THE SPATIAL EPIDEMIOLOGY OF PODOCONIOSIS IN NORTHERN ETHIOPIA

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Abstract

The presence of environmental variables associated with the occurrence of podoconiosis was indicated in studies by Price in the 1970s. Observation of red clay soil of volcanic origin and barefoot people in podoconiosis-endemic areas were starting points for investigating these factors. Recently, demonstration of genetic susceptibility to the disease has shown the added value of understanding individual level variations and the presence of gene-environment interactions in the development of podoconiosis. Deeper understanding of which environmental and individual variables determine the development of podoconiosis, and at what spatial scale these variables act, will assist intervention at national and local levels. The present study aims to investigate individual and environmental level variables related to podoconiosis at local scale.

The study started by gathering basic information on the extent of podoconiosis in the study area, East and West Gojam zones of northern Ethiopia. The diversity of the factors under investigation called for an interdisciplinary approach where the disease endemicity information gathered by epidemiologists was backed by the involvement of geologists in the team during preliminary field trips to the study area. These preliminary trips helped the team to identify epidemiologically and geologically defined traverses and spots for taking samples during subsequent data collection.

After the site selection trips, a baseline study investigating the prevalence of podoconiosis, clinical features, shoe-wearing and foot hygiene practices was done, and patients' perceptions of the causes, prevention and consequences of podoconiosis were investigated. Following the baseline investigation, detailed epidemiological and environmental data were collected. Here the epidemiological

data captured the variation between patients and controls living in predefined disease endemic (high, medium and low) areas. The environmental data collection included soil samples with geographic coordinates to enable linking of data.

The epidemiological data were analysed to identify individual variations between cases and controls. Simultaneously, the soil samples were analysed for soil properties at the Natural History Museum in London. Secondary data including geological and topographic maps at local level were also acquired. Geospatial and statistical techniques were used to explore and analyse correlation between disease prevalence and environmental variables with a range of soil properties. The final stage of the analysis integrated the epidemiological and environmental data.

The baseline study showed high prevalence of podoconiosis and associated morbidities such as adenolymphangitis (ALA), mossy lesions and open wounds in northern Ethiopia. The predominance of cases at early clinical stage of podoconiosis indicates the potential for reversing the swelling and calls for disease prevention interventions. Moreover, the study shows that podoconiosis has strong psychosocial, physical and economic impacts on patients in East and West Gojam zones of northern Ethiopia. Concerns related to familial clustering and poor understanding of the causes and prevention of podoconiosis all add to the physical burden imposed by the disease. Strategies that may ease the impact of podoconiosis include delivery of tailored health education on the causes and prevention of disease, involving patients in intervention activities, and the development of alternative income-generating activities for treated patients.

The individual level correlates study revealed late use of shoes, usually after the onset of podoconiosis, and inequalities in education, income and marriage were found among cases, particularly among females. There was clustering of cases within households, suggesting that interventions against podoconiosis would benefit from household-targeted case tracing. Most importantly, the study identified a secular increase in shoe-wearing over recent years, which may give opportunities to promote shoe-wearing without increasing stigma among those at high risk of podoconiosis.

The environmental level correlates study exhibited clay minerals (smectite and mica) and quartz (crystalline silica) were prominent correlates of podoconiosis while iron oxide, zirconium and kaolinite also were related with podoconiosis spatial distribution. The findings of this study challenged some of the pre-existing assumptions in which metallic oxides or trace elements were given more emphasis.

Over all, the findings of these studies are potentially important clues which can be used to narrow the on-going search for the aetiology of podoconiosis, and provide new ground for further exploration of podoconiosis aetiology using biomedical and toxicology studies.

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Abbreviations

AAU - Addis Ababa University

AIC – Akaike Information Criterion

Al_2O_3 - Aluminium oxide

ALA - Adenolymphangitis/Acute lymphadenitis

ANOVA – Analysis of variance

As – Arsenic

Asl – Above sea level

ASTER - Advanced Spaceborne Thermal Emission and Reflection Radiometer

Ba –Barium

CaO - Calcium oxide

Cd – Cadmium

CHN - Carbon, Hydrogen and Nitrogen

CHPs - Community Health Promoters

CI - Confidence Interval

Co – Cobalt

Cr – Chromium

Cu – Copper

DEM - Digital Elevation Model

DLQI - Cardiff Dermatology Life Quality Index

EMA - Ethiopian Mapping Agency

EWAS - Environment Wide Association Study

Fe_2O_3 – Iron oxide

FMOH - Federal Ministry of Health of Ethiopia

GDP - Gross Domestic Product

GIS - Geographic Information Systems

GLM - Generalized Linear Model

GPS - Global Positioning System

GSE - Geological Survey of Ethiopia

HEWs - Health Extension Workers

IOCC - International Orthodox Church Charities

K_2O – Potassium oxide

MgO – Magnesium oxide

MnO – Manganese oxide

Na_2O – Sodium oxide

NASA - National Aeronautics and Space Administration

Ni –Nickel

NTD - Neglected Tropical Disease

OR - Odds Ratio

P_2O_5 – Phosphorus pentoxide

Pb - Lead

Q-Q plot - Quantil – Quantile Plot

Sb – Antimony/ Stibium

Sc - Scandium

SD – Standard Deviation

SiO_2 – Silicon dioxide

SPSS - Statistical Package for Social Sciences

Sr - Strontium

TiO_2 - Titanium dioxide

UTM - Universal Transverse Mercator

V - Vanadium

VIF - Variance Inflation Factor

WFA - Water Flow Accumulation

WHO World Health Organization

XRD - X-Ray Diffraction

Y - Yttrium

Zr – Zirconium

Operational definitions

- ‘Ever’ owned shoe - had shoe at least once in one’s life time
- Endemicity - a measure of intensity of disease occurrence in a particular region
- First degree relative - parents and children
- ‘Heavy Metal’ – this study adopts the operational definition of heavy metal used in a number of previous literature publications on podoconiosis, to describe any metal with a potential health effect
- Interdisciplinary - involving the combining of two or more academic disciplines into one project
- Interpolation - a method of constructing new data points within the range of a discrete set of known data points
- *Kebeles* the lowest level governmental administrative unit in Ethiopia with a population of 5,000
- Kriging - an interpolation technique that predicts the value of the variable of interest at an unobserved location as a weighted average of values in neighbouring locations
- Lateritic or ‘ferrisol’ – iron rich soil
- Lymphoedema - localized fluid retention and tissue swelling caused by a compromised lymphatic system
- Non-protective - barefoot or wearing open shoes that do not cover the feet completely
- pH - measure of solvated hydrogen ion to define acidity or alkalinity
- Phyllosilicates – silicate minerals
- Podoconiosis case - an individual clinically confirmed to have podoconiosis by a trained HEW or nurse

- Podoconiosis control – an individual living in the household closest to the case, and clinically demonstrated not to have podoconiosis
- Protective shoe - wearing closed shoes that covers the feet completely
- Quartz - crystalline silica
- Regression kriging - a spatial interpolation that combines a regression of the dependent variable on auxiliary variables
- Second degree relatives - grandparents, grandchildren and siblings
- Third degree relatives - aunt, uncle, nephew, cousin and niece
- Traverse – transects (routes) used across geologically defined area
- Variogram - a function which shows spatial dependence or spatial correlation between pairs of points in space
- *Woredas* - administrative regions equivalent to districts
- *Z* - Scores - a statistical measurement of a score's relationship to the mean that is calculated by subtracting the mean from each value and dividing the result by the standard deviation.
- Zone - administrative regions equivalent to province

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Author's declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: 

Date: March, 2014

Chapter 1: BACKGROUND

1.1. Background on podoconiosis

Pre podoconiosis history of elephantiasis

Literature from c.905 to 1784 has documented that the earliest recognition of elephantiasis as “swollen leg” that was distinct from leprosy dates back to the ancient “Tibetan Medicine” book that stated ‘Mountain water that flows slower and less exposed to sun, moon and wind causes elephantiasis’ (Price 1984). Later, translation of the Hippocratic medical text book from Greek to Arab by Rhazes, a Persian physician, showed the distinction between elephantiasis (probably non-filarial) and lepromatous leprosy. After the 15th century, trade travellers to India and the Far East described the frequently seen one-sided and below the knee “big legs” in drawings (Price 1984). Similarly, James Bruce’s observation in Gonder northern Ethiopia documented graphic description of elephantiasis-affected legs in relation to elephant skin and hence its name ‘elephantiasis’ was derived (Davey 2010).

Advancements in the study of the pathogenesis of elephantiasis, inconsistency between the distribution of elephantiasis and filarial disease and repeatedly negative bacteriology and microfilaraemia tests among patients with elephantiasis challenged the pre-existing knowledge and assumptions of a single type of elephantiasis. Robles’ study among Guatemalan elephantiasis patients recognized the occurrence of non-filarial endemic elephantiasis that is life long and common among the barefooted (Price 1984). Different names were coined for the non-filarial elephantiasis. While Roble coined the name ‘pseudo-lepra’, Cohen combined the ‘‘verrucosis lymphatica’ in Kenya and ‘mossy foot’ in Ethiopia and Loen used the title

‘Verrucosis lymphostatica or Lowenthal-Robles Disease’ to refer to the non-filarial endemic elephantiasis (Cohen 1960; Price 1984; Davey 2010). The currently accepted and widely used name of podoconiosis describing the non-filarial endemic elephantiasis was established by Price (Price 1988).

Podoconiosis description

The term podoconiosis is derived from the Greek words Podos meaning “foot” and Konion meaning “dust” (Price 1990). It is also known as “mossy foot” due to the mossy appearance of the skin on the feet (Lienhart, Ashine et al. 2010). Following the invaluable contribution of Dr. Ernest Price, a British Surgeon, in the recognition and understanding of podoconiosis in the 1970’s and 1980’s, the disease was also known as “Price’s disease” (Nenoff, Simon et al. 2010).

Podoconiosis is also known as endemic non-filarial elephantiasis of the lower legs and is thought to be caused by prolonged exposure of the feet to red clay soils of volcanic origin. Walking barefoot, which is a common practice among poor agricultural people in tropical highlands, is a common risk factor resulting in exposure to irritant clay soil particles (**Figure 1**). This prolonged exposure when matched with genetic susceptibility to the disease results in damage to the lymphatic vessels and swelling of the lower legs over time (Price 1972; Davey, Gebrehanna et al. 2007; Tekola Ayele, Adeyemo et al. 2012).

