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Epidemiology of podoconiosis in Ethiopia: A systematic review and Meta-analysis protocol

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Epidemiology of podoconiosis in Ethiopia: A systematic review and Meta-analysis protocol

Birhan Alemnew^{1*}, Alebachew Fasil², Tesfahun Mulatu³, Nigus Bililign⁴, Setegn Esthetie⁵, Asmamaw Demis⁶

Author affiliations

¹Department of Medical Laboratory Science, Faculty of Health Sciences, Woldia University, Ethiopia

²Department of Clinical chemistry, College of Medicine and Health Science, University of Gondar, Ethiopia

³Department of Public Health, Faculty of Health Sciences, Woldia University, Ethiopia

⁴Department of Midwifery, Faculty of Health Sciences, Woldia University, Ethiopia

⁵Department of Medical Microbiology, College of Medicine and Health Science, University of Gondar, Ethiopia

⁶Department of Nursing, Faculty of Health Sciences, Woldia University, Ethiopia

*corresponding author, email: birhanalemnew12@gmail.com, phone:+251922204330, p.o.box: 400

ABSTRACT

Introduction: Podoconiosis is a non-filarial swelling of lower extremity endemic in tropical regions, North America and India. The etiology and pathophysiology of the disease remained unknown. We propose conducting a systematic review and a meta-analysis to evaluate the burden and risk factors of Podoconiosis in Ethiopia reported in studies from 2000 to 2019.

Methods and analysis: We will search the following electronic databases: PubMed (MEDLINE), EMBASE, Hinari, CINAHL, ISI (Web of science), and Google scholar. Medical subject headings (MesH) will be used to extensively search the appropriate literature on electronic databases using related key words such as: epidemiology, podoconiosis, and Ethiopia. Two reviewers will screen all retrieved articles, conduct data extraction, and then critically appraise all identified studies. We will analysis data by using STATA 14 statistical software. We will demonstrate pooled estimates of podoconiosis and associated factors with effect size and 95% confidence interval. The presence of heterogeneity among studies will be examined by forest plot as well as I^2 heterogeneity test. Potential causes of heterogeneity will be explored by carrying out sensitivity and subgroup analyses. Moreover, the presence of publication bias will be examined by observing funnel plots, and objectively by Egger's regression test. If the funnel plot is asymmetric and/or Egger's test was found to be statistically significant ($p < 0.05$), the trim and fill (Duval and Tweedie's) analysis will be performed.

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PROSPERO registration number CRD42019127459.

Strength and limitations of the study

- This will be the first systematic review and meta-analysis presenting the epidemiology and determinants of podoconiosis in Ethiopia.
- This study could potentially inform policy and practice to reduce the impact of podoconiosis.
- Strong and robust statistical methods will be employed to summarize the data.
- Establishment of casual relationships may be difficult.

INTRODUCTION

Podoconiosis is non-filarial elephantiasis and a non-infectious geochemical disease caused by exposure of bare feet to red clay soil derived from volcanic rock. Mineral particles from the soil penetrate the skin and are taken up by macrophages in the lymphatic system which causes inflammation and fibrosis of the vessel lumen leading to blockage of the lymphatic drainage (1). It is associated with chronic barefoot exposure to volcanic soil. Local inflammation is thought to be caused by an abnormal inflammatory reaction to irritant mineral particles in red volcanic clay(2), which may lead to fibrosis and obstruction of lymphatic vessels (3). A major and serious complication of podoconiosis is acute adenolymphangitis (ALA), which presents as a warm, painful sensation in the limbs, accompanied by fever (2).

Podoconiosis is common in more than ten countries across tropical Africa, Central and South America and northwest India (4, 5), including Ethiopia (6). In Ethiopia, prevalence of podoconiosis is about 5% in areas with irritant soil (1) and an estimate based on prevalence data from an endemic area in southern Ethiopia reported that between 500,000 and 1 million people were affected (7, 8). Podoconiosis imposes huge economic burdens that worsen the prevailing poverty, and results in considerable social stigmatization associated with the belief that the condition is familial and incurable (9). In Cameroon, podoconiosis imposed financial burdens to affected households through direct treatment cost and reduced ability to work (10). Similarly, food insecurity was reported higher among households of Ethiopian podoconiosis patients (11).

Podoconiosis is endemic in 345 districts of Ethiopia: the majority of cases in Oromia, Southern Nations, Nationalities and Peoples' and Amhara regional states (12). In Ethiopia, studies have shown that podoconiosis was significantly associated with soil texture and land topography (13), washing practices and frequency of shoe wearing (14, 15), family history and bare foot (16). Although simple and effective treatment strategies are available in Ethiopia, podoconiosis patients tend to discontinue their treatment. Some of the factors for discontinuation were remoteness from treatment sites, stigma and misconceptions about the treatment (17). On the top of this, podoconiosis patients had stigma (18), depression (19) and lower quality of life in Ethiopia (20).

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3 A systematic review and meta-analysis showed that footwear use was associated with decreased
4 risks of Neglected Tropical Diseases (NTDs) (21). The WHO underscored the importance of
5 integrated control of NTDs, including podoconiosis (22). Thus, identifying the predictors of
6 podoconiosis is the first essential step in controlling the contributing factors. Despite many
7 efforts have been conducted in Ethiopia, yet holistic and integrated strategy is warranted to halt
8 the impact of podoconiosis. Hence, this systematic review and meta-analysis aims to determine
9 the pooled prevalence of podoconiosis in Ethiopia. The findings from this systematic review will
10 highlight the prevalence and associated factors of podoconiosis with implications to improve
11 interventions, to ensure cost-effectiveness, and to accelerate the reduction of podoconiosis.
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20 Objectives

21 General objective

22 The objective of this review is to conduct a systematic review and meta-analysis of studies
23 assessing the prevalence and its associated risk factors podoconiosis in Ethiopia.
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28 Specific objective

- 29 ✓ To review and estimate the pooled prevalence of podoconiosis in Ethiopia.
- 30 ✓ To review and estimate the pooled prevalence of podoconiosis in different regions of the
31 country.
- 32 ✓ To review and determine the pooled effect sizes of the determinants of podoconiosis in
33 Ethiopia.
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39 Methods and Analysis

40 Protocol and registration

41 This protocol was developed with guidance in accordance to the Preferred Reporting Items for
42 Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement(23), and the review that
43 is to be guided by this protocol will be carried out in accordance with PRISMA guidelines.
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48 The protocol was registered with the International Prospective Register of Systematic Reviews
49 PROSPERO in 2019 and has been assigned the identification number CRD42019127459. The
50 full documentation is available online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019127459).
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Literature search

We will systematically conduct a comprehensive literature search using different bibliographic databases. We will search the following online databases: PubMed (MEDLINE), EMBASE, Hinari, CINAHL, ISI (Web of science), and Google scholar. We will use Medical Subject Headings (MesH), keywords, and free text search terms. An extensively and comprehensive search will be made by using alternative terms such as epidemiology, prevalence, podoconiosis, and Ethiopia.. This search strategy will be performed by combine them using Boolean operators. To check that the searches are exhaustive, we will utilize snowballing to screen the references of identified articles for potentially relevant studies. During the search process, to suppress the number of irrelevant studies, the search will be restricted to only 'human studies' and 'English language' in the advanced search. Authors' personal profiles will also be searched to ensure that other relevant articles are captured. The search activity will be done by BA, AD and SE, and the whole process is expected to be completed by 4 October 2019.

