Study of Lymphoedema of Non-Filarial Origin in the North West Region of Cameroon: Spatial Distribution, Profiling of Cases and Socio-economic Aspects of Podoconiosis.

Samuel Wanji [1,2*], Jonas A. Kengne-Ouafo[1,2], Kebede Deribe [3,4], Ayok M. Tembei[1,2], Abdel Jelil Njouendou[1,2], Dizzel Bita Tayong [1,2], David D. Sofeu-Feugaing[5], Fabrice R. Datchoua-Poutcheu[2], Jorge Cano[6], Emanuele Giorgi [6,7], Yolande F. Longang-Tchounkeu[2], Peter A. Enyong[1,2], Melanie J. Newport[3] and Gail Davey[3]

* Correspondence: swanji@yahoo.fr

1. Epidemiology and Control of Infectious Diseases (ECID), Department of Microbiology and Parasitology, University of Buea, Buea, Cameroon.
2. Research Foundation for Tropical Diseases and the Environment (REFOTDE), Buea, Cameroon.
3. Wellcome Trust Brighton and Sussex Centre for Global Health Research, Brighton and Sussex Medical School, Brighton, UK
4. School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia
5. Department of Biochemistry and Molecular Biology, University of Buea, Buea, Cameroon.
6. London School of Hygiene & Tropical Medicine, London, UK
7. Lancaster Medical School, Faculty of Health and Medicine, Lancaster University, Lancaster, UK

ABSTRACT

Background: Although podoconiosis is endemic in Cameroon, little is known about its epidemiology and spatial distribution.

Methods: In this cross-sectional, population-based study, we enrolled all adults (≥15 years) residing in the districts of North-West Region of Cameroon for more than 10 or more years. Participants were interviewed, had physical examination. The study outcomes were prevalence estimates lymphoedema and podoconiosis. House-to-house screening was conducted by Community Health Workers (CHIs). CHIs registered all individuals with lymphoedema and collected additional individual and household-related information. A panel of experts re-examined and validated all lymphoedema cases registered by CHIs.

Results: Of the 439,781 individuals registered, 214,195 were adults (≥15 years old) and had lived in the districts of the Region for more than 10 years. A total of 2,143 lymphoedema cases, were identified by CHIs, giving a prevalence of lymphoedema 1.0% (95% confidence interval [CI]; 0.96-1.04) (2,143/214,195). After review by experts, podoconiosis prevalence in the study area turned out to be 0.48% (1,049/214,195) (95% CI; 0.46-0.52). The prevalence of podoconiosis varied by health district, from 0.16% in Oku to 1.92% in Bafut ($p < 0.05$).

Conclusion: This study provides insight into the geographical distribution and epidemiology of podoconiosis in the North West region of Cameroon, yet management is limited. Evidence-informed targeted interventions are needed to manage people with lymphoedema.

Keywords: non-filarial lymphoedema; podoconiosis; spatial distribution; epidemiology; Cameroon

BACKGROUND

Lymphoedema of the lower limbs is a consequence of localized fluid retention resulting from a compromised lymphatic system [1]. In Africa, it is mostly driven by a nematode (roundworm) parasites of the family Filariodidea (*Wuchereria bancrofti*), whose adult forms obstruct the lymphatic system, leading to the swelling of a limb or other tissue [2]. Another form of lymphoedema, called podoconiosis, occurs in volcanic highland zones of Africa due to prolonged exposure to certain soil chemicals. This form of lymphoedema mostly affects individuals who do not wear shoes regularly since childhood.

Podoconiosis has also been reported from southeast Asia and Central and South America [3]. In Africa, the disease has been identified in at least 18 countries, including; Angola, Burundi, Cameroon, Cape Verde, Chad, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Kenya, Madagascar, Mozambique, Niger, Nigeria, Rwanda, São Tomé and Príncipe, Sudan, Tanzania, and Uganda.[3].

Previous studies have documented the association of the disease with irritant red clay soils, which are generated in areas over 1,000 meters above sea level (m.a.s.l.), with 1,000 mm annual rainfall and maximum temperatures of 20^0C [4]. High concentrations of phyllosilicate clays (smectite and kaolinite) and mica groups, quartz (crystalline silica), iron oxide, and zirconium have been described in high prevalence areas of northern Ethiopia [5]. Additionally, the genetic heritability to the disease has been confirmed, and specific genetic associations with susceptibility to disease have been demonstrated [6, 7].

65 The distribution of podoconiosis in the North West Region of Cameroon is not clearly understood,
66 in spite of the few studies conducted in this area [8-10]. Mapping is important to design successful
67 control and prevention measures [11, 12]. Information collected through mapping surveys is
68 important for planning, monitoring, and evaluation of control programmes [13-17].

69 The objective of this study was to determine the spatial distribution and epidemiology of
70 podoconiosis in the Northwest Region of Cameroon. This was done with the involvement of
71 trained Community Health Implementers (CHIs), who have proven to be capable of clinically
72 identify podoconiosis patients with acceptable positive predictive value after thorough training
73 [18]. The findings will enable implementation of a scheme for podoconiosis-related lymphoedema
74 management in the study area.

75

METHODS

Study area

This study included all the 19 health districts of the North West Region of Cameroon. Podoconiosis had previously been demonstrated in some of these health districts [10], and was suspected across large parts of the region. The North West region is mostly hilly with a mean altitude of 1,403 m above sea level. It experiences two seasons (dry and wet) with a mean annual rainfall of 2,500 mm [18]. The very fertile soils in the region are used to grow rice, maize, beans and other vegetables [18]. Farming is therefore the main mean of subsistence and source of household income in the region.

Study design

A cross-sectional study was carried out to establish the spatial distribution, the profile and disease assessment for clinical and socio-economic aspects of podoconiosis in the North West Region.

Prior to the study, the feasibility of using CHIs to screen for podoconiosis was tested and details of the methods used for training have been described elsewhere [18]. CHIs conducted house-to-house clinical screening of lymphoedema cases within the communities in the study area whilst a team of supervisors simultaneously collected geographical coordinates and supervised CHIs' work. A sample of confirmed podoconiosis cases were interviewed to measure preventive behaviours and potential economic loss due to the disease.

