RESEARCH ARTICLE

Estimating the number of cases of podoconiosis in Ethiopia using geostatistical methods [version 1; peer review: 3 approved, 1 approved with reservations]

Kebede Deribe1,2, Jorge Cano3, Emanuele Giorgi3,4, David M. Pigott5, Nick Golding6,7, Rachel L. Pullan3, Abdisalan M. Noor8,9, Elizabeth A. Cromwell5, Aaron OsgoodZimmerman5, Fikre Enquselassie1, Asrat Hailu10, Christopher J. L. Murray5, Melanie J. Newport12, Simon J. Brooker11, Simon I. Hay5,12, Gail Davey12

1School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia
2Wellcome Trust Brighton and Sussex Centre for Global Health Research, Brighton and Sussex Medical School, Brighton, UK
3London School of Hygiene & Tropical Medicine, London, UK
4Lancaster Medical School, Faculty of Health and Medicine, Lancaster University, Lancaster, UK
5Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA
6Spatial Ecology and Epidemiology Group, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
7School of BioSciences, University of Melbourne, Parkville, VIC, Australia
8Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
9Kenya Medical Research Institute-Wellcome Trust Collaborative Programme, Nairobi, Kenya
10Department of Microbiology, Immunology and Parasitology, Faculty of Medicine, Addis Ababa University, Addis Ababa, Ethiopia
11Bill and Melinda Gates Foundation, Seattle, WA, USA
12Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK

Abstract

Background: In 2011, the World Health Organization recognized podoconiosis as one of the neglected tropical diseases. Nonetheless, the number of people with podoconiosis and the geographical distribution of the disease is poorly understood. Based on a nationwide mapping survey and geostatistical modelling, we predict the prevalence of podoconiosis and estimate the number of cases across Ethiopia.

Methods: We used nationwide data collected in Ethiopia between 2008 and 2013. Data were available for 141,238 individuals from 1,442 villages in 775 districts from all nine regional states and two city administrations. We developed a geostatistical model of podoconiosis prevalence among adults (individuals aged 15 years or above), by combining environmental factors. The number of people with podoconiosis was then estimated using a gridded map of adult population density for 2015.

Results: Podoconiosis is endemic in 345 districts in Ethiopia: 144 in Oromia, 128 in Southern Nations, Nationalities and People’s [SNNP], 64 in Amhara, 4 in Benishangul Gumuz, 4 in Tigray and 1 in Somali Regional
State. Nationally, our estimates suggest that 1,537,963 adults (95% confidence intervals, 290,923-4,577,031 adults) were living with podoconiosis in 2015. Three regions (SNNP, Oromia and Amhara) contributed 99% of the cases. The highest proportion of individuals with podoconiosis resided in the SNNP (39%), while 32% and 29% of people with podoconiosis resided in Oromia and Amhara Regional States, respectively. Tigray and Benishangul Gumuz Regional States bore lower burdens, and in the remaining regions, podoconiosis was almost non-existent.

Discussion: The estimates of podoconiosis cases presented here based upon the combination of currently available epidemiological data and a robust modelling approach clearly show that podoconiosis is highly endemic in Ethiopia. Given the presence of low cost prevention, and morbidity management and disability prevention services, it is our collective responsibility to scale-up interventions rapidly.

Keywords
Ethiopia, podoconiosis, elephantiasis, lymphoedema, neglected tropical disease, mossy foot

Corresponding author: Kebede Deribe (kebededeka@yahoo.com)

Author roles: Deribe K: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Cano J: Formal Analysis, Methodology, Resources, Software, Visualization, Writing – Review & Editing; Giorgi E: Formal Analysis, Methodology, Software, Validation, Writing – Review & Editing; Pigott DM: Formal Analysis, Methodology, Software, Visualization, Writing – Review & Editing; Golding N: Formal Analysis, Methodology, Supervision, Writing – Review & Editing; Pullan RL: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Resources, Supervision, Writing – Review & Editing; Noor AM: Methodology, Supervision, Writing – Review & Editing; Cromwell EA: Methodology, Writing – Review & Editing; Osgood Zimmerman A: Methodology, Writing – Review & Editing; Enquaselassie F: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing; Hailu A: Data Curation, Funding Acquisition, Investigation, Methodology, Resources, Writing – Review & Editing; Murray CJL: Conceptualization, Methodology, Supervision, Writing – Review & Editing; Newport MJ: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing; Brooker SJ: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Resources, Supervision, Writing – Review & Editing; Hay SI: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Writing – Review & Editing; Davey G: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Review & Editing

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Introduction

Estimating the number of people with podoconiosis according to geographical location is important for programme planners and health care providers, who plan, monitor and evaluate control and elimination efforts. Despite a growing interest in understanding the number of people with podoconiosis, the figures available are largely estimates (Davey et al., 2012). Estimation of the number of people with podoconiosis has relied upon expert opinion and a few market-based surveys (Oomen, 1969; Price, 1974). More robust estimates and a better understanding of how podoconiosis-affected individuals may be spatially distributed are vital (Deribe et al., 2013; Deribe et al., 2015b). Data on the geographical distribution of podoconiosis are also important to identify populations disproportionately affected by the disease, which need priority intervention.

In our previous analysis, we identified the individual and environmental risk factors of podoconiosis in Ethiopia (Deribe et al., 2015a; Deribe et al., 2015b), delineated the environmental limits, and estimated the population at risk (Deribe et al., 2015b). However, the number of people with podoconiosis and its geographical variation remains to be determined. Previous complete censuses of cases have estimated the number of podoconiosis cases in localized areas (Alemu et al., 2012; Molla et al., 2012; Tekola Ayele et al., 2013). Here we present the results of a modelling exercise intended to analyse the spatial distribution of podoconiosis prevalence across Ethiopia and produce robust estimates of number of cases of podoconiosis for the year 2015.