Criteria for considering studies for the review

Inclusion criteria

- ✓ This review will account all observational and population based studies reporting the incidence or prevalence of podoconiosis.
- ✓ Studies describing the prevalence of podoconiosis as well as associated factors across all age groups, and region within in Ethiopia.
- ✓ Articles published in English language will be eligible for inclusion

Exclusion criteria

- ✓ Studies conducted before 2009 and conducted outside of Ethiopia will be excluded
- ✓ Narrative reviews, expert opinions, case reports and case series will be excluded.
- ✓ Articles without full text and data that are difficult to extract, despite contacting the corresponding author(s)

Study selection and data extraction

First, systematic searching will be conducted through all identified data bases, search engines, and additional references will be retrieved from other published articles. Second, studies conducted before 2009, conducted other than Ethiopia, and unrelated articles based on their title will be excluded. Third, those potentially eligible for inclusion will be imported to Endnote

version 8, and duplicates will be removed, the study published earlier or the one that provides more information will be included. Lastly, the studies will be screened and selected for full-text review based on inclusion criteria. The Preferred statement for Reporting Systematic review and Meta-analysis (PROSPERO) will be used to clearly present the study inclusion, exclusion and reason for exclusion information in diagram. In conclusion, the following data will be abstracted using a structured data abstraction form and presented using a prepared format on Microsoft Excel spreadsheet. Information such as the primary investigator's name, year of publication, region, residence, study design, sample size, tool used to diagnose podoconosis will be extracted. Moreover, prevalence, adjusted associated factors with their effect size (OR) and 95% confidence intervals(lower and upper confidence interval) will be extracted. Before analysis, transforamtion of Odds ratios and prevalences will be made. For any difficulties that might be encountered during data extraction, the corresponding author(s) will be contacted by any means of communication

Risk of bias (quality) assessment

Once all searches have been completed, the included studies will be assessed independently by the three researchers (BA, SE and AD), using quality assessment tool. Newcastle-Ottawa Scale (NOS) will be used to assess the quality of included studies for Observational Cohort and Cross-Sectional (24). Study quality will be assessed using a quality assessment tool (25). Based on this tool, studies are rated as low risk, moderate risk and high risk for scores ≤ 5 , 6-8 and > 8 respectively. Discrepancies will be discussed and resolved by consensus between the authors and an independent reviewer. In addition to quality assessment, the reporting of the systematic review and meta-analysis result will be based on Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement. All tools have 'Yes' and 'No' types of questions and scores will be given 1 and 0 for 'Yes' and 'No' responses, respectively. Scores will be summed and transformed into a percentage. Only studies that scored $\geq 50\%$ will be considered for both systematic review and meta-analysis of prevalence. For any scoring disagreements, which might happen between the assessors, the sources of discrepancy will be investigated by a thorough revision. For persistent disagreements in spite of the detailed review, the average scores of the reviewers will be calculated. Similarly, for determinants, each factor with each outcome variable will be critically appraised. The similar cut-off point that we will be using for prevalence studies

will be applied to factors. Moreover, the quality results of primary studies will be placed in a separate column of the data extraction format.

Data analysis and assessment of publication bias

The extracted data will be exported to STATA version 14 (STATA, Corporation, College Station, Texas) software for further analysis. The prevalence of podoconiosis in Ethiopia will be pooled from each study and determined as a single estimate. The existence of heterogeneity among the included studies will be examined by forest plot and I^2 -heterogeneity test (26). The I^2 -values greater than 75%, 50-75%, 25-50%, and less than 25% will be interpreted as the presence considerable, substantial, moderate, and low heterogeneity, respectively. I^2 heterogeneity test of $\geq 50\%$ and a p value of <0.05 will be declared as the presence of heterogeneity. Thus, the DerSimonian and Laird random-effects model will be employed (27). To identify the influential studies that resulted in variation, sensitivity analysis will be carried out using the 'metaninf' command (28). Similarly, subgroup analysis will be employed by considering year of the study, the region, and sample size as source of variation. Moreover, funnel plot and Egger's regression test will be conducted to check potential publication bias (29). Accordingly, asymmetry of the funnel plot and/or statistical significance of Egger's regression test ($p < 0.05$) will be suggestive of publication bias. In case of minor publication bias, using the 'metatrim' command, a non-parametric trim and fill (Duval and Tweedie's) method of analysis will be done (30).

Discussion

Due to paucity of data, which addresses epidemiology of podoconiosis in Ethiopia, we intend to fill this gap by reviewing available literatures as outlined in this protocol. The findings of this systematic review and meta-analysis will have implications for stakeholders, which work on Neglected Tropical Diseases including podoconiosis. We also anticipate that the findings of this review will have much contribution for the development of prevention strategies to factors associated with podoconiosis in the country.

Ethics and dissemination

No formal ethical review was required as the systematic reviews will use publicly available data and will not identify authors of the publication by name. In light of these and as has been indicated, research ethics clearance is not required for evidence syntheses in such reviews. The findings of this systematic review will be published in a reputable peer-reviewed journal and presented at scientific national and international conference.

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Contributors: BA and AD wrote the protocol. BA and AF will individually perform the abstract extraction and critique the literature, and TM will be the third reviewer. NB, SE, and TM provided insight on the epidemiological aspects of the review and helped draft the manuscript. BA, AF, TM, NB, SE, and AD advised on background and revised the manuscript. All authors approve the final version and take responsibility for its content. The guarantor of the review is AD.

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Birhan Alemnew^{1*}, Alebachew Fasil², Tesfahun Mulatu³, Nigus Bililign⁴, Setegn Esthetie⁵, Asmamaw Demis⁶

Author affiliations

¹Department of Medical Laboratory Science, College of Health Sciences, Woldia University, Ethiopia

²Department of Clinical chemistry, College of Medicine and Health Science, University of Gondar, Ethiopia

³Department of Public Health, College of Health Sciences, Woldia University, Ethiopia

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⁵Department of Medical Microbiology, College of Medicine and Health Science, University of Gondar, Ethiopia

⁶Department of Nursing, College of Health Sciences, Woldia University, Ethiopia

*corresponding author, email: birhanalemnew12@gmail.com, phone:+251922204330, p.o.box: 400

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In addition to prolonged exposure to soil, many studies showed that the prevalence of podoconiosis was associated with feet hygiene, shoe wearing habit, gender, age, occupation, housing condition, and income status (4-7).