Figure 1 A farmer working barefoot in a podoconiosis endemic area in East Gojam zone of north Ethiopia, (*Picture taken by Yordanos B. Molla***)**

Podoconiosis is an important yet neglected problem of social, economic, development and public health relevance in endemic countries as described in the subsections that follow. The disease has recently gained global and national attention. It has recently been recognized by the World Health Organization (WHO) as a neglected tropical disease (NTD) because of the disabling impact it has on affected communities (WHO 2011). The Federal Ministry of Health of Ethiopia (FMOH) has also endorsed inclusion of podoconiosis in the National Master Plan for Neglected Tropical Diseases (FMOH 2011).

Geographic Distribution

Globally, podoconiosis is common in the highlands of tropical Africa, Central America, and Northwest India. Podoconiosis had previously been reported in some parts of Europe (France, Ireland, and Scotland) and North Africa (Algeria, Tunisia, Morocco, and the Canary Islands); however, currently there is no report of the disease in these countries, most likely because of widespread use of footwear (Price 1990; Nenoff, Simon et al. 2010).

The global distribution of podoconiosis is shown in **Figure 2**. African countries with a high prevalence of podoconiosis include Uganda, Tanzania, Kenya, Rwanda, Burundi, Sudan, and Ethiopia. Other African countries where podoconiosis has been reported include Equatorial Guinea, Cameroon, Chad, Niger, Nigeria, and the islands of Bioko, Sao Tome & Principe and Cape Verde. The Central American countries Mexico and Guatemala and the South American countries, Colombia, Ecuador, and Brazil had been reported to have podoconiosis in their highland area. It was also found in Sri Lanka and Indonesia (Price and Bailey 1984; Price 1990; Nenoff, Simon et al. 2010).

Figure 2 Geographic distribution of countries in which podoconiosis has been documented (Footwork 2012)

In Ethiopia alone, up to 1 million podoconiosis cases are estimated to exist, and most of them are in the economically productive age group (Tekola, Mariam et al. 2006). The average prevalence of the disease in Ethiopia is > 5% in endemic areas (Davey 2008).

Price developed a map showing the location of villages with elephantiasis patients overlaid on geological map with basaltic rock in Ethiopia. The map was developed by locating the villages from where podoconiosis patients visiting elephantiasis clinic in Addis Ababa, the capital of Ethiopia, came from. The locations were then correlated with the geological map of the country prepared in small scale (1:2,000,000 scale). Based on the distribution an association was made between disease distribution and soil derived from basaltic rock (Price 1976). The map gave a good insight into the presence of environmental factors for the development of podoconiosis. But the patients sampled were not representative of the national case distribution and the scale of the geological map was too small to capture variation in geology and soil types at a larger scale. A detailed survey based national podoconiosis mapping in Ethiopia has yet to be conducted.

Genetic susceptibility to podoconiosis

In endemic areas, podoconiosis is considered to be a familial disease because of clustering of the disease in families. Community members use terms such as “bone” and “blood” to indicate that the disease runs in families (i.e., is genetic) (Yakob, Deribe et al. 2008; Tekola, Bull et al. 2009). A recent study has also reported that community members erroneously perceive that clustering of podoconiosis in families was due to the contagious nature of the disease or a curse from God (Ayode, McBride et al. 2012). The genetic basis of podoconiosis has been investigated using segregation analysis in multiply affected families in Ethiopia. The study estimated a sibling recurrence risk ratio of 5.07 (i.e., an individual with an affected sibling is five times more likely to develop podoconiosis than a randomly selected individual in the general population), a heritability of 0.63 (i.e., 63% of the variance in occurrence of podoconiosis is explained by genetics), and age and footwear were significant environmental covariates (Davey, Gebrehanna et al. 2007). Following this, a genome-wide association study showed that genetic variants in the HLA class II loci confer susceptibility to podoconiosis (Tekola Ayele, Adeyemo et al. 2012).

Clinical Manifestations of Podoconiosis

Podoconiosis usually has an asymmetric bilateral presentation limited to below the level of the knees. The disease progresses over years and symptoms become apparent after the first and second decades of life (Price 1990).

For a long period, podoconiosis (also known as “mossy foot” in Ethiopia) was misclassified as a range of other diseases including filarial lymphoedema, onchocerciasis, leprosy, and in children, malnutrition. Clinical features of podoconiosis that help distinguish it from filarial elephantiasis include the foot being the site of first symptoms (rather than elsewhere in the leg) and bilateral but asymmetric swelling usually confined to the lower leg (compared to the predominantly unilateral swelling extending above the level of the knees in filarial elephantiasis). Groin involvement, which is common in filarial elephantiasis, is extremely rare in podoconiosis. Moreover, podoconiosis may be distinguished from lepromatous lymphoedema by the preservation of sensation in the toes and forefoot, the lack of trophic ulcers, thickened nerves or hand involvement (Davey, Tekola et al. 2007).

Price classified the clinical type of podoconiosis lesion based on the degree of fibrosis as the soft “water bag” or more fibrotic nodular “wooden” types (Price 1977). Recently, a validated podoconiosis clinical staging system that enables clinicians to assess the results of medical and surgical treatment, and investigators to document the effects of public health preventive interventions, has been developed. The staging system helps grade the severity of the disease and monitor treatment outcome (Tekola Ayele, Mariam et al. 2008). Based on the staging:

Stage 1- Swelling that is reversible overnight

Stage 2- Swelling below knee that is not completely reversible overnight and if present, knobs/bumps are below ankle only

Stage 3- Swelling below knee that is not completely reversible overnight and knobs/bumps are above ankle

Stage 4- Swelling above knee that is not completely reversible overnight knobs/bumps are located anywhere in the foot or leg

Stage 5- Joint Fixation **-** swelling anywhere in the leg or foot

Prevention and treatment of podoconiosis

Podoconiosis can be prevented by consistently wearing shoes and washing feet with soap and water. Early forms of the disease can also be controlled using the same measures. Podoconiosis prevention interventions include health education on personal hygiene and shoe-wearing practice, provision of locally made and affordable shoes, and improving access to water and soap for washing feet (Price 1990).

A study conducted among podoconiosis patients in southern Ethiopia has shown that the Amharic version of the Cardiff Dermatology Life Quality Index (DLQI) can effectively be used to assess the quality of life of patients (Henok and Davey 2008). Later, the effectiveness of a simple lymphoedema treatment regimen for podoconiosis management among patients in southern Ethiopian was assessed using the staging system and the DLQI. The study showed that a simple, resource-appropriate regimen had a considerable impact both on clinical progression and self-reported quality of life of affected individuals (Sikorski, Ashine et al. 2010).

Recently, a community podoconiosis program has been started in northern Ethiopia. The main lesson from the start up implementation assessment showed the need to integrate the podoconiosis prevention and treatment services with the existing government health programs and to involve the community at large (Tomczyk, Tamiru et al. 2012).

Social and economic burdens of podoconiosis

Poor knowledge and unfavourable attitudes towards podoconiosis contribute to severe stigmatisation suffered by patients and their families. Lack of knowledge about the disease's risk factors, transmission, care and prevention was common among both the community and health professionals living in podoconiosis endemic areas (Yakob, Deribe et al. 2008; Yakob, Deribe et al. 2010).

The economic effect of podoconiosis on patients and affected patients' families is also huge. There is a vicious cycle of poverty and podoconiosis. Poverty contributes to the disease because the number one reason that patients do not wear shoes is inability to afford them (Yakob, Deribe et al. 2008). Podoconiosis contributes to poverty because patients are half as productive as their age and sex-matched non-affected controls. A study showed that in Wolaita zone of southern Ethiopia (population 1.6 million), the disease results in an annual economic loss of 16 million US dollars. Each patient loses 45% of their economically productive time due to podoconiosis related morbidity (Tekola, Mariam et al. 2006).

1.2. Podoconiosis and the environment

Environmental factors observed in podoconiosis endemic areas

Environmental factors have long been known for their effects on incidence and prevalence of diseases. The ill health effects of the environment can be a result of pathogenic microorganisms or may originate from the soil, air, or water found in a specific place. Previous studies on podoconiosis have suggested the presence of environmental triggers for podoconiosis (Price 1974; Price 1976; Price, McHardy et al. 1981; Price and Bailey 1984). In particular, similarities in mineralogical and geochemical composition of the soil, altitude and rainfall pattern among podoconiosis endemic areas have drawn attention towards assessment of the environmental level correlates of the disease (Price 1974; Price 1976).

In 1973 a survey conducted in southern Ethiopia (where *Wuchereria bancrofti* and *Onchocerca volvulus* the causes of lymphatic filariasis and river blindness respectively, are non-existent) showed an association between podoconiosis and "tropical red soil". The study showed that as one goes 25 km from the endemic area, the change in soil type is matched with simultaneous reduction in podoconiosis prevalence. Moreover, the disease prevalence was higher among people who did not wear shoes, suggesting a direct relationship between podoconiosis and the environment (Price 1974). Similar assessment of the soil type in other East African countries showed that the "high altitude" elephantiasis in these countries had a geochemical rather than a filarial cause (Price 1976).

Price further described geologic factors related to the specific soil type responsible for the development of podoconiosis in Ethiopia. The soil parent material was explained to be a product of weathering of volcanic rock particularly basalt (Price

1974). A follow-up study in four East African countries (i.e., Kenya, north-west Tanzania and adjacent parts of Burundi and Rwanda) corroborated the previous observation that the disease endemic areas had volcanic basalt rocks (Price 1976). Furthermore, the high altitude and associated high rainfall in podoconiosis endemic areas pointed out possible similarities in soil mineralogy. In Ethiopia the disease was prominent at an altitude of > 1500 m and an annual rainfall of > 1000 mm (Price 1974). Similarly, endemic areas in Kenya and Tanzania had an altitude of 1220 - 2300 m and 1220 -1830 m, respectively (Price 1976).

