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Review

Intestinal parasites and HIV in Ethiopian tuberclosis patients: A systematic review and meta-analysis

Getenet Dessie, MSc[1,*], Ayenew Negesse, MPH[2], Fasil Wagnew, MSc[3], Desalegne Amare, MSc[1], Balew Zeleke Tiruneh, MSc[1], Henok Mulugeta, MSc[3], Berhanu Abebaw Mekonen, MPH[4], Dessalegn Haile, MSc[3], Tilksew Ayalew[1], Tesfa Dejenie Habtewold, PHD[5,6,7]

[1] *Department of Nursing, School of Health Science, College of Medicine and Health Science, Bahr Dar University, Bahir Dar, Ethiopia*
[2] *Department of Human Nutrition and Food Science, College of Health Science, Debre Markos University, Debre Markos, Ethiopia*
[3] *Department of Nursing, College of Health Science, Debre Markos University, Debre Markos, Ethiopia*
[4] *Department of Nutrition, School of Public Health, College of Medicine and Health Science, Bahir Dar University, Bahr Dar, Ethiopia*
[5] *Department of Quantitative Economics, School of Business and Economics, Maastricht University, Maastricht*
[6] *Department of Clinical Psychological Science, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht*
[7] *Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands*

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A B S T R A C T

Background: The distribution of intestinal parasites among patients with tuberculosis in Ethiopia is not well understood.
Objective: This systematic review and meta-analysis was designed to determine the pooled national prevalence of intestinal parasites and its association with HIV among patients with tuberculosis in Ethiopia.
Methods: Original articles were searched in PubMed, Google Scholar, EMBASE, World Health Organization's HINARI portal, and supplemented by the hand searching of cross-references. Data were extracted using a standard data extraction checklist. Random-effects model was used to estimate the pooled prevalence of intestinal parasites and odds ratio of the association. The I^2 statistic was utilized to quantify statistical heterogeneity across studies. Funnel plot asymmetry and Egger regression tests were used to check for publication bias. The analysis was done by STATA version 14 for Windows.
Results: Of 725 identified studies, 12 articles were eligible for inclusion in the final analysis. The pooled national prevalence of intestinal parasites among patients with tuberculosis in Ethiopia was 36.1% (95% CI, 22.1–50.1; $I^2 = 98.7\%$). Subgroup analysis based on study design indicated that the prevalence of intestinal parasite among case-control studies was 41.69% (95% CI, 28.6–54.8; $I^2 = 95.1\%$). The odds of intestinal parasites among patients with tuberculosis–HIV coinfection was not significantly different compared with patients with tuberculosis without HIV/AIDS (odds ratio = 0.99; 95% CI, 0.7—4.7; $P = 0.96$).
Conclusions: In Ethiopia, at least 1 out of 3 patients with tuberculosis have an intestinal parasite. These findings suggest a need of more attention on increasing screening tuberculosis patients for intestinal parasites and deworming interventions. (*Curr Ther Res Clin Exp*. 2020; 81:XXX–XXX)

Introduction

Parasitic and tuberculosis (TB) infections are among the most prevalent infections in humans in developing countries.[1] The overlap of TB and parasitic disease morbidity presented with high and consistent figures all over the world.[2–6] More than half of people with latent or active TB infections have intestinal parasite infection (IPI), which is common in high TB burden nations.[7] In Africa, one-third of TB patients have an IPI[8] that contributes to the high rate of therapeutic failure of pulmonary TB.[9]

It is evident that pulmonary TB and parasitic diseases were shown to be risk factors for each other and represented with high magnitude of comorbidity in developing countries.[8,10] Coinfection

* Address correspondence to: Getenet Dessie, Department of Nursing, School of Health Science, College of Medicine and Health Science, Bahr Dar University, PO Box 79, Bahr Dar, Ethiopia

E-mail address: ayalew.d16@gmail.com (G. Dessie).

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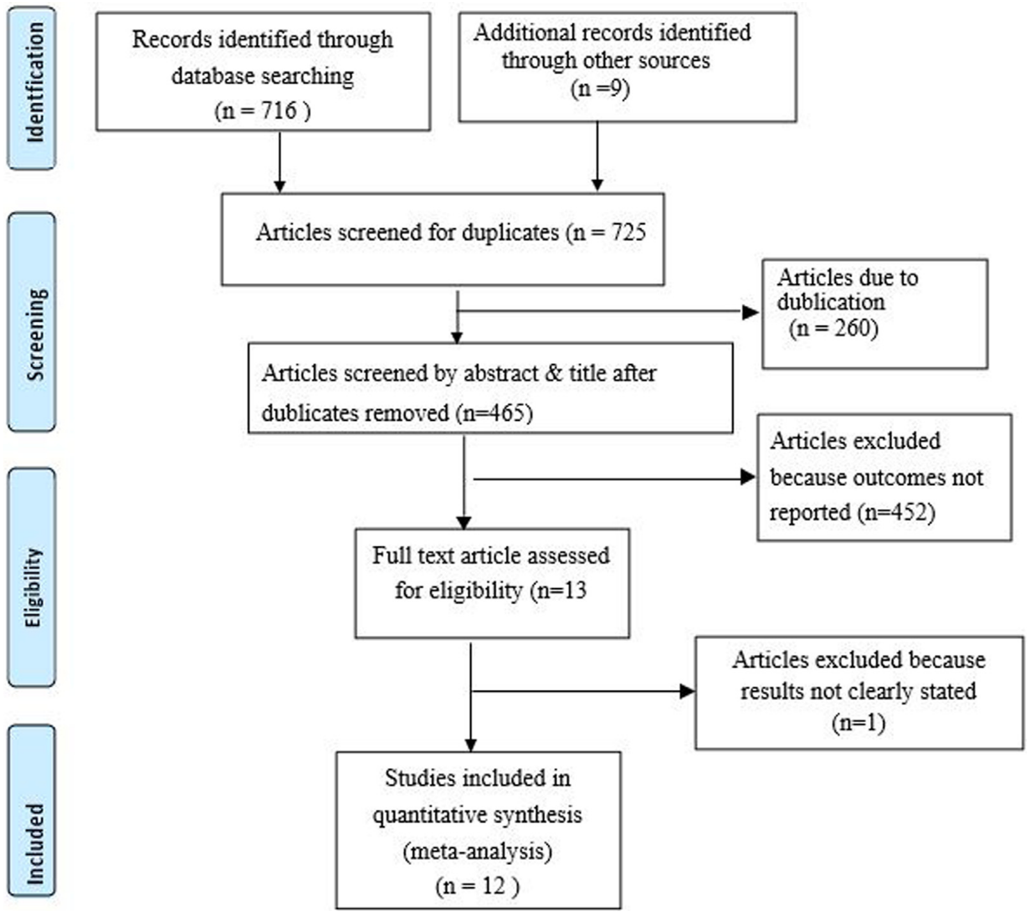