Podoconiosis is common in more than ten countries across tropical Africa, Central and South America and northwest India (8, 9), including Ethiopia (10). In Ethiopia, the prevalence of podoconiosis is about 5% in areas with irritant soil (1) and an estimate based on prevalence data from an endemic area in southern Ethiopia reported that between 500,000 and 1 million people were affected (11, 12).

Podoconiosis imposes huge economic burdens that worsen the prevailing poverty and results in considerable social stigmatization associated with the belief that the condition is familial and incurable (13). In Cameroon, podoconiosis imposed financial burdens on affected households through direct treatment cost and reduced ability to work (14). Similarly, food insecurity was reported higher among households of Ethiopian podoconiosis patients (15).

Podoconiosis is endemic in 345 districts of Ethiopia: the majority of cases in Oromia, Southern Nations, Nationalities and Peoples' and Amhara regional states (16). In Ethiopia, studies have shown that podoconiosis was significantly associated with soil texture and land topography (17), washing practices and frequency of shoe-wearing (4, 18), family history and barefoot (5). Although simple and effective treatment strategies are available in Ethiopia, podoconiosis patients tend to discontinue their treatment. Some of the factors for discontinuation were remoteness from treatment sites, stigma, and misconceptions about the treatment (19). On top of this, podoconiosis patients had a stigma (20), depression (21) and lower quality of life in Ethiopia (22).

A systematic review and meta-analysis showed that footwear use was associated with decreased risks of Neglected Tropical Diseases (NTDs) (23). The WHO underscored the importance of

integrated control of NTDs, including podoconiosis (24). Thus, identifying the predictors of podoconiosis is the first essential step in controlling the contributing factors. Despite many efforts that have been conducted in Ethiopia, yet holistic and integrated strategy is warranted to halt the impact of podoconiosis. Hence, this systematic review and meta-analysis aimed to determine the pooled prevalence of podoconiosis in Ethiopia. The findings from this systematic review will highlight the prevalence and associated factors of podoconiosis with implications to improve interventions, to ensure cost-effectiveness, and to accelerate the reduction of podoconiosis.

Objectives

General objective

The objective of this study is to conduct a systematic review and meta-analysis of studies assessing the prevalence and associated risk factors of podoconiosis in Ethiopia.

Specific objective

- ✓ To review and estimate the pooled prevalence of podoconiosis in Ethiopia.
- ✓ To review and estimate the pooled prevalence of podoconiosis in different regions of the country.
- ✓ To review and determine the pooled effect sizes of the determinants of podoconiosis in Ethiopia.

Methods and Analysis

Protocol and registration

This protocol was developed with guidance following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement(25), and the review that is to be guided by this protocol will be carried out following PRISMA guidelines.

The protocol was registered with the International Prospective Register of Systematic Reviews PROSPERO in 2019 and has been assigned the identification number CRD42019127459. The full documentation is available online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019127459).

Literature search

We will systematically conduct a comprehensive literature search using different bibliographic databases. We will search the following online databases: PubMed (MEDLINE), EMBASE,

Hinari, CINAHL, ISI (Web of Science), and Google scholar. We will use Medical Subject Headings (MesH), keywords, and free text search terms. An extensive and comprehensive search will be made by using alternative terms such as epidemiology, prevalence, podoconiosis, and Ethiopia. This search strategy will be performed by combining the above terms using operators. To check that the searches are exhaustive, we will utilize snowballing to screen the references of identified articles for potentially relevant studies. During the search process, to suppress the number of irrelevant studies, the search will be restricted to only 'human studies' and 'English language' in the advanced search. Authors' profiles will also be searched to ensure that other relevant articles are captured. The search activity will be done by BA, AD, and SE, and the whole process is expected to be completed by 4 October 2019.

Criteria for considering studies for the review

Inclusion criteria

- ✓ This review will account for all observational and population-based studies reporting the incidence or prevalence of podoconiosis.
- ✓ Studies describing the prevalence of podoconiosis as well as associated factors across all age groups, and regions within Ethiopia.
- ✓ Articles published in the English language will be eligible for inclusion

Exclusion criteria

- ✓ Studies conducted before 2009 and conducted outside of Ethiopia will be excluded
- ✓ Narrative reviews, expert opinions, case reports and case series will be excluded.
- ✓ Articles without full text and data that are difficult to extract, despite contacting the corresponding author(s)

Study selection and data extraction

First, systematic searching will be conducted through all identified databases, search engines, and additional references that will be retrieved from other published articles. Second, studies conducted before 2009, conducted in countries other than Ethiopia, and unrelated articles based on their title will be excluded. Third, those potentially eligible for inclusion will be imported to Endnote version 8, and duplicates will be removed, the study published earlier or the one that provides more information will be included. Lastly, the studies will be screened and selected for full-text review based on inclusion criteria. The Preferred statement for Reporting Systematic

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2
3 review and Meta-analysis (MOOSE) will be used to present the study inclusion, exclusion and
4 reason for exclusion information in a diagram. In conclusion, the following data will be
5 abstracted using a structured data abstraction form and presented using a prepared format on the
6 Microsoft Excel spreadsheet. Information such as the primary investigator's name, year of
7 publication, region, residence, study design, sample size, a tool used to diagnose podocnosis
8 will be extracted. Moreover, prevalence, adjusted associated factors with their effect size (OR)
9 and 95% confidence intervals(lower and upper confidence interval) will be extracted. Before
10 analysis, a transformation of Odds ratios and prevalences will be made. For any difficulties that
11 might be encountered during data extraction, the corresponding author(s) will be contacted by
12 any means of communication
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21 **Risk of bias (quality) assessment**

22 Once all searches have been completed, the included studies will be assessed independently by
23 the three researchers (BA, SE, and AD), using a quality assessment tool. Newcastle-Ottawa
24 Scale (NOS) will be used to assess the quality of included studies for Observational Cohort and
25 Cross-Sectional (26). Study quality will be assessed using a quality assessment tool (27). Based
26 on this tool, studies are rated as low risk, moderate risk and high risk for scores ≤ 5 , 6-8 and > 8
27 respectively. Discrepancies will be discussed and resolved by consensus between the authors and
28 an independent reviewer. In addition to quality assessment, the reporting of the systematic
29 review and meta-analysis result will be based on the Meta-analysis Of Observational Studies in
30 Epidemiology (MOOSE) statement (28). All tools have 'Yes' and 'No' types of questions and
31 scores will be given 1 and 0 for 'Yes' and 'No' responses, respectively. Scores will be summed
32 and transformed into a percentage. Only studies that scored $\geq 50\%$ will be considered for both
33 systematic review and meta-analysis of prevalence. For any scoring disagreements, which might
34 happen between the assessors, the sources of discrepancy will be investigated by a thorough
35 revision. For persistent disagreements in spite of the detailed review, the average scores of the
36 reviewers will be calculated. Similarly, for determinants, each factor with each outcome variable
37 will be critically appraised. The similar cut-off point that we will be using for prevalence studies
38 will be applied to factors. Moreover, the quality results of primary studies will be placed in a
39 separate column of the data extraction format.
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Data analysis and assessment of publication bias