Methods

Data sources

Podoconiosis. Ethiopia is located in the Horn of Africa and is the second most populated country in sub-Saharan Africa. The total population was estimated at 94.4 million in 2017, of which over 75 million (79.7%) live in rural areas (Federal Democratic Republic of Ethiopia Ministry of Health, 2016). The data used in this study are derived from nationwide mapping of lymphatic filariasis (LF) and podoconiosis conducted between 2008 and 2013 (Deribe et al., 2015a; Deribe et al., 2015b). Detailed information about the surveys has been provided elsewhere (Deribe et al., 2015a; Deribe et al., 2015b). Briefly, the study was conducted in all nine Regional States and two City Administrations (Addis Ababa and Dire Dawa). In each district (woreda), two villages were surveyed purposively following WHO guidelines for LF mapping (World Health Organization, 2000). In each village, 100 randomly selected adults (215 years) were studied for LF infection and podoconiosis-related morbidity. In total 141,238 individuals from 1,442 villages in 775 districts were included in the study.

Trained health professionals conducted the survey; lymphoedema was diagnosed clinically by history and physical examination, and cases were tested for LF using a point-of-care test. Participants were requested to provide a finger-prick blood sample, which was tested for circulating *Wuchereria bancrofti* antigen using an immunochromatographic test (ICT). For individuals with lymphoedema, an algorithm was used to identify possible differential diagnoses of podoconiosis (Sime et al., 2014). All individuals with ICT negative results underwent physical examination for signs and symptoms of podoconiosis. In this study, a confirmed podoconiosis case was defined as a person residing in the surveyed district for at least 10 years (to exclude cases who acquired the disease elsewhere) (Kloos et al., 1992), with lymphoedema of the lower limb present for more than 3 months, excluding other potential causes of lymphoedema (Sime et al., 2014). Geographic coordinates of the sampled communities were recorded.

We used information from the available community data (sample size and number of positive cases) at known locations (longitude and latitude) with a selection of environmental and socio-demographic datasets, to produce a gridded map of predicted prevalence of podoconiosis by implementing a geostatistical modelling approach.

Covariates. A suite of remote sensing derived datasets was selected based on previous modelling work (Deribe et al., 2015b). The relationship between the following covariates and podoconiosis prevalence was explored: elevation and derived slope; long-term average of precipitation; enhanced vegetation index (EVI); clay and silt content of the top soil (0–15 cm), and night light-emissivity (see Supplementary File 1).

The elevation dataset was derived from a gridded digital elevation model produced by the Shuttle Radar Topography Mission (http://srtm.csi.cgiar.org) (Farr & Kobrick, 2000) and subsequently resampled to 1 km² resolution to match the resolution of the other datasets. The elevation surface was processed to obtain slope in degrees. The gridded precipitation layer was downloaded from the WorldClim database. The WorldClim database provides a set of global climate layers obtained by interpolation of precipitation data for the period 1950–2000 collected from weather stations distributed across the world (Hijmans et al., 2005). A raster surface of averaged EVI for the period 2000–2015 was obtained from the African Soil Information System (AISIS) project (http://africasoils.net/services/data/remote-sensing/land). Soil data (clay and silt content at the top soil) were downloaded from the ISRIC-World Soil Information project included in the Harmonized Soil Map of the World (http://www.isric.org/explore/isric-soil-data-hub). These datasets were obtained at 250m² and were subsequently resampled using bilinear interpolation to match the spatial resolution of the other gridded datasets (1 km²). Finally, night-light emissivity captured by the Operational Linescan System instrument on board a satellite of the Defence Meteorological Satellite Programme was used as a proxy measure of poverty across Ethiopia (https://ngdc.noaa.gov/eog/dmsp/downloadV4composites.html). Elvidge et al., 1996). This instrument measures visible and infrared radiation emitted at night-time, resulting in remote imagery of lights on the ground. The brightness of light pixels varies on an arbitrary scale from 0–63 units, with the largest, well-electrified, urban areas yielding the highest values. This information has been correlated with gross domestic product in developed countries (Doll et al., 2006; Ebener et al., 2005) and, although far from precise, would provide an indirect measure of poverty in developing countries.
(Noor et al., 2008). The major advantage of this dataset is that it can be obtained in a gridded continuous format at 1 km² resolution and by year since 1992.

Survey and covariate data were linked in ArcGIS 10.3 (Environmental Systems Research Institute Inc. [ESRI] Inc., Redlands CA, USA) based on the WGS-1984 Web Mercator projection at 1 km² resolution. Input grids were resampled, when necessary, to a common spatial resolution of 1km² using a nearest neighbour approach, clipped to match the geographic extent and aligned to a land mask template of Ethiopia.