Figure 1. Flow diagram showing the procedure of selecting of studies.

may significantly inhibit the host's immune system, increase antibacterial therapy intolerance, and be detrimental to the prognosis of the disease. In addition, infection with parasitic diseases can alter the protective immune response to mycobacterium TB. This indicates that concomitant helminthic infections weaken immune resistance to mycobacterial infections.[11,12] Furthermore, the presence of intestinal parasites affects the effectiveness of vaccine against TB and increases the chance of developing active TB diseases after vaccination.[13]

In addition, parasitic infection presented with more severe radiological pulmonary disease in the number of involved lung zones at the end of TB treatment. In particular, simultaneous intestinal helminth infection in patients with newly diagnosed TB alters a patient's immunity profile that could favor persistent mycobacterium TB infection and a more protracted clinical course of the disease.[14,15]

In developing countries, parasitic worm infections among TB patients are common and increases the chance for TB complications.[16,17] Parasitic infection increases the chance of TB lung damage and induces the progression of a latent TB infection to active TB disease.[16,17] The presence of high TB progression, delay in clinical response and sustained infectiousness leads to high transmission rate of TB to healthy individuals.[18–20]

There are factors that increase the risk of having parasites infection among TB patients. Personal hygiene, residence, eosinophils count, and habit of washing vegetables/fruits are some of the factors listed in previous studies.[10,21,22] On 1 hand, the presence of immunocompromised diseases, such as HIV/AIDS, are associated with TB. On the other hand, HIV/AIDS is supposed to be a risk factor for IPIs.[23] Currently, there is high prevalence of TB/HIV comorbidity that was estimated to be from 22% to 25.6% in Ethiopia.[24–26] Parasitic infections represent a major public health problem in immunocompromised individuals.[23] HIV infection accounts for the highest prevalence of IPIs among TB patients in comparison with TB patients without immunodeficiency,[27] whereas another finding indicates significantly lower prevalence of IPIs among HIV-positive TB patients.[2]

In sum, high prevalence of TB and IPIs comorbidity can be explained by low level of socioeconomic and immunity status.[28] Literature about the prevalence of and risk factors for intestinal parasites among these vulnerable populations exhorts policy makers and program planners to pay due attention and take appropriate measures. There is limited understanding of the extent of parasitosis comorbidities with TB in Ethiopia. The few available evidences are inconclusive and inconsistent. Hence, pointing out the overall level of comorbidity might alarm policy makers and ministries of health into developing interventional guidelines or bidirectional frameworks for effective treatment of TB and parasite infection comorbidity as well as successful implementation of a national TB control and prevention strategy. This systematic review and meta-analysis aimed to determine the pooled national prevalence of IPI and its association with HIV among patients with TB in Ethiopia.

Methods

Search approach and appraisal of studies

Articles were accessed through web-based electronic database searches, desk reviews of the grey literature, and cross-references

Table 1
Characteristics of included studies for the present systematic review and meta-analysis, 2004–2018, in Ethiopia.