Training of research assistants and community health implementers

Training was done in two phases both taking place in the North West region. Supervisors provided the first phase, and supervisors plus researchers the second phase. Training on the disease, its causes, clinical manifestations, differential diagnosis, staging, treatment, prevention and socio-economic impact took place at district hospitals. The training also focused on community sensitization and data recording. A practical exercise was conducted with either patients or photographs of the different podoconiosis stages including guidelines for their identification.

Sampling strategy and study population

A mixed sampling approach was used for the mapping exercise. All health areas in each of the 19 health districts of the region were considered for mapping. Within each health area, systematic sampling was used to select 50-60% of communities within each health area. A few communities (<0.01%) were not visited because they were inaccessible during the rainy season. All households within selected communities were surveyed. Within each household, individuals of both sexes, older than 15 years of age and who had lived in the area for at least 10 years were recruited. The CHIs visited registered individuals in all the households of the assigned quarter or zone and examined them for lymphoedema. Geographical coordinates of surveyed villages were taken at the centre of the community, most often at the chief's place or a public space such as the market. A team of experienced researchers familiar with podoconiosis re-examined and validated all lymphedema cases registered by CHIs, following a differential diagnosis protocol published by Desta et al (2007)[6]. Therefore, anyone with lymphedema, as recorded by CHIs, was considered a *suspected podoconiosis case*, whereas *confirmed podoconiosis cases* were those with lymphedema of the lower legs with bilateral asymmetry who had no history or clinical signs of

lymphatic filariasis (LF), systematic disease, or leprosy and residing in the district for more than 10 years[19].

Podoconiosis clinical features and socio-economic assessment

After the mapping exercise, a stratified random sampling approach was used to select a subsample of confirmed podoconiosis cases for more in-depth clinical and socio-economic assessment.

All the validated cases were stratified by disease stages (stages 2, 3, 4 and 5) and by age. Based on total number within each disease category, patients were selected by proportion to represent about 1/5 of the total affected population. Using a semi-structured questionnaire, socio-demographic data and information on shoe wearing habits, family history of the disease, disease morbidity, economic loss and patient mean monthly income, were collected. Patients' earnings were estimated based on salaries for employed patients over the last month extrapolated to a calendar year plus the total annual agricultural products multiplied by average market price, to give an annual per patient sum. Monthly mean income per patient was then estimated from the annual income. Patients were asked to provide an estimate of their daily hours of work when sick and prior to developing podoconiosis, to estimate the number of productive days lost by patients due to illness. Patients were also clinically staged and examined for the presence of podoconiosis clinical features such as mossy changes, wounds, bilateral swelling and enlarged inguinal nodes. Clinical features were selected based on a previous study in Ethiopia [20], which included criteria such as being a long-term resident of a podoconiosis-endemic area and lower leg changes consistent with podoconiosis (bilateral but asymmetric leg involvement; swelling, mossy changes and/or nodules). Clinical staging was done according to Tekola et al. [21].

Data entry and analysis

The census data were recorded in printed registers and then entered in a standardized database created in EpiInfo v.3.5.3 while geographical coordinates were collected in a Microsoft Excel 2013 spreadsheet. Analysis of collected data was carried out using SPSS version 20 (Chicago, IL, USA). Crude prevalence was computed as the number of affected people in a health district divided by the total number of people registered, multiplied by 100. The Chi-squared test was used to compare prevalence data or proportions of individuals affected between health districts, age groups and by gender. Crude prevalence data (generated from CHIs' case records) were adjusted using a factor determined by comparing CHIs' and supervisors' findings by health districts. The adjustment factor (positive predictive value) was defined as the ratio of total number of confirmed cases to the total number of suspected cases (present during the validation survey) and multiplied by 100. Adjusted prevalence data were then mapped using ArcGIS version 10.3 software.

Descriptive statistics such as frequency tables and bar charts were used to determine the profile of podoconiosis cases by age group and gender, and prevalence by disease stages was calculated. The profile of clinical features with respect to disease stage was examined, and differences established using the chi-squared test. Patients' preventive behaviours, acute attacks and economic loss were descriptively analysed. All the statistical tests were performed at a 5% significance level.

Finally, to improve the visualization of spatial distribution of podoconiosis cases, we estimated the density of podoconiosis cases across North West region using a Kernel Density Estimator, which is a non-parametric way to estimate the probability density function of a random variable [22, 23]. We opted for applying a Gaussian function as density estimator, and results where fed into a spatial grid of 100 x 100 meters resolution. This analysis was implemented using in R v3.4.3 using the *splancs* package and final map layouts made in ArcGIS version 10.3 software.

RESULTS

Characteristics of study participants

Of the 439,781 individuals registered, 214,195 were 15 years old or older and had stayed in the region for more than 10 years. The male/female ratio was 0.78. 2,143 people with lymphedema s were identified by CHIs, resulting in lymphoedema prevalence of 1.0% (2,143/214,195).The prevalence of podoconiosis was 0.48%, 95% CI [0.46-0.52]. The majority of health districts (16/19) had disease prevalence less than 1% (Table 1).

Table 1: Lymphoedema and podoconiosis prevalence within Health Districts in North West Cameroon

Health District	Number of communities surveyed	Number of eligible screened 15-10 (years)*	Lymphoedema cases	Prevalence of lymphoedema (%)	Prevalence of podoconiosis (%) 95%CI**
Ako	22	4288	24	0.56	0.27 [0.11-0.43]
Bafut	39	9946	393	3.95	1.92 [1.65-2.19]
Bali	25	3546	27	0.76	0.37 [0.17-0.57]
Bamenda	53	26441	181	0.68	0.33 [0.26-0.40]
Batibo	46	8934	303	3.39	1.64 [1.41-1.95]]
Benakuma	19	4988	43	0.86	0.42 [0.24-0.60]
Fundong	45	17579	91	0.52	0.25 [0.18-0.32]
Kumbo East	67	18624	129	0.69	0.33 [0.25-0.41]
Kumbo West	34	9509	48	0.5	0.24 [0.14-0.34]
Mbengwi	43	8076	96	1.19	0.58 [0.41-0.75]
Ndop	76	25605	232	0.9	0.44 [0.360.52]
Ndu	34	9918	87	0.87	0.42 [0.29-0.55]
Njikwa	12	1233	29	2.35	1.14 [0.55-1.73]
Nkambe	49	12572	114	0.91	0.44 [0.320.56]
Nwa	33	8215	61	0.74	0.36 [0.230.49]
Oku	47	15911	55	0.34	0.16 [0.10-0.22]
Santa	35	9449	125	1.32	0.64 [0.48-0.80]
Tubah	34	8364	41	0.49	0.24 [0.140.34]
Wum	60	10997	64	0.58	0.28 [0.18-0.38]