Geostatistical analysis
Empirical data and spatially matched covariates were used within a geostatistical framework. We developed a spatially explicit logistic regression model to predict podoconiosis prevalence at village level across Ethiopia. In the model, podoconiosis risk depended on the most relevant environmental risk factors, namely those most strongly associated with podoconiosis prevalence, as described above. Let \( p(x) \) denote the prevalence of podoconiosis at location \( x \); the linear predictor for the log-odds is

\[
\log \left( \frac{p(x)}{1 - p(x)} \right) = \beta_0 + \beta_1 \text{Rainfall}(x) + \beta_2 \text{NLE}(x) + \beta_3 \text{Slope}(x) + \beta_4 \text{EVI}(x) + \beta_5 \text{Elevation}(x) + \beta_6 \text{Elevation}^2(x) + \\
\beta_7 \text{Silt}(x) + \beta_8 \text{Clay}(x) + S(x) + Z(x)
\]

where \( S(x) \) are spatial random effects that account for spatial variation in podoconiosis prevalence between villages, not explained by the predictors, and \( Z(x) \) are unstructured random effects, also known as “nugget effect”, which capture extra-binomial variation within villages. For example, such differences might be due to individual variability (e.g. genetic predisposition or behavioural traits). More details on the model formulation of the geostatistical model can be found in Supplementary File 1.

We carried out validation of the model using a variogram-based procedure, which tested the compatibility of the adopted spatial structure with the data. More details are provided in Supplementary File 1. The model parameters were estimated by Monte Carlo maximum likelihood using the R 3.4.1 version package `PrevMap`, which implements parameter estimation and spatial prediction of generalized linear geostatistical models (Giorgi & Diggle, 2017). The final fitted model was applied to produce continuous predictions of prevalence of podoconiosis among adults (≥15 years) at 1 km² resolution. A probability map of areas exceeding 1% prevalence (the threshold used to define podoconiosis endemicity) was also developed (Deribe et al., 2015d).

We used gridded maps of population density and age structure, obtained from the WorldPop project (Linard et al., 2012; Tatem et al., 2007), to estimate the number of podoconiosis cases among the adult population. The map of predicted prevalence of podoconiosis was multiplied with the corresponding gridded map of estimated adult population resampled at the same spatial resolution. Using the resulting gridded map, the aggregate number of adults with podoconiosis at different administrative levels was extracted.

Model uncertainty and validation statistics
We checked the validity of the assumed covariance model for spatial correlation using the Monte Carlo algorithm and empirical semi-variogram as described in Supplementary File 1. Additionally, a map of the number of standard errors from the posterior mean prevalence of podoconiosis was used to estimate the lower and upper confidence intervals of the predicted case estimates. Confidence interval maps determined the uncertainty regarding the estimated number of cases of podoconiosis.

Results
Data availability for podoconiosis
Data included in this analysis are summarized in Table 1. In total, we identified 1,442 data points from unique locations in 775 districts. In 41.9% of surveyed districts, no cases of podoconiosis were identified. We have data from the nine Regional States and two City Administrative Councils of Ethiopia resulting in 141,238 individuals surveyed. Most of the community surveys (77%) were conducted in three Regional States: Amhara, Oromia and SNNP. Only Addis Ababa had fewer than 10 data-points. Overall, 91% of the community survey data were from the 2013 mapping study. The mean number of people examined per village was 97.6; the majority of communities (1,350, 93.6%) had more than 90 examined individuals.

Environmental factors associated with podoconiosis prevalence
Seven environmental variables, which were previously identified as potential predictors for podoconiosis in Ethiopia (Deribe et al., 2015b), were used to model podoconiosis prevalence. These included elevation and derived slope, annual precipitation, EVI, clay and silt soil content, and night-light emissivity (see Supplementary File 1). The most parsimonious geostatistical model was fitted with the seven covariates and then used to predict podoconiosis prevalence for unsurveyed areas (Figure 2).

<table>
<thead>
<tr>
<th>Region</th>
<th>Districts surveyed</th>
<th>Number of clusters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addis Ababa</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Affar</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Amhara</td>
<td>144</td>
<td>285</td>
</tr>
<tr>
<td>Benishangul Gumuz</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Dire Dawa</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Gambella</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Harari</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Oromia</td>
<td>298</td>
<td>541</td>
</tr>
<tr>
<td>SNNP</td>
<td>155</td>
<td>285</td>
</tr>
<tr>
<td>Somali</td>
<td>49</td>
<td>99</td>
</tr>
<tr>
<td>Tigray</td>
<td>46</td>
<td>91</td>
</tr>
<tr>
<td>Total</td>
<td>775</td>
<td>1,442</td>
</tr>
</tbody>
</table>
Figure 1. Distribution of 1,442 communities surveyed and prevalence of podoconiosis among adults (≥15 years).

Figure 2. Predicted podoconiosis prevalence maps of Ethiopia; mean predicted prevalence and confidence intervals (95% CI).
Estimation of podoconiosis cases across Ethiopia

Figure 2 and Figure 3 show the predicted podoconiosis prevalence in adults and the distribution of people with podoconiosis (i.e. estimates of podoconiosis cases), respectively. Nationally, our estimates suggest that 1,537,968 adults (95% Confidence Interval [CI], 290,923- 4,577,031) were living with podoconiosis in 2015 in Ethiopia. Three large regions (SNNP, Oromia and Amhara) contributed 99% of the cases. The highest proportion of all individuals with podoconiosis resided in the SNNP (39%), while 32% and 29% of people with podoconiosis resided in Oromia and Amhara Regional States, respectively. Tigray and Beneshangul Gumuz Regional States contributed marginally to the total number of people with podoconiosis, but there were almost no cases in the other regions (Table 2).

Within regions, the distribution of podoconiosis cases is quite heterogeneous. In Amhara region, the majority of the cases were predicted to occur in East Gojam, West Gojam and South Gondar

Figure 3. Estimated number of people with podoconiosis across Ethiopia: estimated number of cases and confidence intervals (95% CI).

Table 2. Estimated number of podoconiosis cases among adults in Ethiopia in 2015.