Reference	Publication year	Region	Diagnostic method for TB	Type of TB	Dominant parasite	Study design	Age of patients, y	Response rate, %	Funding	Prevalence, %	Quality score
Kassu et al[43]	2004	Amhara	Histopathological evidence, sputum smear, radiographic examination consistent with TB, clinical response to anti-TB chemotherapy	Pulmonary and exteral pulmonary TB	*Ascaris lumbricoides*	Cross-sectional	Not stated	100	Ministry of Education, Culture, Sports, Science, and Technology of Japan; Yakult Ltd, Japan; Gondar University	37.3	7
Elias et al[40]	2006	Amhara	Sputum smear microscopy	Pulmonary TB	*A lumbricoides*	Case control	≥10	73.7	Gondar University and SIDA/SAREC	71	6.5
Ramos et al[45]	2006	Oromia	Sputum smear microscopy	Not specified	*A lumbricoides*	Cross-sectional	>12	100	Not stated	44	6.5
Afework, et al[42]	2007	Amhara	Clinical, radiological, histopathological, and laboratory features of the patients following standard procedures	Not specified	*A lumbricoides*	Cross-sectional	15–80	100	University of Gondar	40.5	7
Mohammed et al[46]	2011	Oromia	Sputum smear microscopy	Pulmonary TB	Not stated	Case control	≥15	100	Jimma University	40.1	7
Abate et al[37]	2012	Amhara	Sputum smear, radiographic examination	Pulmonary TB	*A lumbricoides*	Case control	15–65 years	100	Not stated	29	6.5
Alemayehu et al[39]	2014	Amhara	Sputum smear, Xpert MTB/RIF assay, and culture	Pulmonary TB	Hookworm	Cross-sectional	2–80	100	Not stated	33.3	7
Abate et al[38]	2015	Amhara	Sputum smear, radiographic examination consistent with TB, clinical response to anti-TB chemotherapy	Not specified	*A lumbricoides*	Case control	15–60	100	Not stated	40	7
Hailu et al[41]	2015	Amhara	AFB smear microscopy	Pulmonary TB	Not stated	Case control	18–65	100	Hawassa University	49	7
Alemu and Mama[21]	2017	SNNPR	Sputum smear, radiographic examination	Pulmonary TB	*A lumbricoides*	Cross-sectional	15–65	100	Arba Minch University	26.3	7
Alemu et al[20]	2018	Addis Ababa	Sputum smear, Xpert MTB/RIF assay, and culture	Pulmonary TB	*Giardia lamblia*	Case control	19–34	100	Addis Abeba University	22	7
Tegegne et al[44]	2018	Amhara	Sputum smear	Pulmonary TB	*A lumbricoides*	Cross-sectional	≥5	100	University of Gondar	2	6.5

AFB = acid-fast bacilli; MTB/RIF = mycobacterium tuberculosis/rifampin; SAREC = Sustainable Agriculture Research and Extension Center; SIDA = Swedish International Development Cooperation Agency; SNNPR = Southern Nations, Nationalities, and Peoples' Region; TB = tuberculosis.

Table 2
Meta regression results on selected variables.

Variable	Coefficient	*P* value
Publication year	−3.9	0.06
Sample size	0.2	0.03
Adis Ababa[20]	−19	0.51
Amhara[37–42,44]	4.1	0.84
Oromia[45,46]	8.3	0.72
Cross-sectional[21,39,42–45]	14.7	0.23

of identified studies. The electronic databases searched were PubMed, Google Scholar, EMBASE, and the World Health Organization database portal for low- and middle-income countries that includes the Web of Science, SCOPUS, African Index Medicus, Cumulative Index to Nursing and Allied Health Literature, the World Health Organization Institutional Repository for Information Sharing, and African Journals Online databases. In addition, related articles were obtained through review of the grey literature available on institutional repository[29] and from reviewing cross-references of identified articles.

Searching was done using the following key terms: *intestinal diseases*, *parasitic*, *intestinal*, *diseases*, *parasitic*, *parasitic intestinal diseases*, *intestinal*, *parasites*, *intestinal parasites*, *intestinal helminthes*, *intestinal protozoa*, *soil-transmitted helminthes*, *tuberculosis*, *HIV*, *patients*, and *Ethiopia*. These key terms were combined used AND and OR Boolean operators. To allow a comprehensive search strategy, these key terms were predefined that included