Total	773	214195	2143	1	0.49[0.46-0.52]
***People who had more than 15 years and had stayed in the community for more than 10 yrs.** ****95% Confidence interval.**					

169

170 **Influence of sex and age on lymphoedema prevalence**

171 Of the 214,195 participants, lymphoedema was more prevalent among females (0.53%) than males
172 (0.45%) (Table 2), when adjusted for age and duration of stay there was no significant difference
173 between male and female (OR= 1.07; 95%CI [0.98– 1.16], p = 0.149]. The prevalence of
174 lymphoedema increased with age for both sexes. People aged 50 years or above have 7.5 higher
175 odds of lymphoedema risk than younger ones (< 30 years old) (OR= 7.5; 95%CI [6.33 – 8.98], p
176 < 0.001).

177 **Table 2: Influence of sex and age on lymphoedema prevalence**

Variable	Prevalence (%)	Adjusted OR (95% CI)	p-value
Gender			
Male	1010 (0.47)	1.07 (0.98– 1.16)	0.149
Female	1133 (0.53)	Reference category	NA
Age Group			
<30	185 (0.09)	Reference category	NA
30-40	231 (0.11)	1.73 (1.43 – 2.11)	<0.001
40-50	315 (0.15)	2.88 (2.39 – 3.47)	<0.001
50 plus	1412 (0.66)	7.54 (6.33 – 8.98)	<0.001

178 NA: Not Applicable

179 [a] Odds ratio was adjusted for sex, age and duration in community

We found evidence of interaction between age and sex ($p<0.001$) in their association with podoconiosis prevalence. Therefore stratified analysis (age-sex) presented. The prevalence of lymphoedema was shown to increase with age, and men aged 50 or older were more affected (Figure 1).

Figure 1: Lymphoedema prevalence by sex and age in the North West Region.

Lymphedema stages in the North-West

Generally, lymphedema cases on early stages were more frequent than chronic cases. Of the 2,143 lymphedema cases, the highest proportion was recorded on stage 2 (60.6%), followed by stage 3 (25.7%) and stage 4 (11.5%). Stage 5 was the least common (2.2%). (Figure 2)

Figure 2: Prevalence of lymphoedema stages in the North West Region.

With an exception of stage 5, all lymphedema stages appeared to increase with age. Stage 2 and stage 5 were more prevalent within patients over 50 years old (Figure 2).

Spatial distribution of podoconiosis in the North-West region

Overall, in the 19 Health Districts of the North West region of Cameroon, 439,781 individuals were registered from 773 communities. Figure 3A shows the spatial distribution of the communities surveyed in the North-West region of Cameroon. This map shows some areas of the region that remained unsurvey. These areas correspond to dense forest that are uninhabited, such as Wum, Nkambe, Kumbo East, Ako, Fundong and Njikwa. The density map for confirmed podoconiosis cases (Figure 3B) is clearly showing four zones of high incidence in the southern part of the region, including the following health districts: Batibo, Bafut, Tubah, Ndop and parts of Mbengwi, Fundong, and Bamenda. There are areas at the north of the region, which either are environmentally unsuitable for the disease or its endemicity is estimated to be very low.

Figure 3: Distribution of surveyed communities and prevalence of podoconiosis in the North West Cameroon

Table 1 shows the number of health districts and communities surveyed, number of individuals registered and the prevalence rate by health district. The prevalence varied between health districts from 0.16% in Oku to 1.92% in Bafut (p< 005). The disease was more prevalent in Bafut (1.92%), Batibo (1.64%) and Njikwa (1.14%) (Table 1).

Characteristics of people with podoconiosis recruited subsequently for socio-economic and clinical assessment

A total of 374 patients were recruited by stratified random sampling from the validated CHIs' register to assess the clinical features and socio-economic aspects of the disease. Patients reportedly said to have first noticed swelling at an average age of 41.9 ± 19.1 (range: 6-90 years). Women noticed first swelling earlier (35.85 ± 16.5) than men (49.1 ± 20.2, p< 0.001) (Table 3). The average time patients had lived with the condition was 15.8 ± 14.9 years, (range: 1-72 years). This number of years was relatively higher (16.4 ± 14.7 years) in females than males (15 ± 15.1 years, P= 0.42). A total of 134 (35.9%) selected cases declared to have or to have had at least 1 person in the family with the affection (mean= 0.41 ± 0.6-person, range: 1-3, Table 3). Married individuals (86.1%) were significantly more affected than single individuals (13.9%). Farmers and people with no formal education were the most affected (Table 3).

Table 3: Characteristics of sub-population with podoconiosis >15 years of age

Variable	Number (%)
Gender	
Female	206 (55.1)
Male	168 (44.9)
Marital status	
Married	322 (86.1)
Single	52 (13.9)
Occupation/Profession	

Farmer	255 (68.2)
Other	65 (17.4)
Unemployed	54 (14.4)
Literacy	
No formal education	199 (53.2)
Primary	145 (38.7)
Secondary	27 (7.2)
University	3 (0.8)
Number of persons in the family with leg swelling, dead or alive, Mean (±SD)	0.41 (±0.63)
1	113 (84.3)
2	15 (11.1)
3	4(2.9)
Age (years) at first noticing swelling (N=368) Mean (±SD; Range)	41.8 (±19.4; 6-90)
< 10	11 (3.0)
[10-20]	35 (9.5)
[20-40]	124 (33.7)
[40-60]	124 (33.7)
> 60	74 (20.1)
Duration in years with swelling (N= 370) Mean (±SD)	15.88 (±14.9)
< 10	161 (43.8)
[10-20]	81 (22.0)
[20-40]	89 (24.2)
[40-60]	32 (8,7)
> 60	5 (1.4)

Assessment of podoconiosis clinical features

Of the 374 podoconiosis patients examined, 73.3% had bilateral lymphedema. The highest proportion (48.9%) of affected individuals presented clinical forms of stage 2 followed by stage 3 (45.2%). Stage-5 forms were rare (2.7%). Mossy form was present in 66.1% and wounds in 26.7%. Only 35 (9.5%) of patients were found to have enlarged inguinal nodes. All lymphedema types

were observed with the nodular being the most prevalent (59.0%) followed by mixed (26.3%) and water-bag (15.7%).