The extracted data will be exported to STATA version 14 (STATA, Corporation, College Station, Texas) software for further analysis. The prevalence of podoconiosis in Ethiopia will be pooled from each study and determined as a single estimate. The existence of heterogeneity among the included studies will be examined by forest plot and I^2 -heterogeneity test(29). The I^2 -values greater than 75%, 50-75%, 25-50%, and less than 25% will be interpreted as the presence of considerable, substantial, moderate, and low heterogeneity, respectively. I^2 heterogeneity test of $\geq 50\%$ and a p-value of < 0.05 will be declared as the presence of heterogeneity. Thus, the DerSimonian and Laird random-effects model will be employed. To identify the influential studies that resulted in variation, sensitivity analysis will be carried out using the 'metaninf' command(29). Similarly, subgroup analysis will be employed by considering the year of the study, the region, and sample size as a source of variation. Moreover, the funnel plot and Egger's regression test will be conducted to check the potential publication bias(30). Accordingly, asymmetry of the funnel plot and/or statistical significance of Egger's regression test ($p < 0.05$) will be suggestive of publication bias(30). In case of minor publication bias, using the 'metatrim' command, a non-parametric trim and fill (Duval and Tweedie's) method of analysis will be done(29).

Patient and Public Involvement

Patients were not involved in preparing this study protocol.

Discussion

Due to the paucity of data, which addresses the epidemiology of podoconiosis in Ethiopia, we intend to fill this gap by reviewing available literature as outlined in this protocol. The findings of this systematic review and meta-analysis will have implications for stakeholders, which work on Neglected Tropical Diseases including podoconiosis. We also anticipate that the findings of this review will have many contributions to the development of prevention strategies to factors associated with podoconiosis in the country.

Ethics and dissemination

No formal ethical review was required as the systematic reviews will use publicly available data and will not identify authors of the publication by name. In light of these and as has been indicated, research ethics clearance is not required for evidence syntheses in such reviews. The

findings of this systematic review will be published in a reputable peer-reviewed journal and presented at a scientific national and international conference.

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Contributors: BA and AD wrote the protocol. BA and AF will individually perform the abstract extraction and critique the literature, and TM will be the third reviewer. NB, SE, and TM provided insight into the epidemiological aspects of the review and helped draft the manuscript. BA, AF, TM, NB, SE, and AD advised on the background and revised the manuscript. All authors approve the final version and take responsibility for its content. The guarantor of the review is AD.

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Patient consent for publication: Not required.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	-
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4-5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	6 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Epidemiology of podoconiosis in Ethiopia: A systematic review and Meta-analysis protocol

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Global health
Keywords:	Public health < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES, MICROBIOLOGY, PARASITOLOGY, EPIDEMIOLOGY, IMMUNOLOGY

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Epidemiology of podoconiosis in Ethiopia: A systematic review and meta-analysis protocol

Birhan Alemnew^{1*}, Alebachew Fasil², Tesfahun Mulatu³, Nigus Bililign⁴, Setegn Esthetie⁵, Asmamaw Demis⁶

Author affiliations

¹Department of Medical Laboratory Science, College of Health Sciences, Woldia University, Ethiopia

²Department of Clinical chemistry, College of Medicine and Health Science, University of Gondar, Ethiopia

³Department of Public Health, College of Health Sciences, Woldia University, Ethiopia

⁴Department of Midwifery, College of Health Sciences, Woldia University, Ethiopia

⁵Department of Medical Microbiology, College of Medicine and Health Science, University of Gondar, Ethiopia

⁶Department of Nursing, College of Health Sciences, Woldia University, Ethiopia

*Corresponding author, email: birhanalemnew12@gmail.com, phone:+251922204330, P.O.Box: 400

ABSTRACT

Introduction: Podoconiosis is a non-filarial swelling of lower extremity endemic in tropical regions, North America and India. The etiology and pathophysiology of the disease remained unknown. We propose conducting a systematic review and a meta-analysis to evaluate the burden and risk factors of Podoconiosis in Ethiopia reported in studies from 2009 to 2019.

Methods and analysis: We will search the following electronic databases: PubMed (MEDLINE), EMBASE, Hinari, CINAHL, ISI (Web of Science), and Google scholar. Medical subject headings (MeSH) will be used to extensively search the appropriate literature on electronic databases using related keywords such as epidemiology or prevalence or magnitude or burden, podoconiosis, and Ethiopia. Also, grey literature and manual search will be used to retrieve unindexed research articles. Two reviewers will screen all retrieved articles, conduct data extraction, and then critically appraise all identified studies. We will analysis data by using STATA 14 statistical software. We will demonstrate pooled estimates of podoconiosis and associated factors with effect size and 95% confidence interval. The presence of heterogeneity among studies will be examined by forest plot as well as the I^2 heterogeneity test. Potential causes of heterogeneity will be explored by carrying out sensitivity and subgroup analyses. Moreover, the presence of publication bias will be examined by observing funnel plots, and objectively by Egger's regression test. If the funnel plot is asymmetric and/or Egger's test was found to be statistically significant ($p < 0.05$), the trim and fill (Duval and Tweedie's) analysis will be performed.

Ethics and dissemination: - The study will use publicly available data and will not identify the authors of the publication by name. In light of these and as has been indicted, research ethics clearance is not required for evidence syntheses in such reviews. The results of this study will be published in a peer-reviewed journal and presented at national and international conferences.

PROSPERO registration number CRD42019127459.

Strength and limitations of the study

- This will be the first systematic review and meta-analysis presenting the epidemiology and determinants of podoconiosis in Ethiopia.
- This study could potentially inform policy and practice to reduce the impact of podoconiosis.
- Strong and robust statistical methods will be employed to summarize the data.
- The establishment of casual relationships may be difficult.

INTRODUCTION

Podoconiosis is non-filarial elephantiasis and a non-infectious geochemical disease caused by exposure of bare feet to red clay soil derived from volcanic rock. Mineral particles from the soil penetrate the skin and are taken up by macrophages in the lymphatic system which causes inflammation and fibrosis of the vessel lumen leading to blockage of the lymphatic drainage (1-3). A major and serious complication of podoconiosis is acute adenolymphangitis (ALA), which presents as a warm, painful sensation in the limbs, accompanied by fever (2).

In addition to prolonged exposure to soil, many studies showed that the prevalence of podoconiosis was associated with feet hygiene, shoe-wearing habit, gender, age, occupation, housing condition, and income status (4-7).