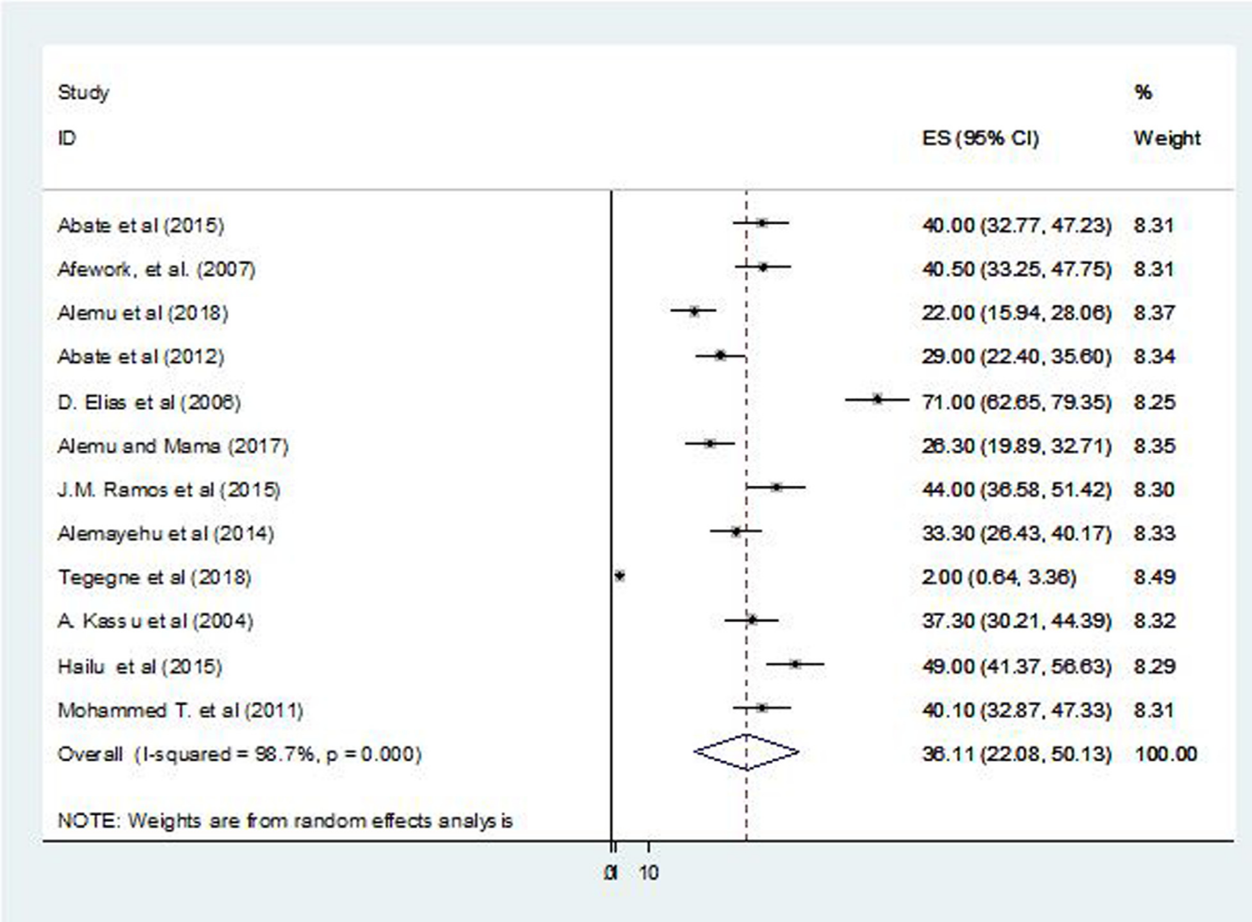

Figure 2. Forest plot presentation showing the pooled prevalence of intestinal parasites among patients with tuberculosis in Ethiopia, 2004–2018.

all fields within records. Medical subject headings terms was also used to help expand the search in advanced PubMed search. The study period for searching of article was conducted from November 10, 2018, to February 1, 2019. Endnote citation manager software version X7 for Windows was utilized to collect and organize search outcomes and for removal duplicate articles.

Inclusion and exclusion criteria

All articles for the study were included if they met the following inclusion criteria: written in English-language, full-text articles on observational studies (case-control or cross-sectional), conducted in Ethiopia from 2004 to 2018, published in peer-reviewed journals or available at university repository, and used valid and reliable diagnostic criteria to diagnose intestinal parasite. Studies that did not report specific outcomes for intestinal parasites quantitatively were excluded from the final analysis.

Data abstraction and quality assessment

After preliminary assessment, 2 reviewers downloaded abstracts to assess for inclusion. The abstracts were assessed for agreement with the inclusion criteria. When it was unclear whether or not an abstract was relevant, it was included for retrieval. At this stage, articles deemed irrelevant or out of the scope of the study were excluded and the full-text of the remaining articles downloaded for a detailed review. Two reviewers then assessed the quality of potentially eligible articles using Newcastle-Ottawa Scale criteria[30] that was validated previously.[31] There are 3 main categories for Newcastle-Ottawa Scale criteria: selection, exposure, and comparability. A study can be awarded a maximum of 1 star for each numbered item within the selection and exposure categories. A maximum of 2 stars can be given for comparability categories. Then the number of stars that was given for each numbered item was computed to determine the quality score of each study. Discrepancies in quality assessment scores were resolved with a third reviewer whenever appropriate. The average of 2 independent reviewer's score was used to determine the quality of each article. The current systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines.[32]

Data analysis

Using an Excel (Microsoft, Redmond, Washington) spreadsheet template based on Joanna Briggs Institute format, author name, publication year, region, dominant parasites, the age range of patients, and funding source were extracted from each study.[33] These data were then imported to Stata version 14 software for Windows (Stata Corp, College Station, Texas) to compute the pooled prevalence of intestinal parasites and to examine the association with HIV. The statistical heterogeneity of study outcomes was assessed using the I^2 statistic.[34] Methodological heterogeneity was evaluated by comparing study design. Additionally, clinical heterogeneity that can arise from differences in participant