Postulated Hypotheses and Knowledge Gaps in Soil Properties in Podoconiosis Endemic Areas

Consistent presence of podoconiosis in high altitude and high rainfall area with underlying volcanic basalt rock were understood as proxy indicators of the resulting soil in podoconiosis endemic areas, since the disease was believed to be a result of prolong contact of feet with the soil. The reddish colour of soil in endemic areas was considered to be due to its ferric oxide content. Similarly, the pH (measure of solvated hydrogen ion to define acidity or alkalinity) of the soils in such areas which was about 5.6-6.8 was mainly attributed to the high rainfall leaching calcium and other bases in the soil (Price 1974). The soil in podoconiosis endemic areas was found to be very slippery when wet and very adhesive if allowed to dry on the skin (Price and Bailey 1984). In addition, penetration of the skin was proposed to be facilitated by the fine particles (< 5 μm) in endemic areas (Price 1990). Mineralogical analysis of both femoral lymph nodes from podoconiosis patients and soils in disease-endemic areas of Ethiopia revealed the presence of iron, silica, aluminium and other heavy metals that are characteristic elements of volcanic rocks (Price 1974).

Earlier studies have also indicated a difference in the metallic content of the lymphatic tissues of podoconiosis patients and non-patients using electronic microscopy and emission spectroscopy. Silicon, aluminium and other trace elements were found on analysis. Nevertheless, the presence of these particles in the clay soil responsible for podoconiosis was not known for some time. Later, with the advancement of technology when micro-analysis of particles less than 2 μm became possible, the particles present in the clay soil became evident. Following this, a comparative study among 20 patients and 18 non-patients in Ethiopia indicated the silicon and aluminium ratio of particles is greater among podoconiosis patients than among non-patients (Price and Henderson 1978). A pilot study in the mineralogical content of the soil in podoconiosis endemic areas of Wolaita and Wolega has shown that the zirconium (Zr) and Beryllium (Be) compositions are also high, in congruence with the previous study by Frommel *et al*. (Frommel, Ayranci et al. 1993; Le Blond, Baxter et al. 2011). A study in Cameroon tested the hypothesis that micro-minerals present in the lymph nodes were similar to the mineral content of the clay soil where podoconiosis cases are observed. It was possible to make a link between soil and tissue only for four cases. The soil sample was dominantly amorphous silica (together with kaolin silicate phase, iron and aluminium oxide, quartz and illite), and the tissue specimen were dominantly crystalline silica-rich (containing quartz and muscovite). However, there was no significant difference between the percentage content of lymph nodes of patients and non-patients although greatly enlarged lymph nodes in patients indicated heavier total mineral load (Price, McHardy et al. 1981).

Most of the previous ad-hoc studies made evaluation of the soil properties in endemic areas a starting point to further knowledge about the disease. For instance, the association of red soil and podoconiosis was established based on Price's visual observation of red soil and higher disease prevalence within a 25 km radius. He explained the redness as a result of ferric oxide content in comparison with tropical lateritic type of soil commonly found in the area (Price 1974).

However, most of the previous studies failed to give a complete picture. First, the sample sizes used in previous studies were small. For instance, a comparative study that postulated association of podoconiosis with heavy metals such as silicon and aluminium used lymphatic tissues from 38 individuals in Ethiopia and 25 in Cameroon (Price and Henderson 1978; Price and Henderson 1981). Second, the soil property analysis was not done and hence the correlation between soil and distribution of podoconiosis was not established. Third, the study areas in Ethiopia and Cameroon were podoconiosis endemic based on the observed "tropical red clay soil". However, the lack of comparative exploration of different soil samples from different levels of podoconiosis prevalence where study subjects were coming from was presented as limitation of the studies (Price and Henderson 1978). In a subsequent study in which 15 soil samples were analysed from plantations in highlands of Cameroon, lymph nodes were examined from only four study subjects from the study area (Price, McHardy et al. 1981).

Fourth, the techniques used for soil property analysis was not advanced limiting consistency of findings of predominant soil properties in multiple studies. For instance, while Frommel *et al*. suggested trace elements such as Zr, Price *et al*. emphasised on heavy metallic oxides such as Silicon and Aluminium oxides. Price *et al*'s study of variation in heavy metals (mainly aluminium and silica) between lymph nodes of cases and controls in Ethiopia was later repeated in Cameroon but did not show statistically significant association (Price and Henderson 1978; Price, McHardy et al. 1981; Frommel, Ayranci et al. 1993). The Cameroon study was aimed at finding supporting evidence for the variations observed in heavy metals between elephantiasis affected cases and unaffected individuals from Ethiopia. However, the study highlighted the presence of statistically significant differences in clay mineral content ratio between the two groups both in Cameroon and Ethiopia, and attributed this to the high kaolinite content of the soil in the studied area (Price and Henderson 1981). Later, with the advancement of soil property analysis techniques, the importance of clay minerals and silt in which quartz is the main component in addition to soil oxides was given due emphasis (Price, McHardy et al. 1981).

In summary, findings of previous studies urged comprehensive exploration of the range of soil chemical composition (oxides, trace elements and mineral content) and soil particle size in podoconiosis endemic areas. Current advances in soil analysis techniques such as XRD (X-ray diffraction) have improved these explorations. Moreover, the introduction of geospatial approaches in epidemiology created the opportunity to comprehensively explore and quantify the link between individual and environmental level variation at different magnitude of podoconiosis prevalence. Understanding this link in-depth will be useful to gain insight into the pathogenesis of podoconiosis.

2. Chapter 2: Exploring the Spatial Epidemiology of Podoconiosis

2.1. Spatial Epidemiology

The use of geographic information systems in epidemiology

The concept of geographic location being related to health outcomes dates back to the 18th century. Despite the knowledge of bacterial origin of some diseases, the epidemics following the First World War called for attention to medical geography. The term "geo-medicine" was coined and used in most of the German literature until the 1990's. The modern term "medical geography" implies the interdisciplinary nature of the term where geographic epidemiology (disease ecology) and health care system are included. Since then, the discipline has been evolving with new ideas (Kistemann, Dangendorf et al. 2002).

Contemporary medical geography has benefited from the model of epidemiological transition where disease patterns are described as the variability in socio-economic and demographic differences with space and time. Simultaneously, the development of Geographic Information Systems (GIS) and their increasing use in public health has benefited epidemiological studies. The use of GIS in epidemiology (Epi-GIS) ranges from research hypothesis generation to detailed monitoring and evaluation of interventions. In particular, Epi-GIS enables determination of health and disease patterns by area, prediction of areas with higher risk of disease occurrence, mapping of patterns of disease over time, and measurement of service adequacy in a defined (buffered) catchment area (WHO and PAHO 1996; Kistemann, Dangendorf et al.

2002). The analysis of disease surveillance in space is summarized in **Figure 3** (Tiwari and Rushton 2010).

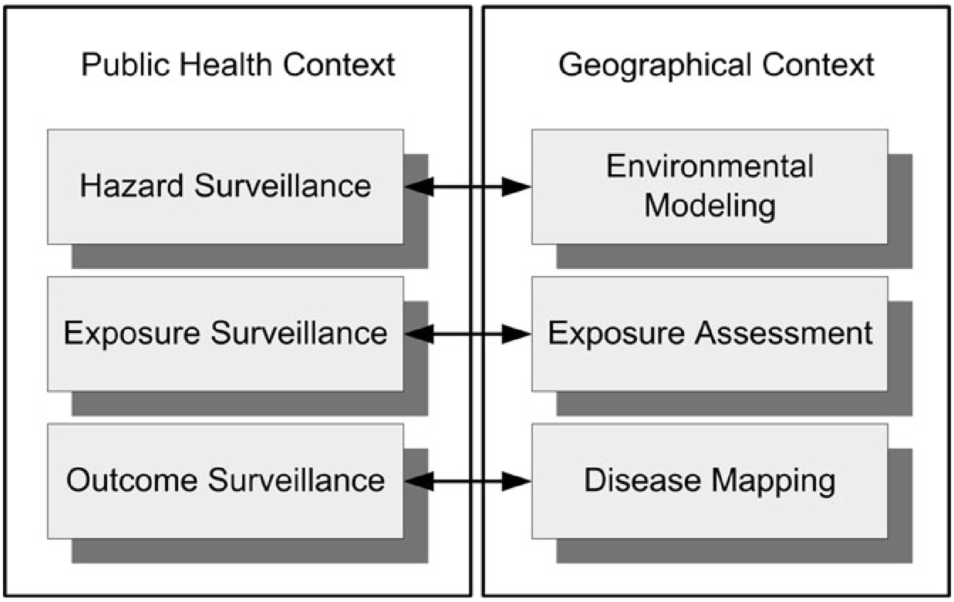

Figure 3 A geographical framework for environmental health surveillance (Source- Spatial Analysis System for Health Surveillance, page 179 (Tiwari and Rushton 2010))

Methodological approaches in spatial epidemiology

The three pillars in epidemiology are person, time, and space/place. Person and time are more frequently investigated, and most epidemiological studies gather individual level information. Although disease mapping is not a new exercise in epidemiological research, little emphasis has been given to the role of "space" or "ecologic environment" in disease causation. Recently, interest in exploring ecological factors related to disease has increased (Moore and Carpenter 1999; Kistemann, Dangendorf et al. 2002; Mauny, Viel et al. 2004).

Conceptualisation of the interplay between different causal factors associated with disease in certain populations has brought about a paradigm shift in identifying health determinants beyond the level of the individual. Uneven spatial distribution of disease provides aetiological insight into disease causation where geographic location can have role in shaping disease outcome. This shift was more pronounced following literature published in the 1980's and early 1990's.

Understanding the effects of environmental insults in disease causation and the effects of environmental factors that shape individual conditions and opportunities became indisputable. However, methodological issues put pressure on researchers to make a choice between the individual and the ecological level approach to disease causation (Moore and Carpenter 1999; Diez Roux 2001; Mauny, Viel et al. 2004).

Ecological studies show the geographical disparity in disease distribution. Nevertheless, such studies do not directly determine if the observed disparities are results of the differences in geographical areas studied or individual variations (Diez Roux 2001). Therefore, the question will be: is the observed difference a "composition" (individual character) or a "context" (geographical setting) effect? (Duncan, Jones et al. 1998; Mauny, Viel et al. 2004)

The theory of a "web of disease causation" has been appreciated for its insight into multiple causations. However, it is challenged by the ideas that all causal factors are not equally important: some are "component causes" whose presence is not necessary, while others are "necessary causes" whose presence is a must to cause the disease (Rothman 1976; Krieger 1994). Besides, the causes of a disease at individual level (causes for cases) might not be the same as causes at population level (causes of incidence) (Rose 2001). Therefore, multilevel modelling in which selected individual and environmental factors are analysed at the same time (Mauny, Viel et al. 2004) or range of factors are analysed separately while capturing data from the lowest level of individual to the next level of household, village and so on, are deemed important.