Podoconiosis is common in more than ten countries across tropical Africa, Central and South America and northwest India (8, 9), including Ethiopia (10). In Ethiopia, the prevalence of podoconiosis is about 5% in areas with irritant soil (1) and an estimate based on prevalence data from an endemic area in southern Ethiopia reported that between 500,000 and 1 million people were affected (11, 12).

Podoconiosis imposes huge economic burdens that worsen the prevailing poverty and results in considerable social stigmatization associated with the belief that the condition is familial and incurable (13). In Cameroon, podoconiosis imposed financial burdens on affected households through direct treatment cost and reduced ability to work (14). Similarly, food insecurity was reported higher among households of Ethiopian podoconiosis patients (15).

Podoconiosis is endemic in 345 districts of Ethiopia: the majority of cases in Oromia, Southern Nations, Nationalities and Peoples' and Amhara regional states (16). In Ethiopia, studies have shown that podoconiosis was significantly associated with soil texture and land topography (17), washing practices and frequency of shoe-wearing (4, 18), family history and barefoot (5). Although simple and effective treatment strategies are available in Ethiopia, podoconiosis patients tend to discontinue their treatment. Some of the factors for discontinuation were remoteness from treatment sites, stigma, and misconceptions about the treatment (19). On top of this, podoconiosis patients had a stigma (20), depression (21) and lower quality of life in Ethiopia (22).

A systematic review and meta-analysis showed that footwear use was associated with decreased risks of Neglected Tropical Diseases (NTDs) (23). The WHO underscored the importance of

integrated control of NTDs, including podoconiosis (24). Thus, identifying the predictors of podoconiosis is the first essential step in controlling the contributing factors. Despite many efforts that have been conducted in Ethiopia, yet holistic and integrated strategy is warranted to halt the impact of podoconiosis. Hence, this systematic review and meta-analysis aimed to determine the pooled prevalence of podoconiosis in Ethiopia. The findings from this systematic review will highlight the prevalence and associated factors of podoconiosis with implications to improve interventions, to ensure cost-effectiveness, and to accelerate the reduction of podoconiosis.

Objectives

General objective

The objective of this study is to conduct a systematic review and meta-analysis of studies assessing the prevalence and associated risk factors of podoconiosis in Ethiopia.

Specific objective

- ✓ To review and estimate the pooled prevalence of podoconiosis in Ethiopia.
- ✓ To review and estimate the pooled prevalence of podoconiosis in different regions of the country.
- ✓ To review and determine the pooled effect sizes of the determinants of podoconiosis in Ethiopia.

Methods and Analysis

Protocol and registration

This protocol was developed with guidance following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (supplementary file1) statement guideline (25), and the review that is to be guided by this protocol will be carried out following MOOSE guidelines.

The protocol was registered with the International Prospective Register of Systematic Reviews PROSPERO in 2019 and has been assigned the identification number CRD42019127459. The full documentation is available online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019127459).

Literature search

We will systematically conduct a comprehensive literature search using different bibliographic databases. We will search the following online databases: PubMed (MEDLINE), EMBASE, Hinari, CINAHL, ISI (Web of Science), and Google scholar. We will use Medical Subject Headings (MesH), keywords, and free text search terms. An extensive and comprehensive search will be made by using alternative terms such as epidemiology, magnitude, burden, prevalence, podoconiosis, and Ethiopia. This search strategy will be performed by combining the above terms using Boolean operators. An example of the search strategy that will be used in PubMed will be as follows: ((Prevalence OR Magnitude OR Epidemiology OR Burden) AND Podoconiosis) AND Ethiopia. To check that the searches are exhaustive, we will utilize snowballing to screen the references of identified articles for potentially relevant studies. Furthermore, grey literature and manual search will be used to retrieve unindexed research works. During the search process, to suppress the number of irrelevant studies, the search will be restricted to only 'human studies' and 'English language' in the advanced search. Authors' profiles will also be searched to ensure that other relevant articles are captured. The search activity will be done by BA, AD, and SE, and the whole process is expected to be completed by 4 October 2019.

Criteria for considering studies for the review

Inclusion criteria

- ✓ This review will account for all observational and population-based studies reporting the incidence or prevalence of podoconiosis.
- ✓ Studies describing the prevalence of podoconiosis as well as associated factors across all age groups, and regions within Ethiopia.
- ✓ Articles published in the English language will be eligible for inclusion

Exclusion criteria

- ✓ Studies conducted before 2009 and conducted outside of Ethiopia will be excluded
- ✓ Narrative reviews, expert opinions, case reports and case series will be excluded.
- ✓ Articles without full text and data that are difficult to extract, despite contacting the corresponding author(s)

Study selection and data extraction

First, systematic searching will be conducted through all identified databases, search engines, and additional references that will be retrieved from other published articles. Second, studies conducted before 2009, conducted in countries other than Ethiopia, and unrelated articles based on their title will be excluded. Third, those potentially eligible for inclusion will be imported to Endnote version 8, and we removed the duplicates by screening the de-duplicated citations by hand, which were recorded on a Microsoft Excel spreadsheet. To be considered duplicates, two or more citations had to share the same author, title, publication date, volume, issue, and start page information. The full text versions of the citations were consulted when we were in doubt. In such cases, we also checked the population sizes, methodology, and outcomes to determine whether the citations were duplicates. Conference abstracts were deemed to be duplicates if full-text articles that shared the same study design, sample size, and conclusion were retrieved, even if their publication dates varied. Lastly, the studies will be screened and selected for full-text review based on inclusion criteria. The Preferred statement for Reporting Systematic review and Meta-analysis (MOOSE) will be used to present the study inclusion, exclusion and reason for exclusion information in a diagram. In conclusion, the following data will be abstracted using a structured data abstraction form and presented using a prepared format on the Microsoft Excel spreadsheet. Information such as the primary investigator's name, year of publication, region, residence, study design, sample size, a tool used to diagnose podocnosis will be extracted. Moreover, prevalence, adjusted associated factors with their effect size (OR) and 95% confidence intervals(lower and upper confidence interval) will be extracted. Before analysis, a transformation of Odds ratios and prevalences will be made. For any difficulties that might be encountered during data extraction, the corresponding author(s) will be contacted by any means of communication

Risk of bias (quality) assessment

Once all searches have been completed, the included studies will be assessed independently by the three researchers (BA, SE, and AD), using a quality assessment tool. Newcastle-Ottawa Scale (NOS) will be used to assess the quality of included studies for Observational Cohort and Cross-Sectional (26). Study quality will be assessed using a quality assessment tool (27). Based on this tool, studies are rated as low risk, moderate risk and high risk for scores ≤ 5 , 6-8 and > 8

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3 respectively. Discrepancies will be discussed and resolved by consensus between the authors and
4 an independent reviewer. In addition to quality assessment, the reporting of the systematic
5 review and meta-analysis result will be based on the Meta-analysis Of Observational Studies in
6 Epidemiology (MOOSE) (supplementary file 2) statement (28). All tools have ‘Yes’ and ‘No’
7 types of questions and scores will be given 1 and 0 for ‘Yes’ and ‘No’ responses, respectively.
8 Scores will be summed and transformed into a percentage. Only studies that scored $\geq 50\%$ will be
9 considered for both systematic review and meta-analysis of prevalence. For any scoring
10 disagreements, which might happen between the assessors, the sources of discrepancy will be
11 investigated by a thorough revision. For persistent disagreements in spite of the detailed review,
12 the average scores of the reviewers will be calculated. Similarly, for determinants, each factor
13 with each outcome variable will be critically appraised. The similar cut-off point that we will be
14 using for prevalence studies will be applied to factors. Moreover, the quality results of primary
15 studies will be placed in a separate column of the data extraction format.