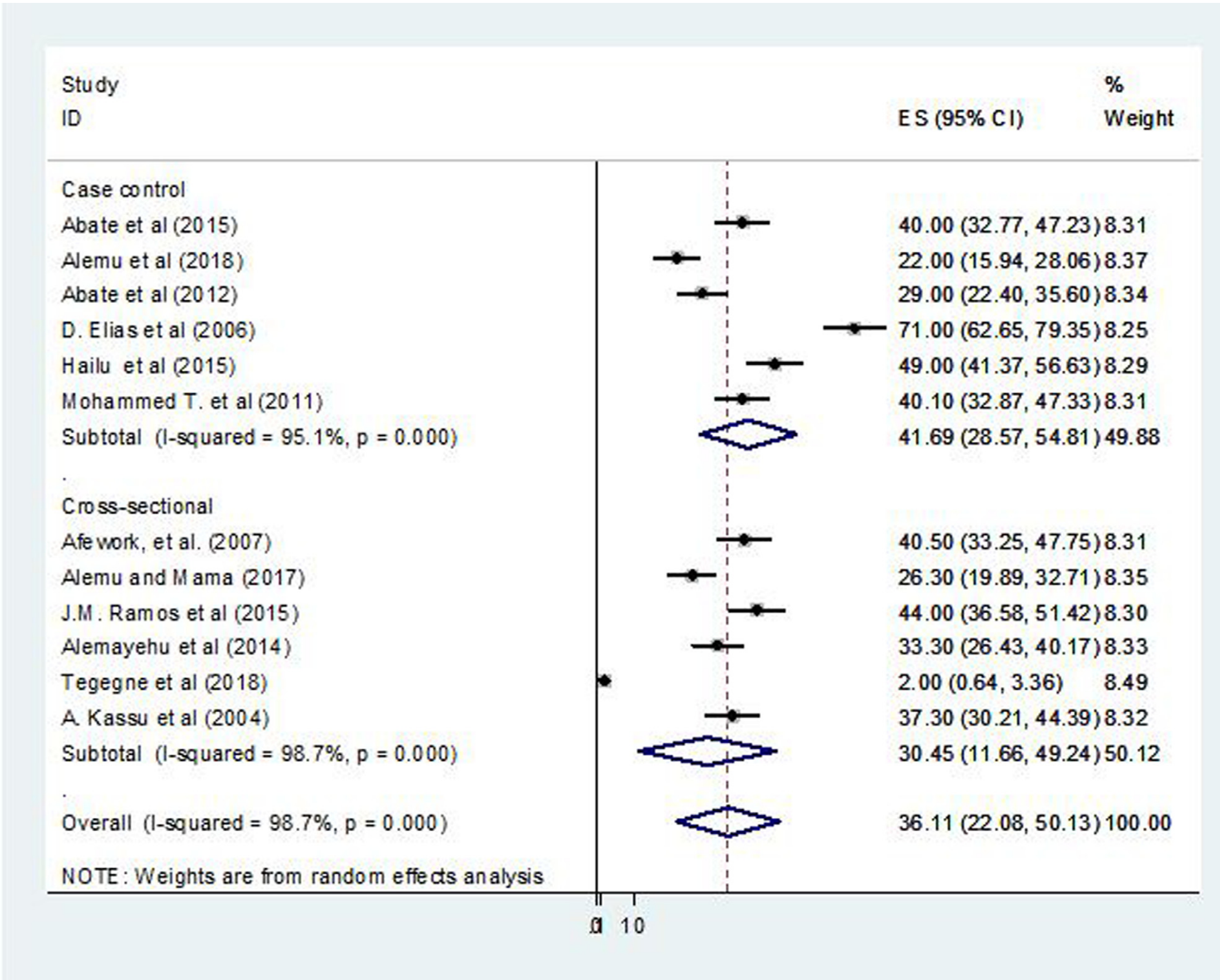

Figure 3. Forest plot presentation showing the pooled prevalence of intestinal parasites by study design among patients with tuberculosis in Ethiopia, 2004–2018.

characteristics (eg, sex, age, baseline disease severity, ethnicity, and comorbidities) and types or timing of outcome measurements was assessed with face-to-face discussion by the authors. First, we set and agreed on definitions of variations in sex, age, baseline disease severity, ethnicity, comorbidities, and types or timing of outcome measurements. Next, we discussed and reached consensus about how much this heterogeneity influenced our pooled analysis. A random-effects model was used to estimate the pooled prevalence of IPIs at a 95% CI. Because theoretically we expected that the study settings and socioeconomic contexts might differ radically across these studies, subgroup analysis was based on study design and group of parasites. We used visual examination of funnel plot asymmetry and Egger regression tests to check for publication bias.[35] Meta-regression analysis was employed to identify the source of heterogeneity using publication years, sample size, and region as covariates. Sensitivity analysis was also performed to examine influence of each study on the overall effect size. We appraised the risk of bias using the 10-item rating scale developed by Hoy et al[36] for prevalence studies. The tool assesses studies on 10 domains, including sampling, data collection, reliability and validity of study tools, case definition, and prevalence periods. Each study was assigned a score of 1 (yes answers to domain questions) or 0 (no answers to domain questions) for each domain, and these scores were summed to provide an overall study quality score. Scores of 8 to 10 were considered as having a low risk of bias, 6 to 7 a moderate risk of bias, and 0 to 5 a high risk of bias. For the final risk of bias classification, disagreements between the reviewers were resolved via consensus (see Supplemental Figure 1 in the online version).

Results

Identification and description of studies

Of 725 identified studies, 260 duplicate articles were excluded after reviewing the titles and abstracts. Next, 452 articles were excluded with a reason of irrelevance. Finally, the full-text of the remaining 13 articles were downloaded and assessed for quality and for the presence of all required information. One article was excluded because the outcome was not clearly stated.[17] The remaining 12 studies were included in the final meta-analysis (Fig. 1).

Characteristics of included studies

Twelve studies with a total sample of 1927 TB patients were included. Most of the study participants belonged to the age range 2 to 100 years. Eight studies were conducted in Amhara region,[37–44] 2 in Oromia region,[45,46] and 2 studies in Addis Ababa and SNNPR.[21,22] All studies used direct microscope examination of stool to identify intestinal parasites. Half of the studies were