Most patients (86.1%) complained of their legs suddenly becoming hot, red and painful with a frequency ranging from less often than a year (3.5%) to everyday (33.44%) (Table 5). Patients with stage 5 and 3 were the most affected with pains, 90% and 91% respectively compared to people with stage 2 and 4 (81.6% and 81.9% respectively). Regarding the influence of seasons on the intensity and frequency of leg pains, 61.6% of the patients declared that there was no difference between seasons while the rest said they felt pains during specific seasons (Table 4).

Table 4: Frequency and regional variation of acute attack experienced by podoconiosis patients and its associations with disease stage

Variable	Number (%)
Leg suddenly becoming hot, red and painful (N= 366)	
Yes	315(86.1)
No	51(13.9)
Frequency of acute attack (N= 311)	
Every day	104(33.44)
Every week	75(24.11)
Every two weeks	29(9.32)
Every month	47(15.11)
Every 03 months	23(7.39)
Every 06 months	8(2.57)
Less often than a year	11(3.53
Every year	14(4.50)
Acute attack with respect to disease stage	
Stage 2	146(81.6)
Stage 3	152(91.0)
Stage 4	9(81.9)
Stage 5	9(90)
Seasons associated with acute attack (N= 358)	
Cold and dry season	15(4.1)
Cold and wet season	53(14.8)
Hot and dry season	46(12.84)
Hot and wet season	24(6.7)
No difference by season	220(61.45)

Assessment of socio-economic aspects of podoconiosis

The majority (309, 96.5%) of the interviewees said they had worn shoes occasionally at some point in their life. The reportedly mean age at first shoe wearing was 14.2 ± 10.1, range (1-77 years). This mean age was significantly lower in women (12.4 ±8.2, range 1-50) than males (16.3 ±11.6, range 1-77), $p< 0.001$, Table 4. A high proportion (82.8%) of the participants wore shoes at the time of interview. Of those wearing shoes, only 67 (21.7%) were wearing protective shoes, among whom 53 were men (79.1%, 95% IC [69.36-88.8]) and 14 women (20.9%, IC [11.16-30.63], $p< 0.001$, Table 6). Regarding the type of shoe, most participants (35.6%) reported they owned closed

leather shoes, followed by plastic shoes, tyre or rope sandals (23.8% for each) and closed plastic shoes (10.7%). Only 173 (46.2%) owned protective (enclosed) shoes, among whom 104 were men (62.7%, 95% IC [55.34-70.05]) and 62 women (37.3%, 95% IC [29.9-44.65], p< 0.001). The majority of the participants reported wearing shoes during recreational activities and less frequently during household-related activities. Only a handful reported wearing shoes during farm-related activities such as planting (21.4%), harvesting (19.0%) and working in a rice farm (17.9%) (Table 5).

Table 5: Podoconiosis patients' preventive social behaviours (Data obtained from a sub-population).

Variable		**Number (%)**
Ever Owned Shoes		361 (96.5)
Age at first shoe wearing (N=352), Mean, (SD)		14.26 (10.1), range(1-77years)
	Female	12.46 (8.2), range (1-50 years)
	Male	16.34 (11.6) range (1-77 Years)
	Wearing shoes at interview	309 (82.8)
Wearing protective shoes at interview		67 (18.0)
	Male	53 (79.1), 95% CI [69.36-88.8]
	Female	14 (20.9), 95% CI [11.16-30.63]
Type of shoes declared		
	plastic sandals	89 (23.8)
	Closed plastic shoes	40 (10.7)
	Closed leather shoes	133 (35.6)
	Tyre rope-made Sandals	89 (23.8)
	Protective shoes (enclosed)	173 (46.2)
	Male	104 (62.7), 95% CI [55.34-70.05]
	Female	62 (37.3), 95% CI [29.9-44.65]
SHOE WEARING HABIT		
Recreational activities (%)		
	Walking to market	323 (86.4)
	Going to Church	332 (88.8)
	Attending wedding	296 (79.1)
	Attending a funeral	306 (81.8)
	Village meeting	302 (80.7)
House-related activities (%)		

	Working at home	188 (50.2)
	Fetching water	192 (51.3)
Farm-related activities (%)		
	Planting	80 (21.4)
	Harvesting	71 (19.0)
	Working in a rice farm	67 (17.9)

Monthly income was very low for people with stage 5 compared to people with other stages (Table 6). The mean time lost due to pains potentially associated to their podoconiosis condition was estimated at 15.3 ± 49.3 days. The majority (71%) declared to lose 1-10 days when they feel pains while a minority said they could lose as many as 90 days.

Table 6: Podoconiosis mean monthly income and income loss (Data obtained from a sub-population).

Variable	**Number (%)**
Mean monthly income (SD) in USD	28.33 (31.03)
Time loss (days) when legs are paining (N= 252) mean (SD)	15.3(49.3)
Zero	15 (6.0)
[1-2]	73 (29.0)
[3-5]	48 (19.0)
[6-10]	60 (23.0)
[11-20]	14(5.6)
[21-30]	30 (11.9)
[31-90]	6 (2.4)
Always paining	6 (2.4)
Income by disease stage, Mean (SD) in USD	
2.	24.07 (23.6)
3.	31.3 (34.7)
4.	57.4 (53.6)
5.	9.0 (3.5)
Mean monthly income loss due to the disease per patient, Mean (SD) in USD	14.1 (50.9)

DISCUSSION

The overall prevalence was estimated to be 0.49% ranging from 0.16-1.92% by Health District. Sex and age were identified to be risk factors for podoconiosis. The mean prevalence was far lower than that (8.1%) reported from two health districts in this region[10]. Higher prevalence rates have also been reported in Ethiopia [24-27] and in Uganda [28]. However, it is similar to the prevalence documented in Rwanda (0.6%) in the 1970s [4]. The low prevalence documented in the present study could be attributed to the fact that only podoconiosis stage 2 and above was identified. This decision was made to minimize the chance of false positives since the survey was carried out by CHIs who were not too familiar with podoconiosis. In a study conducted in Ethiopia, the proportion of patients with stage one disease was 16.7% [20]. It is worth mentioning that prevalence rates were presented per health district, so high prevalence rates in some health areas or communities may have been diluted out. Prevalence rates as high as 3% or more were recorded in some health areas of the Bafut, Bamenda and Batibo health districts, hence the need for control measures to be implemented in the region. This will also aid targeted interventions for priority areas within the region.