<table>
<thead>
<tr>
<th>Region</th>
<th>Adult estimated cases</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Population living in areas exceeding 1% podoconiosis prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addis Ababa</td>
<td>256</td>
<td>33</td>
<td>930</td>
<td>-</td>
</tr>
<tr>
<td>Affar</td>
<td>36</td>
<td>3</td>
<td>146</td>
<td>-</td>
</tr>
<tr>
<td>Amhara</td>
<td>446,858</td>
<td>77,486</td>
<td>1,331,010</td>
<td>8,852,685</td>
</tr>
<tr>
<td>Benishangul Gumuz</td>
<td>6,400</td>
<td>616</td>
<td>26,158</td>
<td>214,750</td>
</tr>
<tr>
<td>Dire Dawa</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>5,976</td>
</tr>
<tr>
<td>Gambella</td>
<td>201</td>
<td>15</td>
<td>902</td>
<td>11,841</td>
</tr>
<tr>
<td>Harari</td>
<td>8</td>
<td>1</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Oromia</td>
<td>484,014</td>
<td>77,672</td>
<td>1,571,426</td>
<td>13,447,490</td>
</tr>
<tr>
<td>SNNP</td>
<td>598,676</td>
<td>134,920</td>
<td>1,640,511</td>
<td>13,580,281</td>
</tr>
<tr>
<td>Somali</td>
<td>61</td>
<td>2</td>
<td>354</td>
<td>4,860</td>
</tr>
<tr>
<td>Tigray</td>
<td>1,452</td>
<td>173</td>
<td>5,561</td>
<td>75,102</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,537,963</strong></td>
<td><strong>290,923</strong></td>
<td><strong>4,577,031</strong></td>
<td><strong>36,192,985</strong></td>
</tr>
</tbody>
</table>
zones. In Oromia region, most podoconiosis cases were predicted to come from East and West Wellega, Illu Aba Bora and Jimma zones. In the SNNP region, Gamo Gofa, Hadiya, Sidama and Wolayita zones were predicted to be the most affected.

Probability contour map and model validation
We also estimated the continuous probability of exceeding 1% podoconiosis prevalence (the threshold considered for intervention) across the endemic areas (Figure 4). The population living in areas that require intervention was estimated using the map. Overall, we estimated that 36 million people live in areas where the probability of exceeding 1% prevalence is greater than 75% (Table 2).

The estimated podoconiosis prevalence was associated with varying degrees of uncertainty. The model was validated using the Monte Carlo simulation based on the fitted model and computing an empirical semi-variogram with the residuals, obtained by fitting a standard logistic regression with simulated data and predictors (see Supplementary File 1). We concluded that the adopted covariance model was compatible with the data, as the empirical

![Figure 4. Map of probability of exceeding 1% podoconiosis prevalence.](image-url)
Our analysis gives an estimate of 1,537,963 podoconiosis cases in Ethiopia in 2015. This figure is substantially higher than the previous estimate of 550,000 cases in 1974 (Price, 1974). Nonetheless, the 1974 estimate is within the confidence interval of our estimates. It is unclear whether this difference is because of a sharp increase in the absolute number of cases due to neglect, or previous underestimation, or simply dramatic population growth (the Ethiopian population has increased fourfold since 1974) (Federal Democratic Republic of Ethiopia Ministry of Health, 2016; Price, 1974). Podoconiosis has been recognised only recently by the health system, since it was first reported in the country in 1969. The scarcity of allocated resources, low prioritization, and poor understanding of the disease amongst programme planners and health care providers, have been the biggest obstacles to podoconiosis control in Ethiopia over the last four decades. The methods used to assess the number of people with podoconiosis have changed since 1974 (Deribe et al., 2015b), when previous work by Price was sustained by market surveys (Oomen, 1969; Price, 1974). In recent years, community-based surveys with full clinical diagnosis and diagnostic tests to exclude other causes of elephantiasis have been used (Deribe et al., 2015a; Deribe et al., 2015b; Sime et al., 2014). The availability of better differential diagnosis and assessment methods are also contributing factors to the difference in the number of estimated cases.

Ninety-nine percent of podoconiosis cases were estimated to occur in the three largest Regional States (Amhara, Oromia and SNNP) of Ethiopia, which is consistent with previous prevalence studies. For example, a 2007 study conducted in SNNP estimated the prevalence of podoconiosis in Wolayita zone to be 5.46% (approximately 81,000 cases) (Desta et al., 2003; Tekola et al., 2006). Our model estimates that 72,723 people are predicted to be suffering from podoconiosis in Wolayita zone, with the 2007 estimate falling within the 95% confidence interval of our prediction.

Our results clearly reflect the magnitude of the problem for the Ethiopian public health system. The number of people living with podoconiosis is unacceptably high and indicates the need for rapidly increased coverage with interventions. Our model and the derived estimates have been produced at a high spatial resolution (1 km²), which will enable planning at lower administrative levels such as the health facility catchment zone or district. This level of planning will increase the efficiency, effectiveness and scale-up of prevention and morbidity management plans. These results will influence prioritization of geographical areas based on caseloads, and will guide local health facilities to strengthen surveillance to detect new cases.

The predicted probability that the local prevalence of podoconiosis exceeds 1% (the threshold to define endemic areas) (Deribe et al., 2015c; Deribe et al., 2015d) in most of the surveyed areas is clearly demarcated. There appears to be little uncertainty in the map (Figure 4), as the probability of the prevalence exceeds the threshold in most areas is either very high (>0.9) or very low (<0.1). However, in a few areas, such as north and south Wello, the results are less clear. In such areas, it will be important to inspect the available data in detail to assess the operational implications for local prevention and morbidity management interventions.