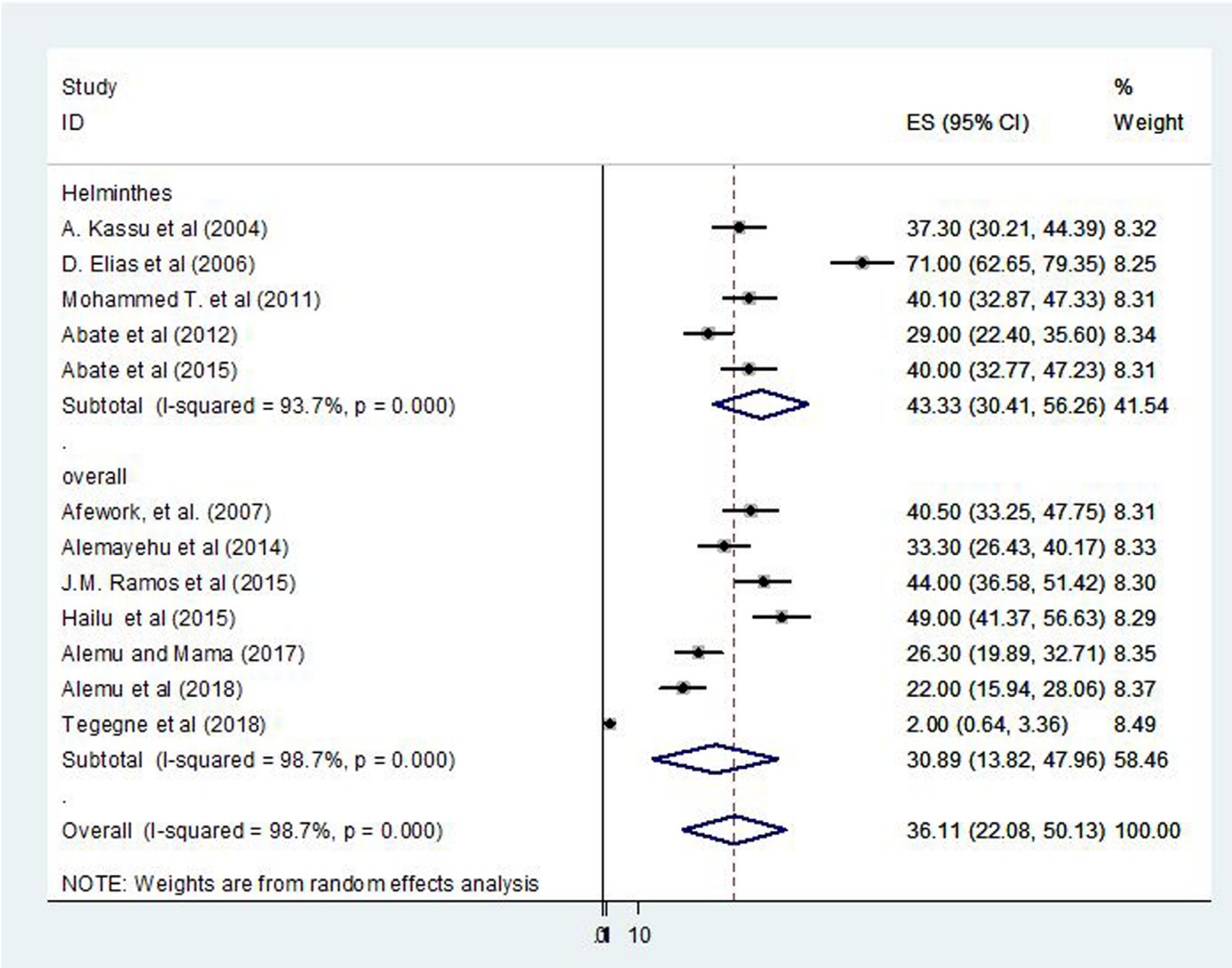

Figure 4. Forest plot presentation showing the pooled prevalence of intestinal parasites by category of intestinal parasite among patients with tuberculosis in Ethiopia, 2004–2018.

case-control study. The quality score ranges from 6 to 7 with mean (SD) score of 6.8 (0.25) (Table 1).

Prevalence of intestinal parasite

Both the lowest (2%)[44] and highest (40.5%)[42] prevalence of intestinal parasites were reported in Amhara region. The pooled national prevalence of intestinal parasites among TB patients in Ethiopia was 36.11% (95% CI, 22.08–50.13; $I^2 = 98.7\%$; $P = 0.01$) (Fig. 2). Visual examination of the funnel plot revealed deviation (see Supplemental Figure 2 in the online version). However, both Begg ($P = 0.27$) and Egger tests ($P = 0.57$) of the intercept indicated the absence of significant publication bias.

Subgroup and sensitivity analysis

Based on the subgroup analysis, the pooled prevalence of intestinal parasites among case-control studies was 41.69% (95% CI, 28.57–54.81; $P = 0.01$; $I^2 = 95.1\%$) and 30.45% (95% CI, 11.66–49.24; $P = 0.01$; $I^2 = 98.7\%$) in cross-sectional studies (Fig. 3).

Additionally, subgroup analysis based on types of intestinal parasites showed that the highest percentage was reported for helminths species with a prevalence of 43.3% (95% CI, 30.4%–56.3%; $I^2 = 93.7\%$) (Fig. 4). The sensitivity analysis showed that none of the studies significantly influenced the overall pooled estimate of IPI.

Meta-regression analysis

The univariate meta-regression analysis showed that a 1-person increases of sample size brought a variation on prevalence of each study by 0.2 ($P = 0.03$) (Table 2).

HIV status and IPI

Six studies[22,37,38,40,42,43] reported the association between HIV status and IPI. The odds of intestinal parasites among TB patients with HIV/AIDS was not significantly different compared with TB patients without HIV/AIDS (odds ratio = 0.99; 95% CI, 0.71–4.71; $I^2 = 41.5\%$; $P = 0.13$) (Fig. 5). Although the funnel plot showed slight deviation (see Supplemental Figure 3 in the online version), Begg ($P = 0.57$) and Egger ($P = 0.91$) tests showed the absence of significant publication bias.