The density map (Figure 4B) depicted heterogeneous distribution of podoconiosis in the region with the South (Bafut, Batibo, Njikwa, Mbengwi and Santa) being more affected than the North. Similar heterogeneous distribution of podoconiosis was observed in Ethiopia [11, 24]. The significant geographical variation in Ethiopia was said to be consistent with findings from individual studies and environmental characteristics studied [11, 24].

The low prevalence registered in the younger individuals is in line with Desta's work [6] and adds to the assumption long term environmental exposure to red clay soil is required for development

297 of the condition [4, 24, 29]. In our study, individuals aged >50 years were the most affected and
298 were close to 8 times more likely to have the disease than younger individuals, and stage of disease
299 increased with age.

300 Women noticed first swelling earlier (mean age, 35 years) than men (mean age, 49 years). This
301 might be the reason that females were more affected than males in the age group 40-50 years and
302 males in the age group > 50 years. This could also account for the fact that the mean age people
303 had lived with the disease was higher in women than men because the disease starts relatively
304 earlier in women. The same observations have been made in Ethiopia [24].

305

306 The majority of patients were farmers, and most had no formal education. Most farmers work
307 barefoot for hours including those working in swampy (rice-growing) areas. This behaviour is
308 likely to expose them to the irritant particles thought to be implicated in triggering disease. Since
309 they had little formal education, they are likely to be less informed about disease prevention than
310 educated people, who were found to be less affected [24].

311 Foot hygiene and shoe wearing so far remain the most important preventive measures against
312 podoconiosis [30]. The majority (96.5%) of the study participants said they had worn shoes at least
313 once in their lifetime. The prevalence of shoe wearing (82.8%) at the time of interview was far
314 higher than that reported in Ethiopia [24, 31, 32]. This may in part explain the lower prevalence
315 of podoconiosis in Cameroon. The mean age (14.26 years) at first shoe wearing was still relatively
316 high. This means that a large proportion of the population started wearing shoes many years after
317 birth, suggesting a long period of exposure to the environmental factors associated with the
318 disease. Most participant said that they owned protective shoes, however, only a handful (67/374,

17.9%) wore them at the interview. The same observation has been made in Ethiopia [24]. People wore shoes mostly for recreational activities but rarely for the house- and farm-related activities during which they were most likely to be exposed to irritant particles. Men were found to wear protective shoes more than women.

Eighty-six percent of the patients interviewed said their legs became hot, red and painful at least once a year. The mean time lost to such attacks was 15.3 ± 49.3 days, (range 1-90 days). Since patients usually cannot work during these attacks, there is loss of productivity. Patients in Ethiopia have been shown to lose close to 45% of their economically productive time due to morbidity associated with the disease [33].

Over one third of interviewees had at least one relative with the condition. This is in line with previous studies. Family pedigrees collected in Ethiopia demonstrated high heritability, evidence for an autosomal co-dominant inheritance [6] and recent GWAS from an Ethiopian population indicated disease susceptibility associations in HLA class II region, chromosome 6 [7] though this has not yet been demonstrated in Cameroon.

A major limitation of the study was its reliance on clinical examination, and the lack of a diagnostic test to rule out infectious-related causes of lymphoedema such as lymphatic filariasis. No parasitological or molecular technique was used to check for the presence of *W. bancrofti*. Nevertheless, previous parasitological, entomological and immunological studies in the region have revealed that lymphoedema cases found in the North West Cameroon are of non-filarial origin [8, 10, 33].

Conclusions

Through this study, the geographical distribution of podoconiosis in North West region has been established in detail and the profile of disease, preventive behaviours and economic aspects assessed. The study has revealed a mean podoconiosis prevalence of 0.49%, ranging across health districts from 0.16% to 1.92%, with some health areas registering prevalence rates greater than 3%. Age and sex were identified to be risk factors for the disease, women and older individuals were the most affected. Although the majority of participants said they possessed shoes, they wore them only occasionally. Podoconiosis-related morbidity was still a major problem for patients, leading to loss of working time and productivity. Awareness raising through education and sensitization will be invaluable in this setting to alleviate these multiple podoconiosis-related burdens.

Authors' contributions: Conceived and designed the study: SW, GD JAKO, PAE, MJN Conducted training of CHIs and COCs; coordinated CHIs activities in the field: JAKO, FRDP, AJN, DDSF, YFLT PAE, SW. Confirmed podoconiosis cases presumably identified by CHIs: JAKO, GD, NAA, BAF, NT PAE. Analyzed and interpreted the data: KD, JAKO, AMT, FRDP, JC, EG, FTA, AJN, SW. Wrote the paper: KD, JAKO, AMT, SW, GD. Read critically the paper and approved final version: KD, JAKO, AMT, FRDP, JC, EG, AJN, DBT, DDSF, YFLT, PE, GD, SW. All authors read and approved the final manuscript.

Acknowledgments: The authors wish to thank: -The Ministry of Public Health, Cameroon, north-west regional delegation of health, the district medical officers and the chiefs of various health centres for their assistance and support during this field exercise. - The community heads and community health implementers for their support and inputs. - The populations of the 19 health

districts (North West region Cameroon) who willingly participated in this study. - All those who helped in the execution of this study, and particularly Mr (s) J. Bonekeh, E. Dim, N. Nkemkang, S. Saidou, Enuh Blaise, Mbuh Salioh, Nchanji Gordon, Ms F. Malange, A. Chia, Nathalie Amvongo-Adjia, Bridget A. Fovennso and all the REFOTDE and Mbebah Vigilantic Farming and Development Association (MVIFAD) members.