26 **Data analysis and assessment of publication bias**

27 The extracted data will be exported to STATA version 14 (STATA, Corporation, College
28 Station, Texas) software for further analysis. The prevalence of podoconiosis in Ethiopia will be
29 pooled from each study and determined as a single estimate. The existence of heterogeneity
30 among the included studies will be examined by forest plot and I^2 -heterogeneity test(29). The I^2 -
31 values greater than 75%, 50-75%, 25-50%, and less than 25% will be interpreted as the presence
32 of considerable, substantial, moderate, and low heterogeneity, respectively. I^2 heterogeneity test
33 of $\geq 50\%$ and a p-value of < 0.05 will be declared as the presence of heterogeneity. Thus, the
34 DerSimonian and Laird random-effects model will be employed. To identify the influential
35 studies that resulted in variation, sensitivity analysis will be carried out using the ‘metaninf’
36 command(29). Similarly, subgroup analysis will be employed by considering the year of the
37 study, the region, and sample size as a source of variation. Moreover, the funnel plot and Egger's
38 regression test will be conducted to check the potential publication bias(30). Accordingly,
39 asymmetry of the funnel plot and/or statistical significance of Egger's regression test ($p < 0.05$)
40 will be suggestive of publication bias(30). In case of minor publication bias, using the ‘metatrim’
41 command, a non-parametric trim and fill (Duval and Tweedie's) method of analysis will be
42 done(29).
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Discussion

Due to the paucity of data, which addresses the epidemiology of podoconiosis in Ethiopia, we intend to fill this gap by reviewing available literature as outlined in this protocol. The findings of this systematic review and meta-analysis will have implications for stakeholders, which work on Neglected Tropical Diseases including podoconiosis. We also anticipate that the findings of this review will have many contributions to the development of prevention strategies to factors associated with podoconiosis in the country.

Ethics and dissemination

No formal ethical review was required as the systematic reviews will use publicly available data and will not identify authors of the publication by name. In light of these and as has been indicated, research ethics clearance is not required for evidence syntheses in such reviews. The findings of this systematic review will be published in a reputable peer-reviewed journal and presented at a scientific national and international conference.

Acknowledgments

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Contributors

BA and AD wrote the protocol. BA and AF will individually perform the abstract extraction and critique the literature, and TM will be the third reviewer. NB, SE, and TM provided insight into the epidemiological aspects of the review and helped draft the manuscript. BA, AF, TM, NB, SE, and AD advised on the background and revised the manuscript. All authors approve the final version and take responsibility for its content. The guarantor of the review is AD.

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Competing interests

None declared.

Patient and Public Involvement:

No patient involved.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	-
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4-5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	4-5 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	4-6
5	Type of study designs used	5-7
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5, Table 1
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	8, Table 2, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6-7
22	Assessment of heterogeneity	7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7-8
24	Provision of appropriate tables and graphics	Tables 2-7, Figs 2-7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 3-7
26	Table giving descriptive information for each study included	Table 2
27	Results of sensitivity testing (eg, subgroup analysis)	Fig 3, Table 3
28	Indication of statistical uncertainty of findings	12-16

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	12, Fig 2
30	Justification for exclusion (eg, exclusion of non-English language citations)	6
31	Assessment of quality of included studies	6-7
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	17-19
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	20
34	Guidelines for future research	-
35	Disclosure of funding source	20

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

BMJ Open

Epidemiology of podoconiosis in Ethiopia: A systematic review and Meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032850.R3
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Date Submitted by the Author:	02-Dec-2019
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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Global health
Keywords:	Public health < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES, MICROBIOLOGY, PARASITOLOGY, EPIDEMIOLOGY, IMMUNOLOGY

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Epidemiology of podoconiosis in Ethiopia: A systematic review and meta-analysis protocol

Birhan Alemnew^{1*}, Alebachew Fasil², Tesfahun Mulatu³, Nigus Bililign⁴, Setegn Esthetie⁵, Asmamaw Demis⁶

Author affiliations

¹Department of Medical Laboratory Science, College of Health Sciences, Woldia University, Ethiopia

²Department of Clinical chemistry, College of Medicine and Health Science, University of Gondar, Ethiopia

³Department of Public Health, College of Health Sciences, Woldia University, Ethiopia

⁴Department of Midwifery, College of Health Sciences, Woldia University, Ethiopia

⁵Department of Medical Microbiology, College of Medicine and Health Science, University of Gondar, Ethiopia

⁶Department of Nursing, College of Health Sciences, Woldia University, Ethiopia

*Corresponding author, email: birhanalemnew12@gmail.com, phone:+251922204330, P.O.Box: 400

ABSTRACT

Introduction: Podoconiosis is a non-filarial swelling of lower extremity endemic in tropical regions, North America and India. The etiology and pathophysiology of the disease remained unknown. We propose conducting a systematic review and a meta-analysis to evaluate the burden and risk factors of Podoconiosis in Ethiopia reported in studies from 2009 to 2019.

Methods and analysis: We will search the following electronic databases: PubMed (MEDLINE), EMBASE, Hinari, CINAHL, ISI (Web of Science), and Google scholar. Medical subject headings (MeSH) will be used to extensively search the appropriate literature on electronic databases using related keywords such as epidemiology or prevalence or magnitude or burden, podoconiosis, and Ethiopia. Also, grey literature and manual search will be used to retrieve unindexed research articles. Two reviewers will screen all retrieved articles, conduct data extraction, and then critically appraise all identified studies. We will analysis data by using STATA 14 statistical software. We will demonstrate pooled estimates of podoconiosis and associated factors with effect size and 95% confidence interval. The presence of heterogeneity among studies will be examined by forest plot as well as the I^2 heterogeneity test. Potential causes of heterogeneity will be explored by carrying out sensitivity and subgroup analyses. Moreover, the presence of publication bias will be examined by observing funnel plots, and objectively by Egger's regression test. If the funnel plot is asymmetric and/or Egger's test was found to be statistically significant ($p < 0.05$), the trim and fill (Duval and Tweedie's) analysis will be performed.