Discussion

TB and intestinal parasites overlap geographically, and can represented with high prevalence in the area where there is poor socioeconomic status.[47] Additionally, it is evident that due to complicated immune status of TB patients with immunodeficiency disorders, this group of patients are at higher risk of developing IPI.[27] To our knowledge, this is the first meta-analysis in Ethiopia to pro-

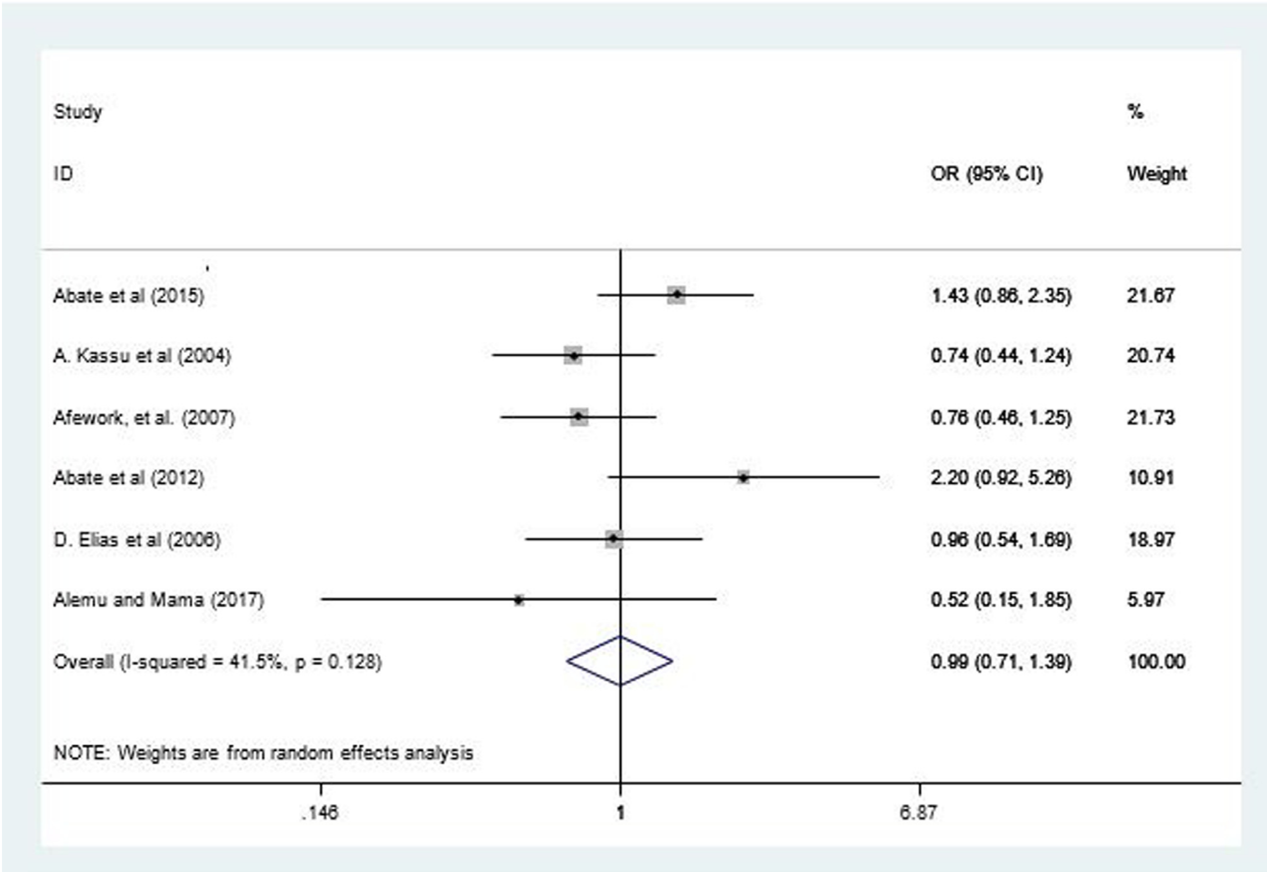

Figure 5. Forest plot of 6 studies examining the effect of HIV sero status on intestinal parasite among patients with tuberculosis in Ethiopia, 2004–2018.

vide the pooled national prevalence of intestinal parasites and its association with HIV among TB patients. The national prevalence of intestinal parasites among patients with TB was 36.11%. This finding is consistent with a report in Tanzania with prevalence of 31.8%.[8]

Our finding was high compared to a report in Egypt (16%)[9] and China (21.7%).[48] The Egyptian study[9] was only assessed the burden of a single parasite, which was not a dominant parasite in our finding. In our study, *Ascaris lumbricoides* was the dominant parasite. Thus, high prevalence of *A lumbricoides* in our study might increase the overall IPIs prevalence and can be accounted for this variation. Ascariasis is the most common parasite that found in warm tropical and subtropical regions of the world, including Ethiopia.[49] Due to the presence of high utilization of unsafe water, unhygienic living conditions, and unsanitary waste management,[50] Ethiopia stands out for having the highest burden of ascariasis cases following Nigeria and the Democratic Republic of Congo. Almost one-third of Ethiopians have been infected with ascariasis.[51] In *A lumbricoides* endemic areas, it is expected to have high rate of *A lumbricoides* and TB/HIV coinfection.[52] Socioeconomic difference between Ethiopia and China explain this discrepancy. Ethiopia is low-income country whose peoples live under poverty whereby risk factors, such as poor sanitation, low health awareness, low urbanization, low health care service, and high burden of parasitosis are evident compared with China.[53] In China, the Chinese Center for Disease Control and Prevention provide specialized hospital care for patients with IPIs. The presence of this care unit attributed to the nationwide scale-up of TB management and a national TB control program. Patients in a specialized care unit have better follow-up, receive appropriate examinations, treatment regimens, and rigorous supervision when compared with patients who take treatment at the hospital level.[54] Consequently, the burden of IPIs in China might decrease.[55]

On the other hand, our finding was lower than the study report in Brazil (65%).[7] This difference can be explained by the variation in the study area. Our study estimated the prevalence in studies conducted without consideration of socioeconomic class. However, the Brazilian study[7] was conducted among a low-income community, in particular in the area where there is inadequate sanitary structure, latrines being shared with other rooms, well water as the main source of drinking water, and near to half of families had low income.