Funding: This work was supported by the Wellcome Trust, UK [grant number 091956] to GD. KD is funded by a Wellcome Trust Intermediate Fellowship in Public Health and Tropical Medicine [grant number 201900]. The funding body had no direct role in the study design, the collection, analysis or interpretation of data, or the writing or submission of this manuscript for publication.

Availability of data and materials: Availability of data and materials from this study can be obtained from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interest.

Ethics approval and consent to participate: The study protocol was approved by the "National Ethics Committee of Research for Human Health", Yaoundé, Cameroon. Administrative clearance was obtained from the delegation of public health of the North West region. Participation was strictly voluntary and the objectives, risks and benefits of the study were fully explained to all the participants. Each study participant gave written consent.

REFERENCES

1. World Health Organization: **Lymphatic Filariasis Managing Morbidity And Preventing Disability. World Health Organization. Geneva, Switzerland**. 2013.
2. Addiss DG: **Global elimination of lymphatic filariasis: addressing the public health problem.** *PLoS Negl Trop Dis* 2010, **4**(6):e741.
3. Price E: **Podoconiosis:Non-filarial Elephantiasis**. *Oxford Medical Publications, Oxford, UK* 1990.
4. Price EW: **The association of endemic elephantiasis of the lower legs in East Africa with soil derived from volcanic rocks**. *Trans R Soc Trop Med Hyg* 1976, **70**(4):288-295.
5. Molla YB, Wardrop NA, Le Blond JS, Baxter P, Newport MJ, Atkinson PM, Davey G: **Modelling environmental factors correlated with podoconiosis**. *Int J Health Geogr* 2014, **13**(1):24.
6. Desta K, Ashine M, Davey G: **Predictive value of clinical assessment of patients with podoconiosis in an endemic community setting**. *Trans R Soc Trop Med Hyg* 2007, **101**:621-623.
7. Tekola Ayele F, Adeyemo A, Finan C, Hailu E, Sinnott P, Burlinson ND, Aseffa A, Rotimi CN, Newport MJ, Davey G: **HLA class II locus and susceptibility to podoconiosis**. *N Engl J Med* 2012, **366**(13):1200-1208.
8. Cho-Ngwa F, Amambua AN, Ambele MA, Titanji VPK: **Evidence for the exacerbation of lymphedema of geochemical origin, podoconiosis, by onchocerciasis**. *Journal of Infection and Public Health* 2009, **2**:198-203.
9. Price EW, Henderson WJ: **Endemic elephantiasis of the lower legs in the United Cameroon Republic**. *Trop Geogr Med* 1981, **33**(1):23-29.

10. Wanji S, Tendongfor N, Esum M, Che JN, Mand S, Tanga Mbi C, Enyong P, Hoerauf A: **Elephantiasis of non-filarial origin (podoconiosis) in the highlands of north-western Cameroon**. *Ann Trop Med Parasitol* 2008, **102**(6):529-540.

11. Deribe K, Brooker SJ, Pullan RL, Hailu A, Enquselassie F, Reithinger R, Newport M, Davey G: **Spatial distribution of podoconiosis in relation to environmental factors in Ethiopia: A historical review**. *PLoS ONE* 2013, **8**(7):e68330.

12. Deribe K, Cano J, Newport MJ, Golding N, Pullan RL, Sime H, Gebretsadik A, Assefa A, Kebede A, Hailu A *et al*: **Mapping and modelling the geographical distribution and environmental limits of podoconiosis in Ethiopia**. *PLoS Negl Trop Dis* 2015, **9**(7):e0003946.

13. Brooker S: **Spatial epidemiology of human schistosomiasis in Africa: risk models, transmission dynamics and control.** *Trans R Soc Trop Med Hyg* 2007, **101**(1):1-8.

14. Brooker SJ, Smith JL: **Mapping neglected tropical diseases: a global view**. *Community Eye Health* 2013, **26**(82):32.

15. Gyapong JO, Remme JH: **The use of grid sampling methodology for rapid assessment of the distribution of bancroftian filariasis**. *Trans R Soc Trop Med Hyg* 2001 **95**(6):681-686.

16. Hay SI, Snow RW: **The malaria Atlas Project: developing global maps of malaria risk**. *PLoS Med* 2006, **3**:e473.

17. Zouré HG, Wanji S, Noma M, Amazigo UV, Diggle PJ, Tekle AH, Remme JH: **The geographic distribution of Loa loa in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA)**. *PLoS Negl Trop Dis* 2011, **5**(6):e1210.

18. Wanji S, Kengne-Ouafo JA, Datchoua-Poutcheu FR, Njouendou AJ, Tayong DB, Sofeu-Feugaing DD, Amvongo-Adjia N, Fovennso BA, Longang-Tchounkeu YF, Tekola-Ayele F *et al*: **Detecting and staging podoconiosis cases in North West Cameroon: positive predictive value of clinical screening of patients by community health workers and researchers**. *BMC Public Health* 2016, **16**:997.

19. Sime H, Deribe K, Assefa A, Newport MJ, Enquselassie F, Gebretsadik A, Kebede A, Hailu A, Shafi O, Aseffa A *et al*: **Integrated mapping of lymphatic filariasis and podoconiosis: lessons learnt from Ethiopia**. *Parasit Vectors* 2014, **7**(1):397.

20. Desta K, Ashine M, Davey G: **Predictive value of clinical assessment of patients with podoconiosis in an endemic community setting**. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2007, **101**(6):621-623.

21. Tekola F, Ayele Z, Mariam DH, Fuller C, Davey G: **Development and testing of a de novo clinical staging system for podoconiosis (endemic non-filarial elephantiasis)**. *Tropical Medicine & International Health* 2008, **13**(10):1277-1283.

22. Diggle P: **A Kernel Method for Smoothing Point Process Data**. *Journal of the Royal Statistical Society Series C (Applied Statistics)* 1985, **34**(2):138-147.

23. Kelsall JE, Diggle PJ: **Non-parametric estimation of spatial variation in relative risk**. *Statistics in Medicine* 1995, **14**(21-22):2335-2342.