Our analysis has, for the first time, enabled detailed subnational estimation of podoconiosis in Ethiopia. We used nationwide survey data to estimate the number of cases and remotely sensed data to model the prevalence of podoconiosis. Nonetheless, it is important to consider limitations in the interpretation of results and their future applications. First, there were regions with limited data; Addis Ababa and Dire Dawa City Administrations had few data points. However, the two City Administrations accounted for only 4% of the national population and 0.34% of the estimated 35 million people at risk of podoconiosis in Ethiopia (Deribe et al., 2015b). Second, we included several sets of spatial covariates, but the covariates included do not represent all the potential drivers of podoconiosis. For example, our model did not account for the use of protective measures such as frequency of shoe wearing, because this information is not available in a continuous gridded format. We tried to minimize this limitation by including a proxy measure of poverty (night-light emissivity). As these covariates become available future studies should incorporate them. Third, the confidence interval of our estimation is very wide, which implies there are factors not accounted for in our modelling that determine the distribution of podoconiosis. Potentially these could be related to individual behaviours (e.g. shoe wearing and foot hygiene) (Deribe et al., 2015a; Molla et al., 2013) or more detailed soil characteristics (Molla et al., 2014). Our modelling included important soil characteristics that might drive the distribution of podoconiosis; however, detailed soil characteristics including mineral contents (such as smectite, quartz and mica) (Molla et al., 2014) found to be associated with podoconiosis distribution, were not available in a high-resolution spatial data or layers. Therefore, our estimates of podoconiosis cases should be interpreted with caution given the wide confidence interval. Nonetheless, it is important to note that our maps on the probability that the local prevalence of podoconiosis exceeds 1% (Deribe et al., 2015d) are of high resolution and can serve as an important input for programme planning and decision making.

Our analysis provides a framework for modelling podoconiosis distribution in Africa and globally. Building on the current work, we will model the distribution of podoconiosis in other highly endemic countries that are generating national data (Deribe et al., 2017). The availability of nationally representative data is...
important for such work, such as the integration of podoconiosis surveys with other ongoing surveys. Endemic countries should also be strengthening the routine surveillance of podoconiosis cases to generate sustainable and more representative data (Deribe et al., 2017). The current work also provides important data for estimating the burden of podoconiosis in terms of disability-adjusted life-years (DALYs) (Murray et al., 2012; Salomon et al., 2015), using the well-established disability weightings for lymphoedema generated by the Institute for Health Metrics and Evaluation (Murray et al., 2012; Salomon et al., 2015).

This high-resolution mapping of podoconiosis has enabled us to better estimate the number of cases in Ethiopia. The estimate presented here clearly shows that podoconiosis is highly endemic throughout Ethiopia and the number of cases over the last 40 years has remained unacceptably high. While we now have a good estimate of the number of people with podoconiosis, it is important to also understand its burden in terms of DALYs and economic and productivity losses (Deribe et al., 2015d). Given the high profile of podoconiosis on the global health agenda and the presence of low cost prevention, and morbidity management and disability prevention services, it is our collective responsibility to scale-up interventions rapidly.

Data availability

The data used in this study is generated through a collaboration between the Ethiopian Public Health Institute (EPHI), Addis Ababa University and Brighton and Sussex Medical School (BSMS). All data sharing requests are reviewed and approved by them. To initiate the data access process, please contact the BSMS Research Governance and Ethic Committee: rgec@bsms.ac.uk, who will provide guidance for accessing the data.

Access to data for covariates are detailed in the Methods.

Supplementary material

Supplementary File 1: Geostatistical analysis. The supplementary file provides maps of the covariates, the model formulation and validation.

Click here to access the data.

References


Competing interests

No competing interests were disclosed.

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Reviewer Report 06 November 2017

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Delenasaw Yewhalaw
Tropical and Infectious Diseases Research Center, Jimma University, Jimma, Ethiopia

Minor essential comments
This paper assessed the prevalence and estimated number of cases of podoconiosis in Ethiopia. It is an important work which provides input to health decision making and planning process for podoconiosis intervention and elimination. This study moreover estimates the number of podoconiosis cases and prevalence at sub-country/sub-regional level such an approach is important for countries like Ethiopia which initiated elimination agenda and where morbidity, disease occurrence and severity varies from one area to the other in the country.

Introduction:
OK

Methodology:
The methodology is sound and clear. However, it would have been good if authors also present additional climatological data such as temperature and relative humidity which have an impact on EVI. Authors performed the analysis based on data collected from 2008 to 2013. Why were authors interested to estimate number of podoconiosis cases and prevalence for 2015? Authors should justify why they didn’t estimate for 2014? or from 2014-2016 to see the trend and distribution? This could also be important to evaluate the impact of intervention on the burden of podoconiosis at local and national level.

Results:
There was wide confidence interval for both estimated number of podoconosis cases and its prevalence in each surveyed region. This shows that the authors didn’t take into account important predictors as it has also been mentioned by the authors or because of the problem of model selection. This could have implication on resource mobilization for disease prevention, morbidity management or elimination efforts.

Discussion:
OK
Conclusion:
OK

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Author Response 12 Dec 2017**

**Kebede Deribe, Brighton and Sussex Medical School, Brighton, UK**

Many thanks for your thoughtful comments. As you rightly indicated the study used data from two surveys conducted between 2008 and 2013. We have estimated the number of podoconiosis cases for the years 2015 because we have raster data of population density data for Ethiopia for 2010, 2015 and 2020. The closest year to our estimates and the current period would be 2015. Given the chronic nature of podoconiosis we do not expect significant incident cases to affect our estimates significantly. Nonetheless we take your point of the need for updating the estimates and figures for the years to come as more epidemiological data and covariates become available.