Our subgroup analysis result showed that estimate from case-control studies was higher than cross-sectional studies. This difference might happen related to the nature of sample selection. The unique advantage of cross-sectional surveys is that it is possible to determine the prevalence of an outcome because the study samples are selected randomly.[56] Conversely, in case-control studies, cases and/or controls are selected on criteria related to the exposure of interest that can influence the overall prevalence.[57] Based on the category of parasite subgroup analysis, the highest percentage was reported for helminths group with a prevalence of 43.3%. This finding was consistent with previous studies conducted among people with TB.[2,10] However, our finding was totally different from large surveys report on non-TB people in Ethiopia,[58] Ghana,[59]and Brazil[60] with higher proportion of protozoal infection reported than helminths. This evidence suggests the presence of strong immunological and geographical connection between helminths and TB that contributes to high burden of helminthiases among TB patients.[61–63]

The present meta-analysis showed that the odds of intestinal parasites among TB patients was not significantly different in patients with or without HIV. Similarly, previous studies concluded that the presence of HIV could not contribute to high parasitosis among TB patients.[8,10] This might be due to the presence of better follow-up for patients with HIV. Currently, there is better awareness of professionals in adopting prevention and treatment measures against opportunistic infection, such as intestinal parasites in HIV patients. In addition, the current Ethiopian antiretroviral therapy guideline recommend anthelminthic for antiretroviral therapy patients for deworming purpose. During the past few years, the presence of appropriate follow-up and treatment for IPIs at antiretroviral therapy clinics dramatically decreased the prevalence among HIV patients.[64] Moreover, patients might regain their immunity after initiation of antiretroviral therapy that can minimize IPI.[65]

The presence high helminths infection among patients with TB in our finding implies that these patients are risk for sustained infectiousness that can lead to high transmission rate of TB to healthy individual. This issue directly interfere with the national TB control and prevention strategy.[18] Antigens from helminths and mycobacteria have immunomodulatory activities that can affect immune responses for microbes. There is immunological evidence demonstrating that helminths clearly alter the magnitude of the mycobacteria-specific cytokine responses and the control of the mycobacteria growth. This delays the clinical response of TB patients.[19,20]

Ethiopia is a country that has a high burden of multidrug-resistant TB.[66,67] Timely management of risk factors like intestinal parasitosis can improve the effectiveness of anti-TB treatment and reduce the magnitude of multidrug-resistant TB. It is known that the effectiveness of anti-TB treatment is greatly influenced by duration and patient adherence with anti-TB drugs.[68] Patients with parasitosis comorbidities with TB presented with difficulty of adherence with anti-TB treatment and low effectiveness of overall TB therapy. Consequently, it increases the burden of health institution workload, the occurrence of new TB infection, and the national burden of multidrug-resistant TB.[11]

In most developing countries where TB infection is prevalent, parasitic infections are also predominant medical problems.[11] Reducing the burden of these parasites is important to reduce the mortality and morbidity associated with TB infection. Parasitic infections have profoundly debilitating effects, particularly on the immune system of the host, potently compromising the host capacity to cope with TB infection and to mount efficacious immune responses. In addition, without the eradication of helminthic parasites, TB treatment would fail to confer protection for TB infection in TB endemic areas. This implies that eradication of helminthic infections or modulation of the immune change that they cause should be instituted before plans to reach TB zero prevalence in the country. For example, de-worming for eradication of helminthic infections throughout the country in the context of TB epidemics should be seriously considered.[14,69]

Study Strengths and Limitations

The present meta-analysis is the first in Ethiopia that can give nationally pooled evidence about the overall national burden of IPIs among patients with TB.

This meta-analysis has also limitations. First, most of the studies reviewed were published in small regional journals, making it difficult to gauge the extent of peer review and quality of studies. However, all included studies passed the quality screening criteria. Second, due to the absence of data, unadjusted odds ratios were used to estimate the effect size of HIV, which prevented us from excluding the confounding effect of other factors. The findings of this meta-analysis would be best interpreted while keeping these analytical limitations and the limitations of the original studies in mind.

Conclusions

In Ethiopia, at least 1 out of 3 patients with TB have intestinal parasites. These findings suggest a need for more attention on increasing screening of TB patients for intestinal parasites and deworming to reduce its influence on patients' overall health status.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Acknowledgments

G. Dessie conceived and designed the research protocol. G. Dessie, B. Zeleke, H. Mulugeta, D. Amare, A. Negesse, D. Haile, T. D. Habetwold, B. Abebaw, and F. Wagnew conducted the literature review, data extraction, data analysis, interpreted the results and drafted the manuscript. G. Dessie, H. Mulugeta, and F. Wagnew assisted with assessment of quality of included studies. H. Mulugeta, T. D. Habetwold, F. Wagnew, and G. Dessie assisted in interpretation of results, manuscript revision and language copyediting. All authors were involved in revising and editing the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2020.100603.

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