24. Deribe K, Brooker SJ, Pullan RL, Sime H, Gebretsadik A, Assefa A, Kebede A, Hailu A, Rebollo MP, Shafi O *et al*: **Epidemiology and individual, household and geographical risk factors of podoconiosis in Ethiopia: results from the first nationwide mapping**. *Am J Trop Med Hyg* 2015, **92**(1):148–158.

25. Alemu G, Tekola Ayele F, Daniel T, Ahrens C, Davey G: **Burden of podoconiosis in poor rural communities in Gulliso woreda, West Ethiopia**. *PLoS Negl Trop Dis* 2011, **5**(6):e1184.

26. Geshere Oli G, Tekola Ayele F, Petros B: **Parasitological, serological, and clinical evidence for high prevalence of podoconiosis (non-filarial elephantiasis) in Midakegn district, central Ethiopia**. *Trop Med Int Health* 2012, **17**(6):722-726.

27. Destas K, Ashine M, Davey G: **Prevalence of podoconiosis (endemic non-filarial elephantiasis) in Wolaitta, Southern Ethiopia**. *Tropical Doctor* 2003, **33**(4):217-220.

28. Onapa AW, Simonsen PE, Pedersen EM: **Non-filarial elephantiasis in the Mt. Elgon area (Kapchorwa District) of Uganda**. *Acta tropica* 2001, **78**(2):171-176.

29. Frommel D, Ayranci B, Pfeifer HR, Sanchez A, Frommel A, Mengistu G: **Podoconiosis in the Ethiopian Rift Valley. Role of beryllium and zirconium**. *Trop Geogr Med* 1993, **45**(4):165-167.

30. Deribe K, Wanji S, Shafi O, Tukahebwa EM, Umulisa I, Molyneuxf DH, Daveya G: **The feasibility of eliminating podoconiosis**. *Bull World Health Organ* 2015, **93**:712-718.

31. Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G: **Podoconiosis in East and West Gojam zones, Northern Ethiopia.** *PLoS Negl Trop Dis* 2012, **6**(7):e1744.

32. Yakob B, Deribe K, Davey G: **High levels of misconceptions and stigma in a community highly endemic for podoconiosis in southern Ethiopia**. *Trans R Soc Trop Med Hyg* 2008, **102**(5):439-444.

33. Tekola F, Mariam DH, Davey G: **Economic costs of endemic non-filarial elephantiasis in Wolaita Zone, Ethiopia**. *Tropical Medicine & International Health* 2006, **11**(7):1136-1144.