Therefore spatial or ecological inferences should primarily take into consideration individual level variation to avoid the "ecological fallacy" while simultaneously examining ecological disparities regardless of individual comparability. Here the underlying assumption is that any single population is not homogenous. The notions "(1) that individual level models are more perfectly specified than ecological level models, (2) that ecological correlations are always substitutes for individual level correlations, and (3) that group level variables do not cause disease" are misleading. Therefore, similarity between populations in different locations is not equivalent to similarity at individual level. Likewise, individual level variation should not necessarily show ecological variations (Schwartz 1994).

The challenge becomes visible when defining the ecological level (spatial scale) at which the outcome of a disease of interest will be affected. This is to say, how well will our cluster capture the environmental or ecological variations? How much will the environmental demarcations indicate population variation regardless of the individual variations such as the mobility, age, or socio-economic status of the individuals assessed (Mauny, Viel et al. 2004; Bian and Liebner 2007).

Recognition of these facts will lead an investigator to decide on the level of spatial scale, that is, the extent of the area to be investigated to identify the most important risk factor for the development of a disease of interest in that particular scale. Risk mapping for helminthic infection gives a good example for this where infection was associated with climatic factor at broader scale and with demography and socio-economic status at local scale (Brooker 2007).

In summary, a study design needs to clearly define the environmental and individual level variables as comprehensively as possible. At the same time, it should take into account the interrelationships and directions of association, and the contribution of each variable to the disease of interest. Inference made should clearly indicate the scale of spatial heterogeneity that a particular study is trying to capture.

Recent efforts in spatial epidemiology of tropical diseases

A range of spatial epidemiological studies have been conducted in recent years. Many of the studies have focused on tropical diseases in Africa (Ngoumou, Walsh et al. 1994; Mace, Boussinesq et al. 1997; Malone, Yilma et al. 2001; Brooker, Beasley et al. 2002; Gyapong, Kyelem et al. 2002; Kabatereine, Brooker et al. 2004; Clements, Lwambo et al. 2006; Clements, Moyeed et al. 2006; Gemperli, Vounatsou et al. 2006; Raso, Vounatsou et al. 2006; Brooker 2007; Pullan, Gething et al. 2011; Ruberanziza E., Mupfasoni D. et al. 2009), although there is an increase in its use in other parts of the world (Ferguson, Cummings et al. 2005; Yang, Vounatsou et al. 2005; Brooker, Alexander et al. 2006; Bellander, Wichmann et al. 2012). Most of the investigations targeted disease mapping and developing prediction models for the purpose of feasible interventions and detecting population at risk of diseases such as schistosomiasis (Traore, Maude et al. 1998; Malone, Yilma et al. 2001; Brooker, Kabatereine et al. 2004; Kabatereine, Brooker et al. 2004; Yang, Vounatsou et al.

2005; Clements, Lwambo et al. 2006; Clements, Moyeed et al. 2006; Raso, Vounatsou et al. 2006; Brooker 2007), onchocerchiasis (Ngoumou, Walsh et al. 1994; Mace, Boussinesq et al. 1997; Thomson, Obsomer et al. 2000), filariasis (Gyapong and Remme 2001; Gyapong, Kyelem et al. 2002; Ruberanziza E., Mupfasoni D. et al. 2009), soil transmitted helminths (Brooker, Beasley et al. 2002; Brooker, Alexander et al. 2006; Raso, Vounatsou et al. 2006; Pullan, Gething et al. 2011), dengue (Carbajo, Schweigmann et al. 2001) and malaria (Kleinschmidt, Bagayoko et al. 2000; Abeku, van Oortmarssen et al. 2003; Gemperli, Sogoba et al. 2006; Gemperli, Vounatsou et al. 2006; Tonnang, Kangalawe et al. 2010).

Graham *et al*. have discussed the advantages and potentials of using spatial analysis which can go beyond recording spatial location and mapping disease risk. They also presented challenges that arise, including: presenting predictions together with associated uncertainties to help decision making; using robust spatial models with clearly stated uncertainty to know precision without the need for validating with other databases; choosing the right model for a specific problem through validation and determining the spatial scale and resolution (Graham, Atkinson et al. 2004).

2.2. Significance of the study: spatial epidemiology of podoconiosis

The complexity of interaction of environmental and individual level correlates of a disease lead into evaluation of a single factor for the development of a particular disease in many cases, including chronic diseases (Patel, Bhattacharya et al. 2010). This is usually a result of limited types of methods that can associate a disease with most of its correlates. As has been discussed in the previous sections, the role of environmental triggers, particularly soil minerals, in the development of podoconiosis has been described by earlier studies. Alike, the role of individual variation ranging from genetic makeup to prolonged behavioural practices for the development of podoconiosis has been explored. However, environment wide association studies (EWAS) of the combined effects of geology, soil properties, topography, climate, and individuals' socio-demographic and behavioural factors have not been conducted in depth. The present study will firstly contribute to fill this gap through systematic investigation of the link between environmental factors (i.e., “ecological level variations”), and their interaction with demographic, behavioural, and clinical factors at individual level (i.e., “individual level variation”).

Previous podoconiosis studies have benefited from the inputs of multiple disciplines (the interdisciplinary approach, (Newell 1999)); brought together to address the problem comprehensively. Epidemiology, genetics, economics and behavioural studies are some of the disciplines used in the study of podoconiosis in Ethiopia. This approach not only helps to understand podoconiosis from different angles, but also supplements understanding of one's own area of expertise. For instance, understanding ethical issues benefited the sample taking for the study of genetic susceptibility for podoconiosis (Tekola, Bull et al. 2009). Similarly, this study of the spatial epidemiology of podoconiosis requires expertise from epidemiology, geology, soil mineralogy and geography.

The current study on spatial epidemiology of podoconiosis is focused more on explaining the correlates of podoconiosis than looking for specific etiology or forecasting its distribution. Therefore, ranges of covariates of the disease were explored in-depth at individual and environmental level. Both “classical” (such as prevalence and baseline survey, case- controls study) and “contemporary” epidemiology techniques (such as spatial analysis) were used in this study. The findings will firstly improve understanding of overall correlates of podoconiosis backed by visual insight of spatial patterns. Secondly, the study will identify the most important risk factors in podoconiosis occurrence, which will in turn enhance implementation of intervention program in other similar settings. This study will also identify the most important soil mineral triggers in podoconiosis, which will be useful to understand the underlying pathogenesis of the disease. Third, the spatial epidemiology of podoconiosis will add into the current endeavours of knowledge in the field of spatial epidemiology and translational epidemiology.

In summary, this study is a good example of “problem-oriented” interdisciplinarity (Schmidt 2011) where individual and environmental level correlates of podoconiosis are explored. Such collaborations among professionals and convergences of disciplines are no longer optional with globalization and the demand for new outputs (Armstrong 2006; Mainzer 2011). The study will also give a good insight not only for future studies in other parts of the world affected by podoconiosis; but also for other diseases with individual and environmental components. Moreover, utilization of different techniques and exploration of range of correlates that coexist naturally makes this study amenable for implementation.

2.3. General objective

To determine the prevalence of and perceptions about podoconiosis, and to identify the individual and environmental triggers and their interplay in the development of podoconiosis in northern Ethiopia

2.4. Specific objectives

a. To determine the prevalence and burden of podoconiosis in northern Ethiopia

b. To assess patients' perceptions about podoconiosis

c. To identify individual level demographic and behavioural factors (i.e. individual variations) related with podoconiosis

d. To identify environmental level correlates of podoconiosis

e. To carry out Environment Wide Association Studies (EWAS) of podoconiosis by including both individual and population level correlates of podoconiosis and using spatial epidemiology techniques

3. Chapter 3: Overview of the study structure

3.1. Background on study organization and administrative structures in Ethiopia

3.1.1. Conceptual framework summering the study

The study was designed to be conducted in two phases. The first part (Part 1) was a baseline survey that addressed the first two objectives of the study: to determine the prevalence of podoconiosis and understand patients' perceptions. The second part, (Part 2) addressed the last three objectives of this study: to determine individual and environmental variables associated with podoconiosis and their interplay in disease development. The schematic presentation of the study components is presented in **Figure 4**.