We have acknowledged and discussed the potential reasons for wide confidence interval.

Multilevel factors are involved in podoconiosis risk and diseases progression (individuals, household and environmental). Individual factors such as genetic susceptibility and footwear use are not available at the format and resolution (continuous gridded format) required for such geostatistical analysis. Given the limitation, nonetheless, our estimates provide important information for planning and monitoring progress in the control and elimination of podoconiosis. Temperature and relative humidity have been considered in our previous analysis and were excluded because of multicollinearity with other covariates and therefore excluded from the analysis.
Thank you again for reviewing our manuscript.

**Competing Interests:** No competing interests were disclosed.

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**Reviewer Report 01 November 2017**

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**Henok Tadesse Ayele**
McGill University, Montreal, QC, Canada

The authors investigated the prevalence and associated environmental factors of Podoconiosis, which is a disease of high public health importance. Their findings have paramount programmatic implications. Overall, this is a well-written manuscript; however, I have some concerns, which are listed below.

**Major concerns**

1. The authors have not adequately mentioned the details of sample size determination. It is not clear whether the WHO definition of village (50X50km grid) apply in their sampling clusters (What is village?) and the WHO study was assessing the prevalence of filarial elephantiasis (how valid to assume the sampling technique is similar for these two diseases and climate stay constant in the last 30 years?). Did they take the clustering effect in to consideration?

Their previous study reported that two kebele (smallest administrative units) were selected from each districts based on reported history of lymphoedema cases collected through interviewing the woreda health officials, health providers, and village leaders 1 day before the survey. How valid is the selection of village with known cases? The potential selection bias might overestimate the prevalence.

2. The model does not look optimally fitted. It only includes environmental factors (individual study participants characteristics were not included). Night light emissivity was assumed to capture individual participants’ characteristics as a proxy measure but not sure, if it is valid assumption. Moreover, from your previous study mean annual land surface temperature and altitude were strong environmental predictors of podoconiosis. Yet they are excluded from the current prediction model.

3. As a follow up of no. 2 what methods you used to select the predictors finally fitted to yield a parsimongious model.

4. A geostatistical model was used to estimate prevalence of podoconiosis in non-surveyed area but the size of non-surveyed area is not mentioned. How comparable were the surveyed and
unsurveyed areas (A purposive sampling was used to select the villages rather than using the random sampling). Do you have data (on seven environmental factors) in non-surveyed areas?

5. The study might have benefited from a multivariate Bayesian generalized linear spatial model since the proper analysis seems a multivariate Bayesian generalized linear spatial modeling (Slater 2013) which would fit both environmental and individual participant’s data. You might probably mention this in the discussion part.

Minor concerns
1. The total population size was frequently cited from the FMOH even though the primary source is Central Statistical Agency.
2. I would mention the coverage measure of prediction model (C statistics for example).

References

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

*Competing Interests:* No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Thanks for taking the time to review our manuscript. We have provided the summary of the response to your comments. The WHO guidelines for lymphatic filariasis (LF) mapping recommend the selection of two villages per district. We have adopted this for integrated mapping of LF and podoconiosis, as detailed in previous publication (Sime et al. 2014). In our subsequent analysis we have demonstrated that podoconiosis has higher range of spatial dependence than LF (50X50km grid) (Deribe et al. 2015a).

We take communities as common name for administrative level next to kebele, this could be “gote”, which differs from region to region. The detailed sampling strategy used and their implications have been discussed in our previous publications (Deribe et al. 2015a, Sime et al. 2014). In the current model we have included seven covariates which have shown to be associated with podoconiosis in Ethiopia; clay fraction, silt fraction, elevation (altitude), slope, distance from closest waterway, Enhanced Vegetation Index [EVI]) and precipitation (Deribe et al. 2015a, Deribe et al. 2015b). The covariates were available as gridded maps and therefore suitable for being used eventually for projection on unsampled areas. Mean annual land surface temperature showed multicollinearity with other variable and was excluded from the analysis (Deribe et al. 2015a, Deribe et al. 2015b). We decided to include night-light emissivity as a proxy of poverty, as it’s detailed in methods section in the manuscript. Previous studies have demonstrated that night light emissivity can be associated with household consumption, assets and poverty (Jean et al. 2016).

We have acknowledged in the manuscript that the lack of individual and household covariates at the spatial resolution of our analysis is one of the limitation of our study, what would explain the wide confidence interval in the model prediction. As we replied to another reviewer, unfortunately, individual factors such as genetic predisposition and footwear use, key factors for the occurrence of podoconiosis, are not available in a suitable format for making projections (continuous gridded format).

In the discussion, we have acknowledged that one of the possible improvements of the current analysis would be the inclusion of individual-level risk factors. However Slater and Michael (Slater and Michael 2013) developed a geostatistical model for LF that did not differ from our approach; also, they did not include individual-level variables to fit final model. Their model differs from ours in the modelling approach implemented, they used Bayesian inference for fitting a geostatistical model whereas we used a likelihood-based approach. In this regard, we do not expect any tangible difference in our predictive inferences, had we used a Bayesian framework. Our approach pursues to maximize the likelihood function, thereby not making any assumptions on priors which may not be informative.

References


Competing Interests: No competing interests were disclosed.