473

474

475

Figure 1

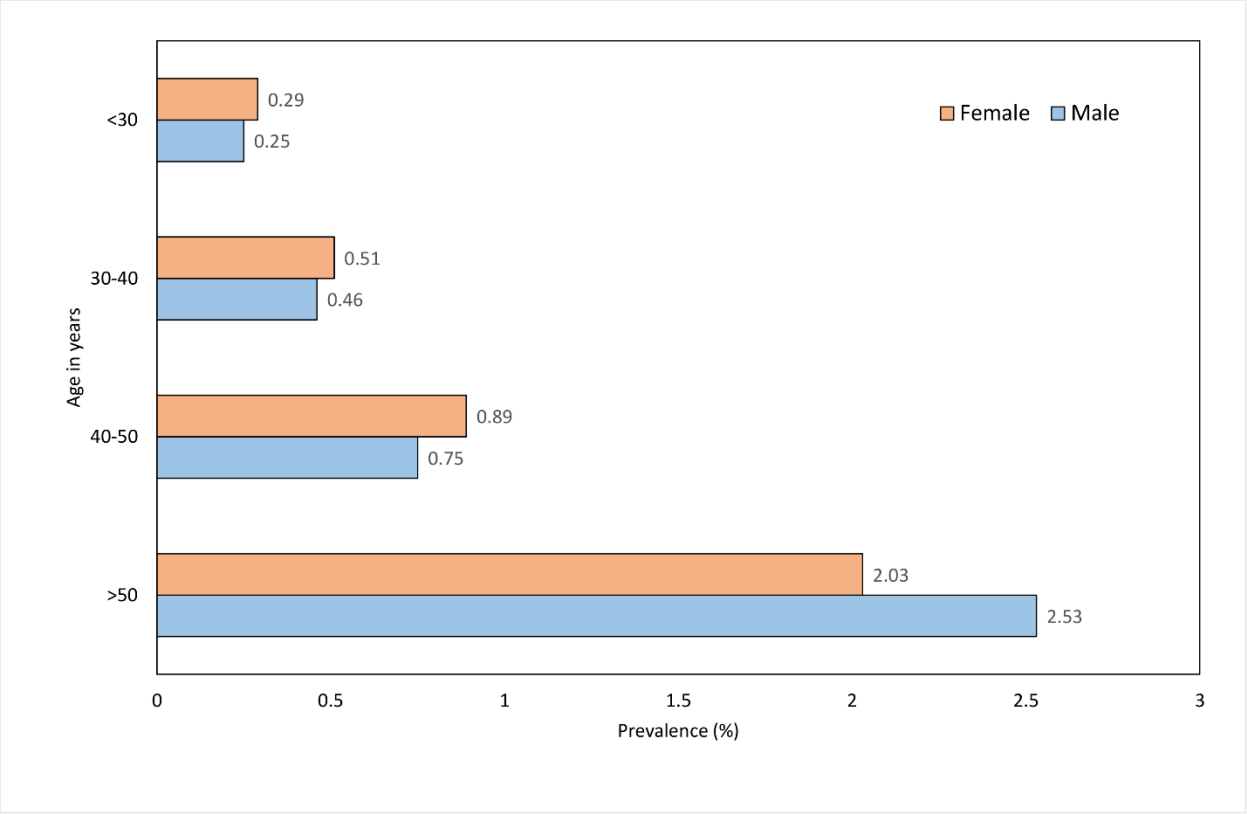
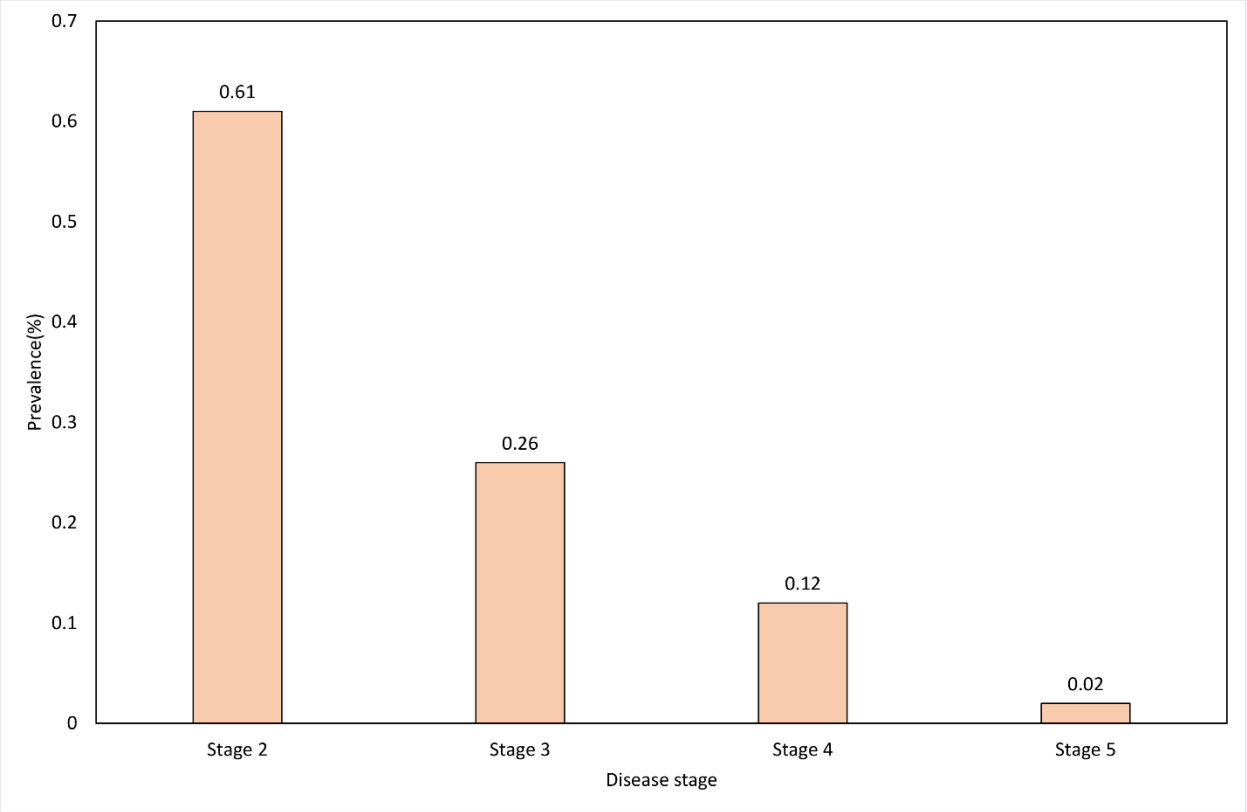
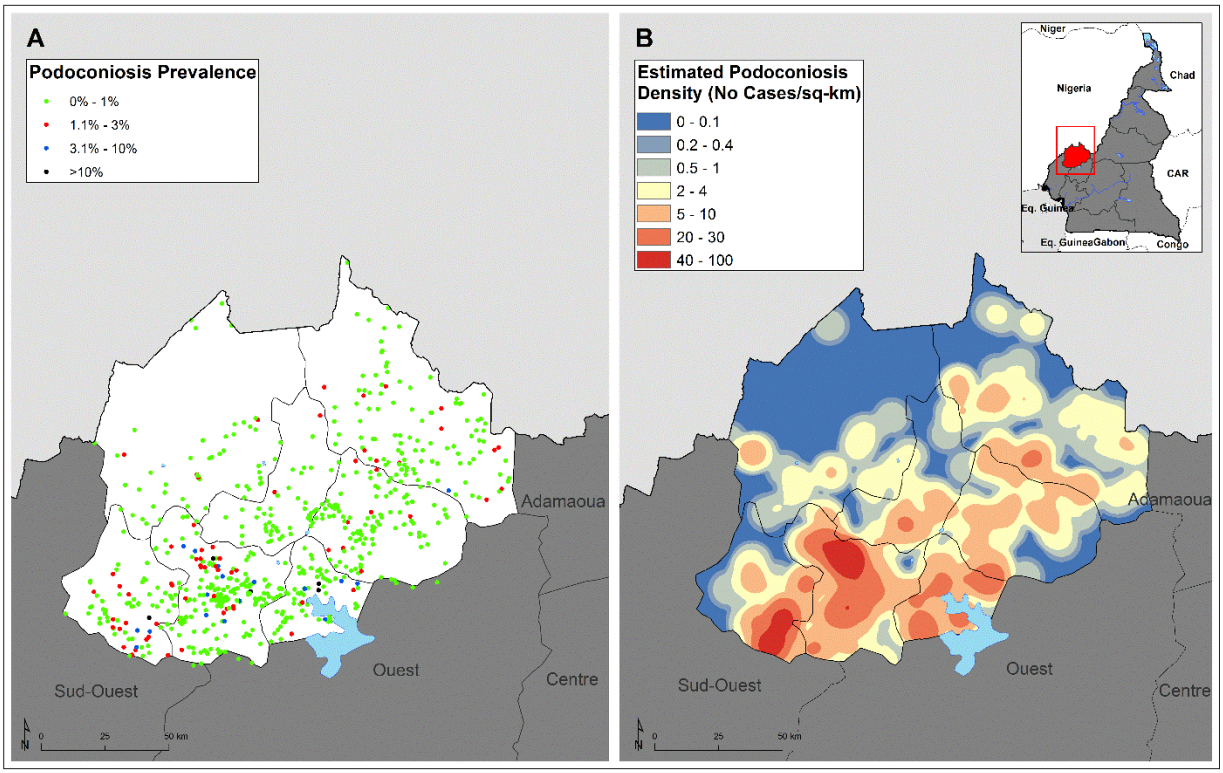

Female
Male
<30
30-40
40-50
>50
Age in years
0.29
0.25
0.51
0.46
0.89
0.75
2.03
2.53
0
0.5
1
1.5
2
2.5
3
Prevalence (%)

Figure 2


0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Prevalence(%)
0.61
0.26
0.12
0.02
Stage 2
Stage 3
Stage 4
Stage 5
Disease stage

487 Figure 3



488

489

490