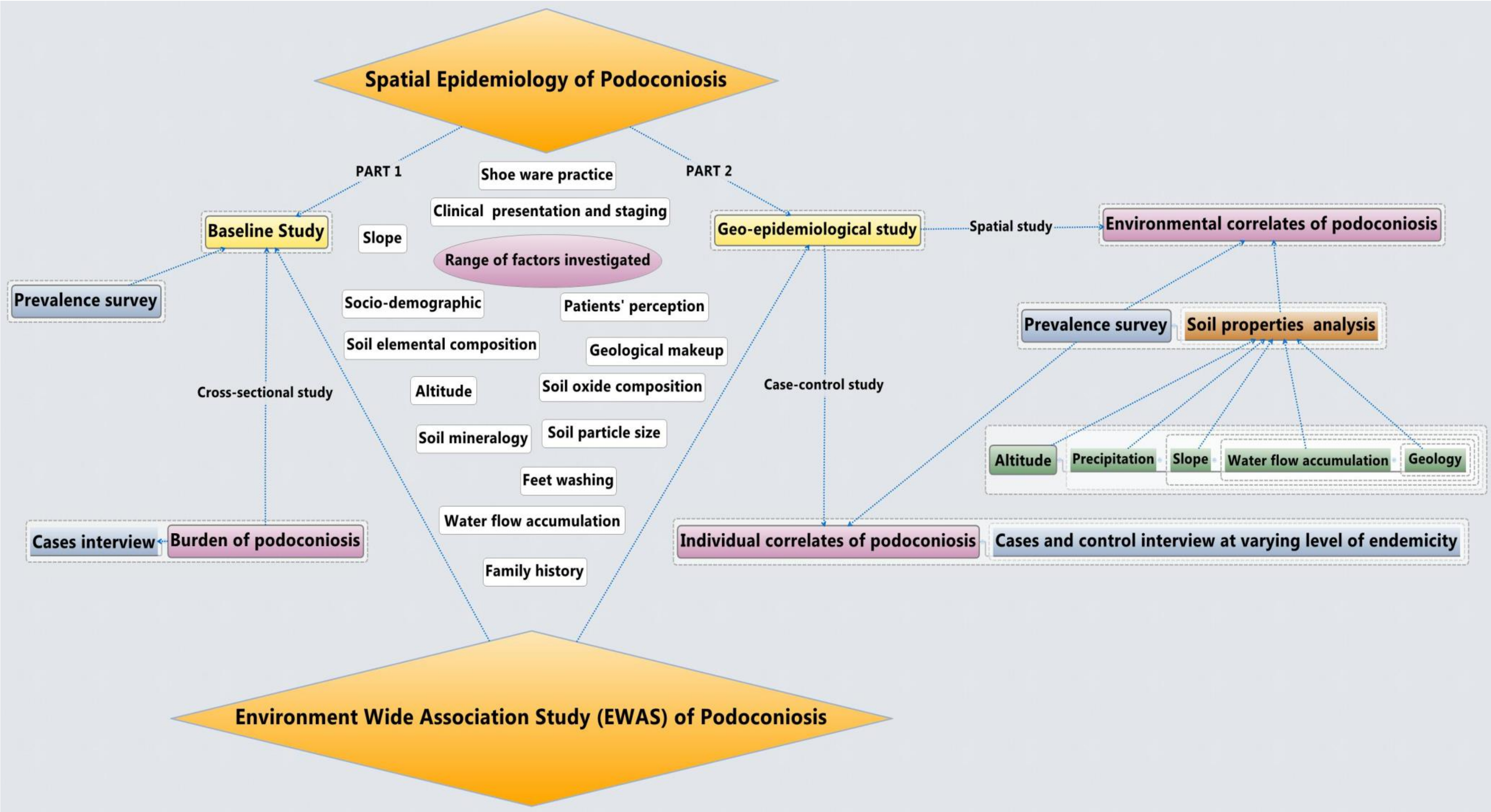

Figure 4 Conceptual frame work showing structure of the study

3.1.2. Administrative structure in Ethiopia

In Ethiopia, administrative clusters are organized in such a way that a zone includes multiple *woredas* (administrative regions equivalent to districts), and a *woreda* includes multiple *kebeles* (the lowest level governmental administrative unit in Ethiopia) that in turn includes multiple villages. The number of villages and the geographic clustering of villages within a *kebele* show variation. The average number of residents per *kebele* is about 5000 people. A *kebele* has a health post with two Health Extension Workers (HEWs) and supports multiple volunteer Community Health Promoters (CHPs). These HEWs and CHPs are mainly involved in health promotion and prevention activities, going door to door to each household in their respective *kebeles*.

The first part of the study, which will be presented as part 1 from now on, was conducted in 20 *kebeles* located in two zones, East and West Gojam zones of Ethiopia (**Figure 5**). The second part, which will be presented as part 2 from now on, was conducted in 12 *kebeles* located in East Gojam zone by following two traverses (routes) starting from Debre Markos town (**Figure 6**).

3.2. Study site selection

3.2.1. Part 1 – Baseline Study

Earlier reports from small scale surveys in northern Ethiopia (Oomen 1969; Price 1974) and current reports indicate that podoconiosis is common in the area. As a consequence, a podoconiosis prevention and treatment centre had been established in Debre Markos town. The podoconiosis treatment centre in Debre Markos, which is located at 10° 21' 00" N, 37° 44' 00" E, is supported by the International Orthodox Church Charities (IOCC), an international non-governmental organisation. Identification of the study area (**Figure 5**) was based on a report by the IOCC podoconiosis treatment centre, written in 2010, summarizing information from key local informants. In addition, the IOCC treatment centre facilitated the baseline study site selection visits.

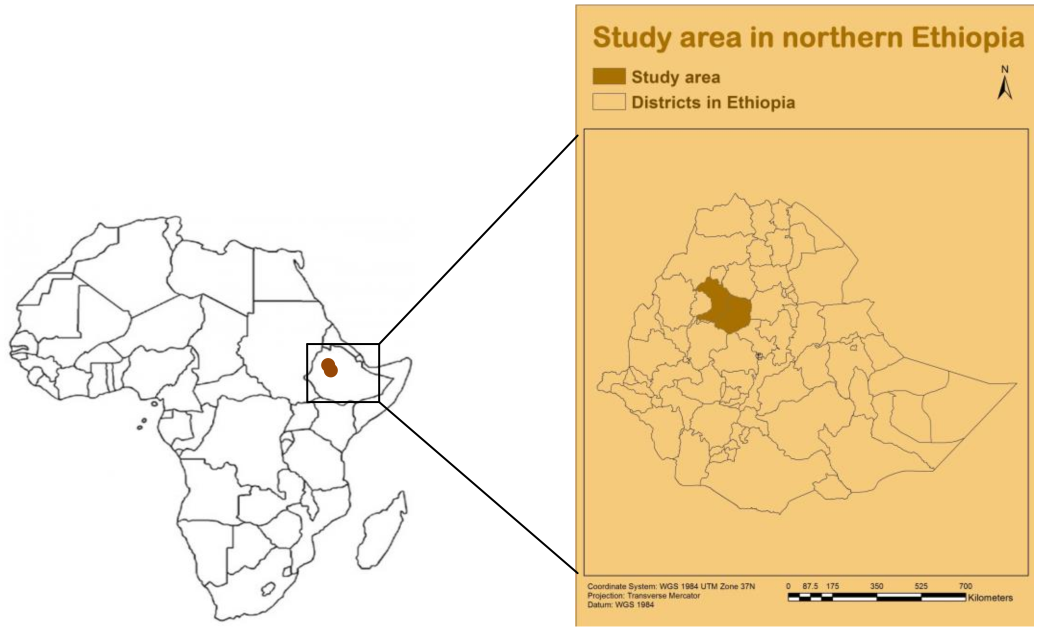

Figure 5 East and West Gojam w*oreda* (districts) of northern Ethiopia

3.2.2. Part 2 – Geo-epidemiological Study

The second part of the study was conducted in East Gojam zone; however, the area covered was not administratively bound. This is because the study site selection activities indicated that geologically and epidemiologically defined study boundaries would give better insight into the variables under investigation. Two site selection visits were conducted before defining the study area.

The first study site selection trip was conducted in June 2011. The aim of this trip was to select podoconiosis endemic and non-endemic sites. On the first day, a team of visitors including three IOCC staff, the research fellow (Yordanos B. Molla) and research supervisor (Gail Davey) travelled to Sinan *woreda* to meet with the head of the *woreda*, the head of Sinan Health Centre and other *woreda* Health Office staff.

Following briefing by the visiting team about the aim of the study, a map of Sinan *woreda* was obtained from the office. The adjacent *kebele* was visited and a meeting with two HEWs was held to get information about the presence of podoconiosis in their catchment population. The second day also continued with visiting *kebeles* and further discussion with seven HEWs and one HEW supervisor to verify if the discussants knew of podoconiosis cases in their respective *kebeles* while conducting routine house-to-house visits.

The information gathered from the *kebeles* from the reports of HEW was triangulated with the podoconiosis patients' treatment and waiting registration lists at the IOCC project office. The selection criteria used to select podoconiosis endemic were:

1. *Kebeles* that are located in *woredas* that are above 1000 m

2. *Kebeles* that are located in *woredas* that have an annual rainfall > 1000 mm
3. *Kebeles* that are located in w*oredas* that are farmed and lived on by people who do not wear shoes consistently and daily
4. Presence of podoconiosis cases in a *kebele*
5. Presence of an adjacent *kebele* with reported podoconiosis cases

For the non - endemic area the first three criteria were used with the absence of podoconiosis in the *kebele* and in adjacent *kebeles* were included.