Reviewer Report 15 September 2017

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Bereket Yakob
Descipline of Public Health Medicine, School of Nursing & Public Health, University of KwaZulu-Natal, Durban, South Africa

General
Overall, the manuscript is written well, has good scientific merit and high practical significance. Below raised are few points to better the paper.

Abstract
Method: You collected most of the data in 2013 but you did not explicitly stated from where the rest of the data came.
Results: Define endemicity of podoconiosis.
Discussion: What are the low cost interventions? What do you mean by “our collective responsibility”?

Introduction
Written well

Methods
Please state if the data were collected from a point in time or repeated overtime from 2008 – 2013
Did the figures in the results (magnitude and spatial distribution) refer to 2008/2013 or estimated for 2017?

Results
Data availability …
What are data points?
What do you mean by unique locations in the districts? Please explain

**Estimation of podoconiosis cases**

In the tables and figures, indicate to which year the data refer to (2008, 2013 or 2017). It’s not clear if they were estimations for 2008 and/or 2013 or projections for 2017

Table 2: insert one column to show prevalence for each of the regions

**Discussion**

Written well, and few queries are forwarded to better the section

Please explain: Why was the magnitude podoconiosis very high in Amhara, Oromia and SNNP regions?

**References**


**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Partly

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Health systems, epidemiology, podoconiosis, maternal and child health, quality of care, health system responsiveness, equity, etc

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Kebede Deribe, Brighton and Sussex Medical School, Brighton, UK

Many thanks for your comments. As it is indicated on the methods section we have used two cross-sectional datasets collected in 2008 and 2013. The data were collected from communities across the country from 775 districts. Podoconiosis endemicity has been defined as prevalence>1%, as it is stated in the methods section of the article. Based on the prevalence data and environmental covariates and using geostatistical modelling we estimated the number of cases of podoconiosis for the year 2015. As can be seen from the results, the magnitude of podoconiosis is estimated to be higher in Amhara, Oromia and SNNP Regional states of Ethiopia. These areas are environmentally more suitable for the occurrence of podoconiosis than others, as it has been demonstrated in a previous ecological modelling exercise (Deribe K et al. 2015b). The prevention of podoconiosis is rooted in promotion of regular footwear use and foot hygiene. The treatment is based on hygiene based morbidity management, as it has been discussed throughout the manuscript. By “collective responsibility” we mean the responsibility of podoconiosis elimination needs the involvement of multiple actors, the government, donors, program planner and implementers, that should act collectively to provide services to the people who need them.

Reference

Competing Interests: No competing interests were disclosed.

Reviewer Report 13 September 2017
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Michelle C. Stanton
Department of Parasitology, Liverpool School of Tropical Medicine, Liverpool, UK

This article is well written and addresses an area of great public health importance in Ethiopia. There are numerous questions/comments about the data and methods used however which I have outlines below, broken down by section.

Abstract: Please provide a clearer idea of the burden of risk in the form of percentage of the population at risk in addition to absolute numbers

Introduction: Please provide a brief introduction to podoconiosis, how it’s transmitted and the currently implemented interventions
Methods:
- Please give a brief description of the rationale of why these covariates may be associated with podoconiosis risk.
- Please describe how elevation was resampled to 1km². What was the original spatial resolution of the data?
- Can averaged (modelled) rainfall over the period 1950-2000 be used to represent rainfall during the study period? What measure of rainfall was used? Total annual rainfall?
- Is average EVI over a 15 year period (2000-2015) a meaningful measure for this analysis? Were other summaries of EVI considered?
- What time period does the Harmonized Soil Map represent?
- What year was selected for the Night Light Emissivity data?
- In the equation for the geostatistical model, please clarify that NLE represents night light emissivity.
- How was the form of the covariate in the model decided upon e.g. elevation² is included in the model. Did you do any exploratory analysis prior to fitting the model?
- Were any other goodness of fit measures considered in addition to using the variogram-based procedure described e.g. some form of assessment of the predictive ability of the model using approaches such as cross-validation?
- Did you perform any model selection?

Results:
- Could you provide a sense of how far apart the surveyed villages were?
- You state that 91% of your data were collected in 2013. Given that you previously state that data is collected between 2008-2013, could you give an indication of the spread of data over these earlier years?
- First paragraph of the ‘Environmental factors associated with podoconiosis prevalence’ appears to repeat information that has already been given in the Methods. Please revise.
- You state that ‘the most parsimonious geostatistical models was fitted’. How did you establish parsimony given no model selection procedure has been described? Could you also include a table to describe the estimates of the parameters in the model, or minimally a description of the direction of their influence on prevalence. How big an impact does the spatial term S(x) have on the fitted model e.g. did the covariates describe most of the spatial variability or did S(x) play a big role?
- Could you use different colours in Figure 2 to represent the different scales, or adjust the maps so that they are all on the same scale. It is difficult to assess the amount of uncertainty in the estimates in its current form. Similarly could you adjust the colours/scale in Figure 3. Alternatively, have you considered producing a map of the width of the confidence interval instead of separate maps of the upper and lower bounds? You mention in the discussion that the confidence intervals are very wide, but this is difficult to discern from the current maps.
- Please indicate the proportion of the populations in each region that are at risk of podoconiosis as well as absolute numbers.
- As mentioned above, have you considered other methods of validating your model predictions in addition to determining that the adopted covariance model was compatible with the data? Some assessment of model fit/model predictions is needed.

