table 3). Heterogeneity among studies was high (I^2 ranging from

ABDOMINAL PAIN

URTICARIA

DIARRHEA

FIGURE 2. Forest plots for the association between *Strongyloides stercoralis* infection and symptoms (abdominal pain, urticaria, and diarrhea).

67% to 85%); hence, the interpretation of these results should be based on the random effects model. However, we also present the results of the fixed effects models to provide a more complete picture of the summary effect.¹⁶

When all eligible studies were analyzed (including 1,606 patients and 4,408 controls), abdominal pain (OR 1.13 [CI 1.00–1.29] fixed effects model and OR 1.74 [CI 1.07–2.94] random effects model), diarrhea (OR 1.15 [CI 1.02–1.29] fixed effects model and OR 1.66 [CI 1.09–2.55] random effects model), and urticaria (OR 1.47 [CI 1.29–1.67] fixed effects model and 1.73 [CI 1.22–2.44] random effects model) were associated with *S. stercoralis* infection, whereas cough and itching were not. The results are shown in Figures 2 and 3. After removing the low-quality studies, the meta-analysis was repeated with a smaller number of individuals (1,491 patients and 4,287 controls); urticaria remained the only symptom significantly associated with *S. stercoralis* infection (OR 1.42 [CI 1.24–1.61] fixed and random effects models) (Figure 4).

Of the included articles, only three reported coinfection with hookworms, two of which in a high percentage of *S. stercoralis*-infected people (38–47%),^{11,13} whereas this figure was not detailed in the third article.¹⁰

Frequency of *S. stercoralis*-associated symptoms in the infected population. Seventeen studies^{10–15,17–27} presented the number of infected individuals who self-reported at least one of the five target symptoms (Table 1). When considering only studies reporting symptoms associated with *S. stercoralis* infection by meta-analysis, abdominal pain was reported by 1,206 individuals (53.08%) of 2,272 investigated by 11 studies, diarrhea by 987 individuals (41.57%) of 2,374 investigated by 14 studies, and urticaria/rash by 730 individuals

(27.79%) of 2,627 investigated by 14 studies. Although we did not carry out a formal quality assessment of the studies used to evaluate the frequency of *S. stercoralis*-associated symptoms, it must be highlighted that in only three studies^{10,11,13} self-reported symptoms experienced in the 2–4 weeks were specifically investigated. In one case,²⁵ symptoms were those reported at the time of therapy, and in all other cases, the recall time frame was not stated.

DISCUSSION

Strongyloides stercoralis infection is among the most neglected and elusive parasitic conditions worldwide. Our review attempted for the first time to explore rigorously the available published evidence of the morbidity due to this infection, to photograph the type of data available, and to assess completeness or knowledge gaps. We found the appalling result that there is a lack of studies exploring this condition. This, as is typically the case for neglected diseases, results in lack of evidence, which should not be interpreted as the absence of relevant morbidity due to chronic infection in the affected populations. Urticaria was the symptom with the strongest association with strongyloidiasis. This was confirmed when considering only studies of high quality. Diarrhea and abdominal pain had weaker associations with the parasitic infection, but this result was not confirmed when only studies with good quality scores were included in the meta-analysis. Cough and itching did not show any association with strongyloidiasis. These results were somehow surprising. Indeed, abdominal pain and diarrhea are commonly reported by infected people, as also confirmed by the results of our

COUGH

ITCHING

FIGURE 3. Forest plots for the association between *Strongyloides stercoralis* infection and symptoms (cough and itching).

systematic review, which found that the proportion of infected individuals reporting these two symptoms was high. It also seems intuitively difficult to exclude itching from the symptoms characterizing affected individuals, when results demonstrated that urticaria is associated with strongyloidiasis.

In general, it should be taken into account that data collection with questionnaires might have been influenced by many factors, including the recall time for the symptoms (which can be intermittent and thus not present in the time frame considered) and the different meaning of the medical terminology used in the questionnaires compared with that meant by lay people. Therefore, these results cannot be considered conclusive and highlight the need for further, well-designed studies more accurately addressing the type and characteristics of symptoms generally considered as associated with strongyloidiasis.

It must also be stressed that, in our present work, it was not possible to evaluate other medically relevant symptoms that may affect infected individuals but that have been only recently addressed in studies focusing on strongyloidiasis (for instance, anemia²⁸ and stunting in children¹¹). Therefore, these should be evaluated in future work and included in the estimate of the clinical burden caused by strongyloidiasis, together with severe and fatal cases that are clearly underdiagnosed and underreported.³

Limitations. Our work has several limitations. First, *S. stercoralis* has been receiving a relatively higher attention

only in recent years, so we found few studies specifically concerning this parasite, and most of them were of low quality. The diagnostic methods used in these studies, although more sensitive than the widely used Kato–Katz, direct smear, and formol–ether concentration techniques, still miss a high proportion of infected people; hence, the control groups might have included many individuals misclassified as “uninfected.” Furthermore, symptoms associated with strongyloidiasis are not constantly present in all affected patients. These factors may contribute to an underestimation of the morbidity. Moreover, very few studies were eligible for the meta-analysis and were further reduced if stringent quality criteria were applied. The presence of coinfections causing similar symptoms is another confounding factor that could be partly overcome by statistical adjustments. However, information on coinfection was often missing or poorly detailed in the included articles, and hence, we could not further analyze this factor. Finally, the small number of studies did not allow the association and frequency of symptoms in subgroups of individuals, such as in children, to be evaluated.

CONCLUSION

In conclusion, our work highlights the appalling lack of studies addressing morbidity associated to chronic strongyloidiasis that makes it difficult to estimate the burden of infection, also in light of the known knowledge gap about the

ABDOMINAL PAIN

Study	S.s infected		Controls	
	Events	Total	Events	Total
Forrer et al. (2017)	709	853	1,479	1,891
Khieu et al. (2014)	278	601	1,121	2,260
Becker et al. (2011)	15	37	34	136
Fixed effects model	1,491		4,287	
Random effects model				
Heterogeneity: $I^2 = 85\%$, $\tau^2 = 0.0994$, $P < 0.01$

DIARRHEA

Study	S.s infected		Controls	
	Events	Total	Events	Total
Forrer et al. (2017)	513	853	1,086	1,891
Khieu et al. (2014)	276	601	1,013	2,260
Becker et al. (2011)	7	37	18	136
Fixed effects model	1,491		4,287	
Random effects model				
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = 0.68$

URTICARIA

Study	S.s infected		Controls	
	Events	Total	Events	Total
Forrer et al. (2017)	472	853	880	1,891
Khieu et al. (2014)	138	601	397	2,260
Becker et al. (2011)	6	37	16	136
Fixed effects model	1,491		4,287	
Random effects model				
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = 0.99$

FIGURE 4. Forest plots for the association between *Strongyloides stercoralis* infection and symptoms after removal of the low-quality studies.

most severe disease manifestations, that is, disseminated strongyloidiasis and associated mortality. Considering that strongyloidiasis is a potentially fatal STH infection, the neglect of this parasitic infection is no longer justifiable, and high-quality studies focusing on this infection are much needed to inform public health policies.

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