Ethics and dissemination: - The study will use publicly available data and will not identify the authors of the publication by name. In light of these and as has been indicted, research ethics clearance is not required for evidence syntheses in such reviews. The results of this study will be published in a peer-reviewed journal and presented at national and international conferences.

PROSPERO registration number CRD42019127459.

Strength and limitations of the study

- This will be the first systematic review and meta-analysis presenting the epidemiology and determinants of podoconiosis in Ethiopia.
- This study could potentially inform policy and practice to reduce the impact of podoconiosis.
- Strong and robust statistical methods will be employed to summarize the data.
- The establishment of casual relationships may be difficult.

INTRODUCTION

Podoconiosis is non-filarial elephantiasis and a non-infectious geochemical disease caused by exposure of bare feet to red clay soil derived from volcanic rock. Mineral particles from the soil penetrate the skin and are taken up by macrophages in the lymphatic system which causes inflammation and fibrosis of the vessel lumen leading to blockage of the lymphatic drainage (1-3). A major and serious complication of podoconiosis is acute adenolymphangitis (ALA), which presents as a warm, painful sensation in the limbs, accompanied by fever (2).

In addition to prolonged exposure to soil, many studies showed that the prevalence of podoconiosis was associated with feet hygiene, shoe-wearing habit, gender, age, occupation, housing condition, and income status (4-7).

Podoconiosis is common in more than ten countries across tropical Africa, Central and South America and northwest India (8, 9), including Ethiopia (10). In Ethiopia, the prevalence of podoconiosis is about 5% in areas with irritant soil (1) and an estimate based on prevalence data from an endemic area in southern Ethiopia reported that between 500,000 and 1 million people were affected (11, 12).

Podoconiosis imposes huge economic burdens that worsen the prevailing poverty and results in considerable social stigmatization associated with the belief that the condition is familial and incurable (13). In Cameroon, podoconiosis imposed financial burdens on affected households through direct treatment cost and reduced ability to work (14). Similarly, food insecurity was reported higher among households of Ethiopian podoconiosis patients (15).

Podoconiosis is endemic in 345 districts of Ethiopia: the majority of cases in Oromia, Southern Nations, Nationalities and Peoples' and Amhara regional states (16). In Ethiopia, studies have shown that podoconiosis was significantly associated with soil texture and land topography (17), washing practices and frequency of shoe-wearing (4, 18), family history and barefoot (5). Although simple and effective treatment strategies are available in Ethiopia, podoconiosis patients tend to discontinue their treatment. Some of the factors for discontinuation were remoteness from treatment sites, stigma, and misconceptions about the treatment (19). On top of this, podoconiosis patients had a stigma (20), depression (21) and lower quality of life in Ethiopia (22).

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3 A systematic review and meta-analysis showed that footwear use was associated with decreased
4 risks of Neglected Tropical Diseases (NTDs) (23). The WHO underscored the importance of
5 integrated control of NTDs, including podoconiosis (24).
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10 Despite many remarkable achievements in reduction of the public health problem of
11 podoconiosis in Ethiopia, there are several important challenges that still exist and need especial
12 consideration at nation and international. Hence, comprehensive figure and continued updates
13 regard the burden of the disease has been warranted to boosting the existing strategy and to
14 design new approach for elimination of podoconiosis. The purpose of this study aimed to
15 demonstrate the pooled prevalence of podoconiosis in the country within the last ten years old.
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21 During the last decade, the Ethiopian Federal Ministry of Health has prioritized and has been
22 working for the elimination of podoconiosis by 2020 in collaboration with international agencies,
23 NGOs, and the World health organization. Although, the national podoconiosis elimination
24 program now out of the track for the 2020 target. The authors designed to this systematic review
25 and meta-analysis to show the overall pooled prevalence of podoconiosis in the second-
26 millennium development goal duration in particular after the year 2009 using available
27 epidemiological study. Moreover, identifying the predictors of podoconiosis is the first essential
28 step in controlling the contributing factors. The findings from this systematic review will
29 highlight the pooled prevalence and associated factors of podoconiosis with implications to
30 improve interventions, to ensure cost-effectiveness, and to accelerate the reduction of
31 podoconiosis.
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40 **Objectives**

41 **General objective**

42 The objective of this study is to conduct a systematic review and meta-analysis of studies
43 assessing the prevalence and associated risk factors of podoconiosis in Ethiopia.
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47 **Specific objective**

- 48 ✓ To review and estimate the pooled prevalence of podoconiosis in Ethiopia.
- 49 ✓ To review and estimate the pooled prevalence of podoconiosis in different regions of the
50 country.
- 51 ✓ To review and determine the pooled effect sizes of the determinants of podoconiosis in
52 Ethiopia.
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Methods and Analysis

Protocol and registration

This protocol was developed with guidance following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (supplementary file1) statement guideline (25), and the review that is to be guided by this protocol will be carried out following MOOSE guidelines.

The protocol was registered with the International Prospective Register of Systematic Reviews PROSPERO in 2019 and has been assigned the identification number CRD42019127459. The full documentation is available online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019127459).

Literature search

We will systematically conduct a comprehensive literature search using different bibliographic databases. We will search the following online databases: PubMed (MEDLINE), EMBASE, Hinari, CINAHL, ISI (Web of Science), and Google scholar. We will use Medical Subject Headings (MesH), keywords, and free text search terms. An extensive and comprehensive search will be made by using alternative terms such as epidemiology, magnitude, burden, prevalence, podoconiosis, and Ethiopia. This search strategy will be performed by combining the above terms using Boolean operators. An example of the search strategy that will be used in PubMed will be as follows: (prevalence OR population OR magnitude OR epidemiology OR burden OR “public health” OR (public AND health) AND (podoconiosis OR “mossy foot” OR (mossy AND foot) OR “non-filarial” OR (non AND filarial) OR elephantiasis) AND (Ethiopia). To check that the searches are exhaustive, we will utilize snowballing to screen the references of identified articles for potentially relevant studies. Furthermore, grey literature and manual search will be used to retrieve unindexed research works. During the search process, to suppress the number of irrelevant studies, the search will be restricted to only ‘human studies’ and ‘English language’ in the advanced search. Authors' profiles will also be searched to ensure that other relevant articles are captured. The search activity will be done by BA, AD, and SE, and the whole process is expected to be completed by 4 October 2019.