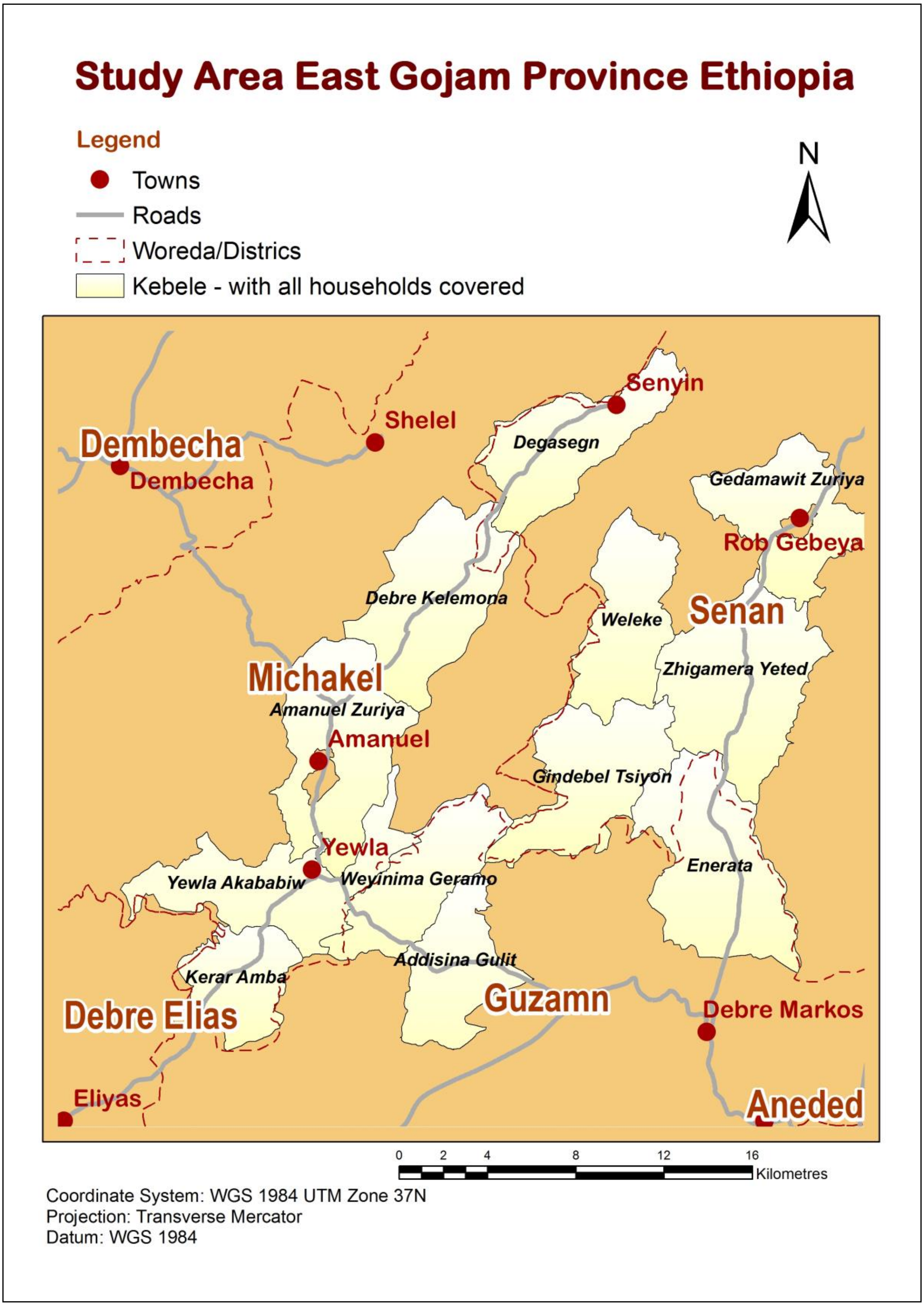

Figure 6 *Kebeles* selected from East Gojam

Based on the site visit the *kebeles* on the west and south of Rob Gebeya town of Sinan *woreda* (Gidimble, Yeted, Weleke) which extends to Yewlana Akababiwu and Amanuel town of Machakel w*oreda* and Eliyas town of Debre Eliyas *woreda* were selected as potential podoconiosis endemic study areas (**Figure 6**). The *Kebeles* at the centre and on the northeast of the Rob Gebeya town were selected as potential controls (i.e. non-podoconiosis areas). After the site visits, we requested an update of newly discovered podoconiosis cases from the head of the *woreda* Health Office.

The second field trip conducted in October 6, 2011 aimed to identify sites based on geological variation around the area. Prior to the field visit, a team comprising research fellow (Yordanos B. Molla), research supervisors and a geologist from Addis Ababa University met and discussed the procedure and material preparation for the field visit. A topographic map of the area surrounding Debre Markos at a scale of 1:50,000 was purchased from the Ethiopian Mapping Agency (EMA), and the Debre Markos Sheet geological map at 1:250,000 scale was obtained from the Geological Survey of Ethiopia (GSE). A compass, Geographic Positioning System (GPS), lens, hammer, digital camera and stationery materials were also acquired prior to the trip. Next, the field visit was done by the research fellow, an MSc student and a geologist from Addis Ababa University (AAU). Based on the previous disease distribution report and geological variability, two main traverses were selected. **Figure 7** shows the geo-referenced geological map with the traverses used. These traverses were from Debre Markos to Choke Mountain through Rob Gebeya (identified as the non-endemic area) and from Debre Markos to Seneyin through Yewlana Akababiwu and Amanuel (identified as the endemic area).

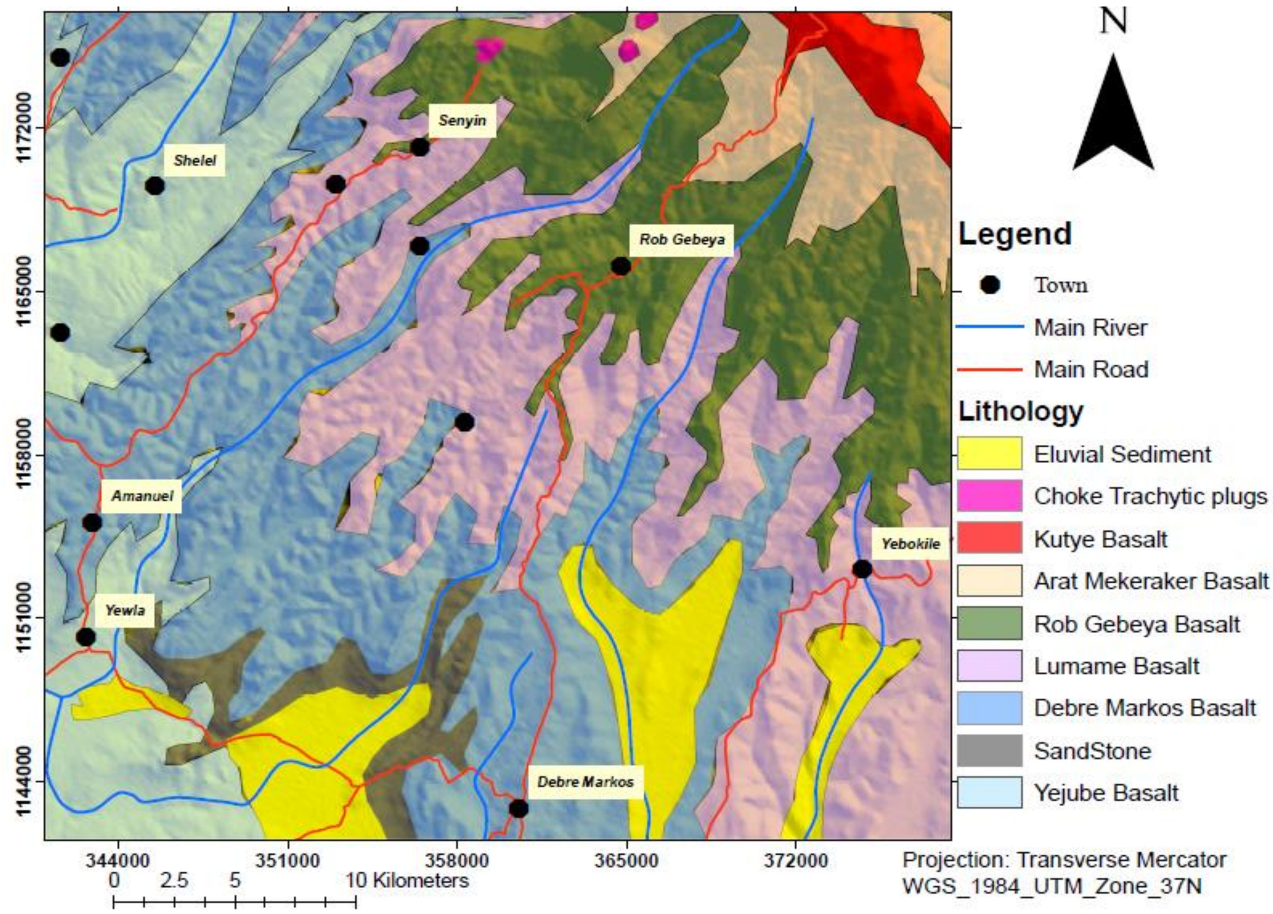

Figure 7 Regional Geology identified and traverses (main road in legend) used for study site selection (Source: Ethiopian Geological Survey)*.

***Note:** According to the Ethiopian Geological Survey: Chocke Trachytic plugs, Kutye Basalt, Arat Mekeraker Basalt, and Rob Gebeya Basalt were reported to be in the range of 22.4-23 Ma (millions of years before the present) old, while Lumame Basalt, Debre Markos Basalt, Sand Stone and Yejube Basalt were 25.3-29.4 Ma old.

Ground truthing activities followed after selecting the traverses. The geologic contact points' locations around the selected traverse were captured through geo-referencing on the map. These locations were also pointed on the topographic map. The location and elevation of the contact points were again taken using GPS on arrival. Two GPS machines were used, one for longitude and latitude and the other (the Universal Transverse Mercator, UTM) for cross referencing. The team took pictures and made descriptive notes of the area surrounding contact points. We took two traverses to characterize the geology and endemicity of podoconiosis as described below.

Traverse One*:* was from Debre Markos to Chocke Mountain through Rob Gebeya town. The geological map shows this route captures geology of: Eluvial Sediments, Debre Markos Basalt, Lumame Basalt, Rob Gebeya Basalt, Arat Mekeraker Basalt and Kutye Basalt. All but the Eluvial Sediment fall under the groups Choke Shield Volcano (Rob Gebeya Basalt, Arat Mekeraker Basal and Kutye Basalt) and Flood Basalt (Debre Markos Basalt, Lumame Basalt).

We found no case of podoconiosis in the Choke Shield Volcano area (around Rob Gebeya town) and few cases in the Debre Markos and Lumame Basalt area (at Gidimbel, Woleke and Yeted *kebeles* that are located at the southwest periphery of Sinan *woreda*).

Traverse Two: was from Debre Markos town to Seneyin going through Yewlana Akababiwu and Amanuel town. This traverse passes through the Eluvial Sediments, Debre Markos Basalt, Lumame Basalt, Sand Stone overlaid by Tuff, and Yejube Basalt. The Yejube Basalt covers most of the podoconiosis endemic *woredas* of Machakel (that neighbours Sinan *woreda* to the west) and Debre Elias (which takes the southwest route from Yewlua Town). Yewlana Akababiwu, Amanuel and Shelel town are all under Machakel *woreda*.

In the second trip the team was able to witness a relatively distinct and clear difference in altitude, topography, soil type and thickness, and climate along the traverses (from Northeast to South-Southwest), i.e. from podoconiosis free to affected areas. In addition, according to the geo-chronologic data indicated on the geologic map, the age of the rocks also increases as one goes from podoconiosis free to affected areas.

Based on the two site visits, it became apparent that three groups of samples were important to capture the individual, geologic and geographic covariates of podoconiosis. The groups were classified as:

1. High (Endemic areas) - around Amanuel town (including Yewlana Akababiwu and Kerer *kebeles*)
2. Low (Non-endemic areas) - around Rob Gebeya town (including Gedamawit and Sinan Mariam *kebeles*).
3. Medium (Transitional areas) - villages around the south-western periphery of Sinan *woreda* (including Zhigamera Yeted, Weleke and Gidembel *kebeles*)

4. Chapter 4 - Baseline Study

The presence of podoconiosis in northern Ethiopia had been noted, and a podoconiosis treatment centre was established in Debre Markos town in the year 2010 (Tomczyk, Tamiru et al. 2012) . However, the magnitude of the problem in northern Ethiopia was not known, and this baseline survey was conducted to determine the prevalence of podoconiosis, and understand patients' perceptions of the disease. This chapter describes the baseline survey with particular emphasis on the prevalence of podoconiosis; socio-demographic, behavioural, clinical characteristics of podoconiosis patients; patient's perception about the cause, control and prevention of the disease; the level of familiar clustering of podoconiosis; and patients' perceived social stigma, physical impairment and economic impairments associated with podoconiosis. The findings inform future research and program implementation endeavours.