Discussion:
- A comparison is made between the estimated podoconiosis cases obtained using this study and the number estimated in 1974. Given that the authors recognise that there’s been a dramatic change in the population since 1974, it is not appropriate to compare absolute numbers. A comparison of prevalence would be much more meaningful.
Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

**Author Response 12 Dec 2017**

**Kebede Deribe,** Brighton and Sussex Medical School, Brighton, UK

Many thanks for your important review. Please kindly see below the summary response we have given to each of your comments. In the current work our objective is to estimate the number of cases of podoconiosis. In a previous work we already estimated the population at risk and the results were published (Deribe K et al. 2015b). The current work is dedicated to estimating the number of cases of podoconiosis. To make the work in the context of our analysis we opted to use comparison of the number of cases. We hope given the clear contextual differences the readers can make the best out of our discussions and estimations.

In the introduction part a brief paragraph about podoconiosis has been included “Podoconiosis is an endemic, non-filarial lymphoedema of the lower limb. It affects genetically susceptible individuals who often go barefoot (Price E 1990). It causes bilateral, often below knee lymphoedema of the lower limb. Based on existing evidence, the most accepted cause of podoconiosis is that of mineral particle-induced inflammation on a background of genetic susceptibility(Price E 1990). Specific control methods include the use of footwear, regular foot hygiene and floor coverings. For those with the diseases management of the lymphoedema-related morbidity is recommended which includes foot hygiene, foot care, wound care, compression, exercises, elevation of the legs and treatment of acute infections (Deribe et al., 2015a).”

The selection of covariates is based on previous works that have been published elsewhere (Deribe K et al. 2015a, Deribe K et al. 2015b). This has been stated in first paragraph of section
describing the selected covariates. We obtained the elevation gridded dataset at 1km² from the CSI-CGIAR project (http://srtm.csi.cgiar.org) (Farr TG and Kobrick M 2000), as we mention under methods. The elevation originally has been obtained by RADAR imagery at 30m resolution by the USGS and it has been resampled by CSI-CGIAR to make it manageable and usable for different purposes. We provide in the manuscript the link to the CSI-CGIAR where more details on data processing is given. The rainfall used in the current model was the mean annual rainfall. Podoconiosis is a chronic disease which is a result of long term exposure to red clay soil. Those with the disease may have developed through decades of exposure to the putative minerals. Therefore, the use of long term average of environmental covariates is justifiable.

General composition of soils is not expected to vary significantly over time. The Harmonized Soil Map is the result of a robust modelling work over a large number of geo-referenced point data (100,000) available at the World Soil Information Service. This corresponds with over 5 million soil records. This project has been improving their model estimates based on increased number of sampled sites and applying more robust modelling approaches. More details on the construction of this gridded maps of soil composition are provided in this reference (Hengl T et al. 2017). The version we have used in this project corresponds to the most updated version released in 2016. Night-light emissivity dataset correspond to year 2011, midpoint between years of data collection. We have included this information in the manuscript.

The equation for the geostatistical model has been revised. Now the equation reads:

We did carry out an initial exploratory analysis which showed a non-linear relationship between elevation and the empirical podoconiosis prevalence. More specifically, we found that the latter increased for increasing elevation up to about 2000 meters and decreased thereafter. For this reason elevation was included in the model using a quadratic polynomial. We have added a comment in the supplementary material (Figure 2) to make this clear.

We did not carry out cross-validation for three main reasons: 1) the data are too noisy to carry out cross-validation reliably; 2) cross-validation does not allow us to test the validity of specific model assumptions; 3) this study was not intended to compare different predictive models where cross-validation would provide more insights.

If by “model selection” is meant “variables selection”, this has already been described in the manuscript. If by “model selection” is meant the selection of different spatial covariance models, this was not done because more complex spatial structures would require a larger amount of data. For example, we did not consider geostatistical model with directional effects, such as anisotropy, because of the large number of parameters that could not be estimated with precision from the available data.

We used two sets of data for the current analysis, the fist was a mapping surveys in the western Ethiopia conducted between 2008-2010 and the other survey was conducted in 2013. The former was a secondary source and we don’t have the precise year for each location. The distance between villages ranges from about 1 km to about 1,450 km. This has now been added to the main manuscript.

We have rephrased the sentence in question and replaced “the most parsimonious geostatistical model was fitted” with “A geostatistical model with an isotropic and exponential spatial covariance function was fitted”. We have already included a table with parameter estimates and 95%
confidence intervals in the Supplementary Material. We have fitted a model without covariates which provides strongly similar predictions to the model with the aforementioned covariates. However, the model with covariates gives prevalence predictions with smaller standard errors. Hence, although S(x) mostly contributes to the point predictions of podoconiosis prevalence, the covariates still help to explain part of S(x) leading more accurate prevalence predictions.

We consider model validation as aimed at assessing the validity of specific modelling assumption in order to develop a credible probabilistic model for the data. Testing the validity of the adopted correlation function is fundamental in order to quantify uncertainty in prevalence estimates reliably (e.g. through the exceedance probabilities). Cross-validation would not help us to pursue this objective since this is intended to assess relative predictive performance which is outside the scope of the paper.

We have revised figure 2, 3 and 4 to show contrasting colours.

References


**Competing Interests:** No competing interests were disclosed.
This is really a great milestone in the effort of tackling this debilitating and can be called easy to handle disease taking in to consideration its treatment and prevention. I heard many times in many occasions like workshops when the number of podo estimated cases in Ethiopia was mentioned and yet it is just this articled that revealed the estimate that one quote boldly from now on wards. The figure of the the cases had been not known having its detrimental effect on planning. They say when you plan, plan to the end and here is the the bench mark for the planning. We were in a dark and now enlightened with this work. Well done.

**Competing Interests:** No competing interests were disclosed.