Criteria for considering studies for the review

Inclusion criteria

- ✓ This review will account for all observational and population-based studies reporting the incidence or prevalence of podoconiosis.
- ✓ Studies describing the prevalence of podoconiosis as well as associated factors across all age groups, and regions within Ethiopia.
- ✓ Articles published in the English language will be eligible for inclusion

Exclusion criteria

- ✓ Studies conducted before 2009 and conducted outside of Ethiopia will be excluded
- ✓ Narrative reviews, expert opinions, case reports and case series will be excluded.
- ✓ Articles without full text and data that are difficult to extract, despite contacting the corresponding author(s)

Study selection and data extraction

First, systematic searching will be conducted through all identified databases, search engines, and additional references that will be retrieved from other published articles. Second, studies conducted before 2009, conducted in countries other than Ethiopia, and unrelated articles based on their title will be excluded. Third, those potentially eligible for inclusion will be imported to Endnote version 8, and we removed the duplicates by screening the de-duplicated citations by hand, which were recorded on a Microsoft Excel spreadsheet. To be considered duplicates, two or more citations had to share the same author, title, publication date, volume, issue, and start page information. The full text versions of the citations were consulted when we were in doubt. In such cases, we also checked the population sizes, methodology, and outcomes to determine whether the citations were duplicates. Conference abstracts were deemed to be duplicates if full-text articles that shared the same study design, sample size, and conclusion were retrieved, even if their publication dates varied. Lastly, the studies will be screened and selected for full-text review based on inclusion criteria. The Preferred statement for Reporting Systematic review and Meta-analysis (MOOSE) will be used to present the study inclusion, exclusion and reason for exclusion information in a diagram. In conclusion, the following data will be abstracted using a structured data abstraction form and presented using a prepared format on the Microsoft Excel spreadsheet. Information such as the primary investigator's name, year of publication, region,

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3 residence, study design, sample size, a tool used to diagnose podoconosis will be extracted.
4 Moreover, prevalence, adjusted associated factors with their effect size (OR) and 95%
5 confidence intervals(lower and upper confidence interval) will be extracted. Before analysis, a
6 transformation of Odds ratios and prevalences will be made. For any difficulties that might be
7 encountered during data extraction, the corresponding author(s) will be contacted by any means
8 of communication
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14 **Risk of bias (quality) assessment**

15 Once all searches have been completed, the included studies will be assessed independently by
16 the three researchers (BA, SE, and AD), using a quality assessment tool. Newcastle-Ottawa
17 Scale (NOS) will be used to assess the quality of included studies for Observational Cohort and
18 Cross-Sectional (26). Study quality will be assessed using a quality assessment tool (27). Based
19 on this tool, studies are rated as low risk, moderate risk and high risk for scores ≤ 5 , 6-8 and > 8
20 respectively. Discrepancies will be discussed and resolved by consensus between the authors and
21 an independent reviewer. In addition to quality assessment, the reporting of the systematic
22 review and meta-analysis result will be based on the Meta-analysis Of Observational Studies in
23 Epidemiology (MOOSE) (supplementary file 2) statement (28). All tools have ‘Yes’ and ‘No’
24 types of questions and scores will be given 1 and 0 for ‘Yes’ and ‘No’ responses, respectively.
25 Scores will be summed and transformed into a percentage. Only studies that scored $\geq 50\%$ will be
26 considered for both systematic review and meta-analysis of prevalence. For any scoring
27 disagreements, which might happen between the assessors, the sources of discrepancy will be
28 investigated by a thorough revision. For persistent disagreements in spite of the detailed review,
29 the average scores of the reviewers will be calculated. Similarly, for determinants, each factor
30 with each outcome variable will be critically appraised. The similar cut-off point that we will be
31 using for prevalence studies will be applied to factors. Moreover, the quality results of primary
32 studies will be placed in a separate column of the data extraction format.
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48 **Data analysis and assessment of publication bias**

49 The extracted data will be exported to STATA version 14 (STATA, Corporation, College
50 Station, Texas) software for further analysis. The prevalence of podoconiosis in Ethiopia will be
51 pooled from each study and determined as a single estimate. The existence of heterogeneity
52 among the included studies will be examined by forest plot and I^2 -heterogeneity test(29). The I^2 -
53 values greater than 75%, 50-75%, 25-50%, and less than 25% will be interpreted as the presence
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3 of considerable, substantial, moderate, and low heterogeneity, respectively. I^2 heterogeneity test
4 of $\geq 50\%$ and a p-value of < 0.05 will be declared as the presence of heterogeneity. Thus, the
5 DerSimonian and Laird random-effects model will be employed. To identify the influential
6 studies that resulted in variation, sensitivity analysis will be carried out using the 'metaninf'
7 command(29). Similarly, subgroup analysis will be employed by considering the year of the
8 study, the region, and sample size as a source of variation. Moreover, the funnel plot and Egger's
9 regression test will be conducted to check the potential publication bias(30). Accordingly,
10 asymmetry of the funnel plot and/or statistical significance of Egger's regression test ($p < 0.05$)
11 will be suggestive of publication bias(30). In case of minor publication bias, using the 'metatrim'
12 command, a non-parametric trim and fill (Duval and Tweedie's) method of analysis will be
13 done(29).
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23 Discussion

24 Due to the paucity of data, which addresses the epidemiology of podoconiosis in Ethiopia, we
25 intend to fill this gap by reviewing available literature as outlined in this protocol. The findings
26 of this systematic review and meta-analysis will have implications for stakeholders, which work
27 on Neglected Tropical Diseases including podoconiosis. We also anticipate that the findings of
28 this review will have many contributions to the development of prevention strategies to factors
29 associated with podoconiosis in the country.
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35 Ethics and dissemination

36 No formal ethical review was required as the systematic reviews will use publicly available data
37 and will not identify authors of the publication by name. In light of these and as has been
38 indicted, research ethics clearance is not required for evidence syntheses in such reviews. The
39 findings of this systematic review will be published in a reputable peer-reviewed journal and
40 presented at a scientific national and international conference.
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45 Acknowledgments

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47 the authors extend our appreciation to Dr. Lemma Derseh and Dr. Tesfaye Gelanew, who
48 provided administrative support and edited the scientific language for reviewing this manuscript.
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Contributors

BA and AD wrote the protocol. BA and AF will individually perform the abstract extraction and critique the literature, and TM will be the third reviewer. NB, SE, and TM provided insight into the epidemiological aspects of the review and helped draft the manuscript. BA, AF, TM, NB, SE, and AD advised on the background and revised the manuscript. All authors approve the final version and take responsibility for its content. The guarantor of the review is AD.

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Competing interests

None declared.

Patient and Public Involvement:

No patient involved.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	-
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4-5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	4-5 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	4-6
5	Type of study designs used	5-7
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5, Table 1
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	8, Table 2, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6-7
22	Assessment of heterogeneity	7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7-8
24	Provision of appropriate tables and graphics	Tables 2-7, Figs 2-7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 3-7
26	Table giving descriptive information for each study included	Table 2
27	Results of sensitivity testing (eg, subgroup analysis)	Fig 3, Table 3
28	Indication of statistical uncertainty of findings	12-16

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	12, Fig 2
30	Justification for exclusion (eg, exclusion of non-English language citations)	6
31	Assessment of quality of included studies	6-7
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	17-19
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	20
34	Guidelines for future research	-
35	Disclosure of funding source	20

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.