4.1. Methods

4.1.1. Study area

I did a baseline survey in Debre Eliyas and Dembecha *woredas* of East and West Gojam zones of Amhara Regional State. These two zones are found adjacent to Debre Markos town, which is located 305 Km north from the capital city of Addis Ababa. I randomly selected 13 *kebeles* from East Gojam and 7 *kebeles* from West Gojam zone. All villages and households in these 20 *kebeles* were included in the study. The populations of Dembecha and Debre Eliyas *woreda* are 111,317 and

82,150 respectively. The majority of the population are farmers and Amharic language speakers in both *woredas* (Central Statistical Agency (Ethiopia) 2007). The study participants were residents of the 20 selected *kebeles* and podoconiosis cases in all households with podoconiosis.

4.1.2. Study design, sampling procedure and sample size determination

The first part of the study was the baseline survey on the extent of podoconiosis in the area. This study was a cross-sectional community-based house-to-house survey. The study was conducted in East and West Gojam zones of Amhara Regional State. A convenience non-random sampling method was used to select the two zones. A list of *woredas* in East and West Gojam zones, known for the presence of podoconiosis based on expert opinion and key informants, was prepared. Second, a random sampling technique was applied to select two w*oredas*, one from each zone. Third, *kebeles* from each of these two *woredas* were sampled randomly proportional to their population size in each *woreda*. A total of 20 *kebeles* from the two *woredas* in East Gojam and West Gojam zones (7 *kebeles* from East Gojam and 13 *kebeles* from West Gojam) were selected. All households in the selected *kebeles* were assessed for the presence of podoconiosis cases through interviews with the household head followed by clinical examination of cases by community health extension workers (HEW).

Households with podoconiosis cases were included for in-depth individual podoconiosis case interviews by clinical nurses. In households where there was more than one podoconiosis patient, all patients were invited to interview and physical examination including measurement of leg circumference.

4.1.3. Data collection

Data collections were done house-to-house by trained HEWs supervised by nurses that work in the respective *woredas.* The HEWs were responsible for house-to-house enumeration of podoconiosis cases and the nurses were responsible for supervising the activities of the HEWs and the detailed assessment of podoconiosis cases (i.e., interviewing and physical examination of patients). All HEWs and nurses received training from the team of researchers before performing data collection. The training consisted of techniques and approaches for obtaining informed consent from prospective participants, interviewing techniques, podoconiosis diagnostic features, clinical staging according to a standard method (Tekola Ayele, Mariam et al. 2008), assessment of ALA (acute adenolymphangitis: a painful inflammation of the foot and leg with swollen lymph nodes and fever (Davey 2010; Alemu, Tekola Ayele et al. 2011)), measurement of leg circumference (the largest circumference between the levels of the ankle and knee measured using a tape, to a precision level of the nearest centimetre (Tekola Ayele, Mariam et al. 2008)), assessment of presence of open wounds, and features that differentiate lymphoedema and leg swelling resulting from podoconiosis from other diseases such as leprosy and filarial elephantiasis. The data collectors were trained on how to advise patients to wear shoes and wash their feet to control disease progression at the end of every interview.

A pre-test of the actual data collection process and the data collection tools was conducted immediately after the training of the data collectors. The pre-test was done in two *kebeles* (one in West Gojam *woreda* and the other in East Gojam *woreda*) which were not included in the main survey. The pre-tests were evaluated in terms of (i) organization of the fieldwork and coordination between the team of investigators, supervisor nurses and HEWs; (ii) ability of the HEWs to effectively conduct the census and complete the questionnaires; (iii) ability of the supervisor nurses to correctly diagnose and stage podoconiosis, and identify ALA symptoms; (iv) completeness, skip patterns, flow and clarity of the questionnaire. At the end of the pre-test, the trainees brought back the data they collected to the training centre. The completed questionnaires were checked by the trainers. Discussion about the challenges the trainees faced during data collection and on the data collection tools was held and the questionnaires were revised accordingly.

The data collection tool was a structured questionnaire. The questionnaire was developed in English, translated into Amharic and back-translated into English to check consistency. The questionnaire was sub-sectioned thematically into socio-demographic characteristics, podoconiosis history, clinical features, treatment-seeking behaviour, sources of water, walking practices, foot hygiene and shoe wearing practices.

4.1.4. Data processing and analysis

Data were entered and analysed using the Statistical Package for Social Sciences (SPSS) software v.17.0. The overall prevalence of podoconiosis was calculated as the ratio of the number of patients with podoconiosis to the total population surveyed aged 15 years and over. Statistical significance was tested using the chi-squared test (X^2) or *t*-test as appropriate to determine if socio-demographic characteristics such as sex were associated with resulting social stigma or disease occurrence and if there were differences between the average values observed in different groups such as age. The level of significance was set at α of 0.05.

4.2. Results

4.2.1. Socio-demographic characteristics

A total of 17,553 households with 51,017 members aged 15 years and above were included in the present survey. Of the surveyed households, 9.7% had one or more podoconiosis patients. A total of 1,319 podoconiosis patients that provided consent and were available during the interview participated in the detailed patient interview. Characteristics of these patients are presented in **Table 1**. Almost all patients were in the age group 15-64 (the age group that includes economically active individuals in Ethiopia), did not read or write, and were farmers. On average, patients had lived in the study area for 40 years. More male than female patients were married (84.6% vs. 53.6%, $\chi^2 = 157.1$, $p < 0.0001$) and divorce was more common among women than men (22.5% vs. 3.6%, $\chi^2 = 102.3$, $p < 0.0001$).

Table 1. Characteristics of interviewed patients (*n* = 1,319), Debre Eliyas and Dembecha w*oredas*, East and West Gojam zones, northern Ethiopia

Characteristics	Category	Men (*n* = 670)	Women (*n* = 649)	Total (*n* = 1,319)
Patients' average age in years (*n* = 1,314)	Mean (SD)	45.6 (14.6)	42.9 (13.8)	44.3 (14.3)
Age distribution in years (n= 1,314), *n* (%)	< 15 years	3 (0.4)	6 (0.9)	9 (0.7)
	15 - 24	39 (5.8)	47 (7.2)	86 (6.5)
	25 - 34	110 (16.4)	128 (19.7)	238 (18)
	35 - 44	161 (24.0)	152 (23.4)	313 (23.7)
	45 - 54	151 (22.5)	160 (24.7)	311 (23.6)
	55 - 64	123 (18.4)	102 (15.7)	225 (17.1)
	> 64 years	79 (11.8)	53 (8.2)	132 (10.0)
	15 - 64 years	584 (87.2)	589 (90.8)	1173 (88.9)
Patients' marital status, *n* (%)	Single	53 (7.9)	44 (6.8)	97 (7.4)
	Married	567 (84.6)	348 (53.6)	915 (69.4)
	Divorced	24 (3.6)	144 (22.2)	168 (12.7)
	Separated	1 (0.1)	5 (0.8)	6 (0.5)
	Widowed	14 (2.1)	100 (15.4)	114 (8.6)
Years lived in the area (*n* = 1,283)	Mean (SD)	42.3 (16.5)	37.1 (16.5)	39.7 (16.7)
Patients' level of education (*n* = 1,307), *n* (%)	Cannot read/ write	488 (72.8)	558 (86.0)	1046 (79.3)
	Primary level	80 (11.9)	51 (7.9)	131 (9.9)
	Secondary level	8 (1.2)	11 (1.7)	19 (1.4)
	College/university	0	1 (0.2)	1 (0.0008)
	Informal education	41 (6.1)	5 (0.8)	46 (3.5)
	Unknown level	47 (7)	17 (2.6)	64 (4.9)
Patients' occupation (*n* = 1,303), *n* (%)	Farming	601 (89.7)	382 (58.9)	983 (74.5)
	Housewife	NA	129 (19.9)	129 (9.8)
	Daily labourer	24 (3.6)	40 (6.2)	64 (4.9)
	Student	19 (2.8)	17 (2.6)	36 (2.7)
	Waiter	0	10 (1.5)	10 (0.8)
	Selling local beverage	1 (0.1)	23 (3.5)	24 (1.8)
	Land rental	1 (0.1)	11 (1.7)	12 (0.9)
	Unemployed	2 (0.3)	5 (0.8)	7 (0.5)
	Handcraft and weaving	5 (0.7)	7 (1.1)	12 (0.9)
	Others*	8 (1.2)	17 (2.6)	25 (1.9)

*__Others__: priest, begging, prostitute, shepherd, private business, retired and guard
SD – standard deviation

4.2.2. Prevalence and clinical characteristics

The prevalence of podoconiosis was found to be 3.3% (95% Confidence Interval (CI) = 3.2% to 3.6%) in people aged 15 years and above. The prevalence was 3.3% (95% CI = 3.1% to 3.6%) in Debre Eliyas and 3.4% (95% CI = 3.2% to 3.6%) in Dembecha w*oredas*. The male to female ratio was 0.98:1. More than 87% of the patients fell within the 15 to 64 year age group, and less than 2% were under the age of 15 years (**Table 2**).

Table 2 Prevalence of podoconiosis (*n* = 88,879)

Category	Population surveyed (age group ≥ 15 years)[#]	Number of households surveyed	Number of cases identified	Prevalence in among ≥ 15 years	Men to women ratio
Debre Eliyas	20,089	7,109	661	661/20, 089 = 3.3%	362/ 299 (1.2:1)
Dembecha	30,531	10,436	1,042	1,042/30, 531 = 3.4%	484/ 558 (0.9:1)
Total	51,017	17,553	1,704	1,704/51,017 = 3.3%	846/ 858 (0.98:1)

[#] The proportion the population of 15 years and above, by sex, was calculated based on the Ethiopian Central Statistics Authority Report: 55.5% for Debre Eliyas *woreda*, 58% for Dembecha *woreda*, and 57.4% for Amhara Region (Central Statistical Agency (Ethiopia) 2007).

The median age of onset of leg swelling was 22 years (range: 10 to 77 years). On average, patients sought treatment 5 years (SD = 6.9) after the start of the leg swelling, predominantly at health centres (39.8%) and from traditional healers (39.1%).

More study subjects had symmetric bilateral swelling than unilateral or asymmetric bilateral swelling. Most subjects had second or third clinical stage disease (**Table 3** and **Figure 8**). Nearly all (97.9%) patients had mossy lesions and 53% had open wounds on at least one of their legs.

Table 3 Clinical stages of podoconiosis among the study subjects

Clinical stage		Male (*n* = 611)	Female (*n* = 572)	Overall (*n* = 1,183)
Unilateral swelling, *n* (%)	Stage I	71 (11.6)	37 (6.5)	108 (9.1)
	Stage II	593 (97.1)	503 (87.9)	1,096 (92.6)
Bilateral and symmetric swelling, *n* (%)	Both legs stage I	26 (4.3)	12 (2.1)	38 (3.2)
	Both legs stage II	255 (41.7)	216 (37.8)	471 (39.8)
	Both legs stage III	147 (24.1)	172 (30.1)	319 (26.9)
	Both legs stage IV	68 (11.1)	63 (11.0)	131 (11.1)
Bilateral and asymmetric swelling, *n* (%)	One leg stage I, other leg stage II	18 (2.9)	12 (2.1)	30 (2.5)
	One leg stage I, other leg stage III	1 (0.2)	1 (0.2)	2 (0.2)
	One leg stage II, other leg stage III	59 (9.7)	47 (8.2)	106 (8.9)

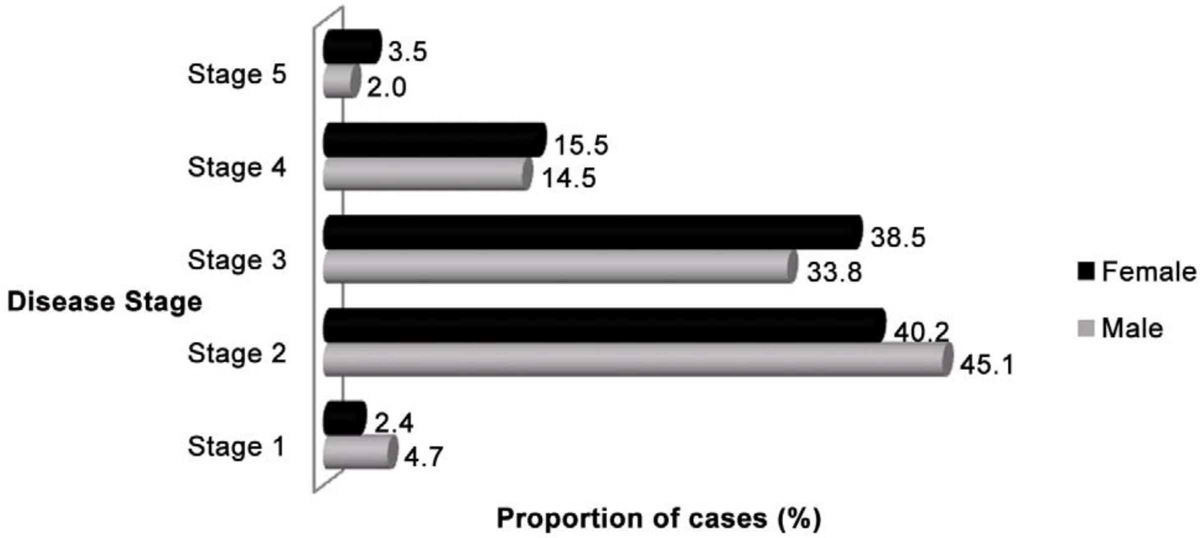

Figure 8. Clinical stages of podoconiosis among female and male patients in Debre Eliyas and Dembecha *woredas*, northern Ethiopia.

4.2.3. Features of acute adenolymphangitis (ALA)

On average, patients had five episodes of ALA per year and had 90 ALA morbidity days per year. Among patients who had ALA episodes more frequently than once per month (n = 323), 73.1% had ALA during the two weeks prior to the date of interview. Similarly, 94.4% of the ALA episodes reported in the year prior to the interview happened in the most recent six months. Nearly half of the participants (49.8%) had ALA during the interview. Physical examination of the interviewees that had ALA showed that hot (49.8%) and tender (60.2%) swelling, and inguinal lymphadenopathies (62.1%) were common features (**Table 4**).

Table 4. Features of acute lymphadenitis (ALA) in podoconiosis patients.

Feature	Category	Male	Female	Overall
Leg circumference (*n* = 922), n (%)	< 21 cm	18 (2.0)	9 (1.0)	27 (2.9)
	21 – 25 cm	147 (15.9)	123 (13.3)	270 (29.3)
	26 - 36 cm	334 (36.2)	361 (39.2)	695 (75.4)
	37 – 47 cm	50 (5.4)	59 (6.4)	109 (11.8)
	> 47 cm	2 (0.2)	1 (0.1)	3 (0.3)
Last time the patient had ALA, *n* (%)	Last 2 weeks (*n* = 323)	104 (32.2)	132 (40.9)	236 (73.1)
	Last 1 month (*n* = 557)	81 (14.5)	79 (14.2)	160 (28.7)
	Last 6 months (*n* = 557)	269 (48.3)	257 (46.1)	526 (94.4)
	Beyond 1 year (*n* = 392)	165 (42.1)	150 (38.3)	315 (80.4)
Sought treatment (*n* = 1,299), n (%)	Yes	325 (49.2)	311 (48.7)	636 (49.0)
	No	336 (50.8)	327 (51.3)	663 (51.0)
Season when symptoms of ALA get worse (*n* = 1,281), *n* (%)	Rainy and wet season	166 (25.7)	158 (24.9)	324 (25.3)
	Hot and dry season	358 (55.4)	340 (53.5)	698 (54.5)
	No specific season	122 (18.9)	134 (21.1)	256 (20.0)
ALA Precipitating factors, *n* (%)	Hard (laborious) work (*n* = 1,161)	167 (28.6)	168 (29.1)	335 (28.9)
	A little more than usual work (*n* = 992)	104 (21.1)	124 (24.8)	228 (23.0)
	Long walk (*n* = 992)	348 (70.6)	368 (73.7)	716 (72.2)
	Mitch (*n* = 167)	45 (51.7)	42 (48.3)	87 (52.1)
	Dust (*n* = 167)	10 (45.5)	12 (54.5)	22 (13.2)
Coping mechanism for ALA, *n* (%)	Resort to less exertion (*n* = 966)	234 (49.6)	193 (39.1)	427 (44.2)
	Stay in bed (*n* = 966)	237 (50.2)	300 (60.7)	537 (55.6)
	Using herb (*Hareg resa*) (*n* = 322)	36 (19.8)	30 (21.4)	66 (20.5)
	Using antibiotics (*n* = 322)	53 (29.1)	30 (21.4)	83 (25.8)
	Sleeping/nothing (*n* = 322)	27 (14.8)	25 (17.9)	52 (16.1)
	Washing (*n* = 322)	14 (7.7)	11 (7.9)	25 (7.8)
	Other (soaking in water, drinking alcohol, etc) (*n* = 322)	15 (8.2)	16 (11.4)	31(9.6)

Half of the study subjects (49%) that had ALA in the past one year (*n* = 1,299) sought treatment for the pain. The commonest treatment facilities visited were health centres (28.7%) and traditional healers (29.4%). Among patients that went to other places for the treatment of ALA (*n* = 196), most (80.6%) went to *tsebel* (holy water) places. Patients stated that on average they spent five days in bed during episodes of ALA.

Over half of the study participants (54.5%) said ALA commonly occurred during the hot and dry seasons, whereas 20% said the episodes were not season specific. The most common ALA precipitating factors mentioned by patients were long walks (72.2%), *mitch* (exposure to the sun inducing inflammation, 52.1%), laborious work (28.9%), and dust (13.2%). The most common coping measures employed by patients to reduce morbidity during episodes of ALA were staying in bed (55.6%), resorting to less laborious work (44.2%), use of antibiotics (25.8%) and *Hareg resa* (a local herb that is boiled generating steam that is inhaled by patients believed to have *mitch*, 20.5%).

4.2.4. Perceptions about the cause, prevention and control of podoconiosis

In the interviews, patients were asked what they thought caused podoconiosis. Many (41.3%) said they did not know the cause, while others conjectured barefoot walking (18%), heritability (7%), and exposure of feet to condensation (7.4%). Additional responses included a curse from God or the action of a witch, injury and *mitch.*

Patients were next asked whether they thought podoconiosis could be prevented and controlled. More than one third (37.5%) believed podoconiosis to be a preventable disease and 40.4% believed that disease progression could be controlled. The remaining respondents said they either ‘knew’ or ‘thought that’ podoconiosis could not be prevented (22.2% and 40.3%, respectively) or controlled (27.3% and 32.3%, respectively). Patients who believed that podoconiosis could be prevented mentioned the following methods of prevention: wearing shoes (82.1%), washing feet (19.1%), avoiding contact with an affected person (3.6%), and avoiding marriage to podoconiosis patients (1.3%). Medical intervention and *tsebel* (holy water) were mentioned by very few. Study participants who believed that progression of podoconiosis could be controlled mentioned the following possible methods: wearing shoes (87.0%), washing feet (17.6%), medical treatment (55.4%), and *tsebel* (35.7%). The reasons given by the study participants who thought that podoconiosis could not be controlled or cured were: absence of drugs for the disease (54%), having not seen a cured patient (51.9%), and because podoconiosis is hereditary (8.7%).

4.2.5. Perceptions about familial clustering of podoconiosis

Clustering of podoconiosis patients within a family was observed. A total of 40% of participants said that there were other patients in their family, of whom most were first (22.5%) or second (13.6%) degree relatives (**Figure 9**). When asked why there might be multiple affected members of one family, most (45.8%) said they did not know, 21% said because podoconiosis is contagious, 18.4% that it is hereditary and 9.6% that it is a curse on the family from God.

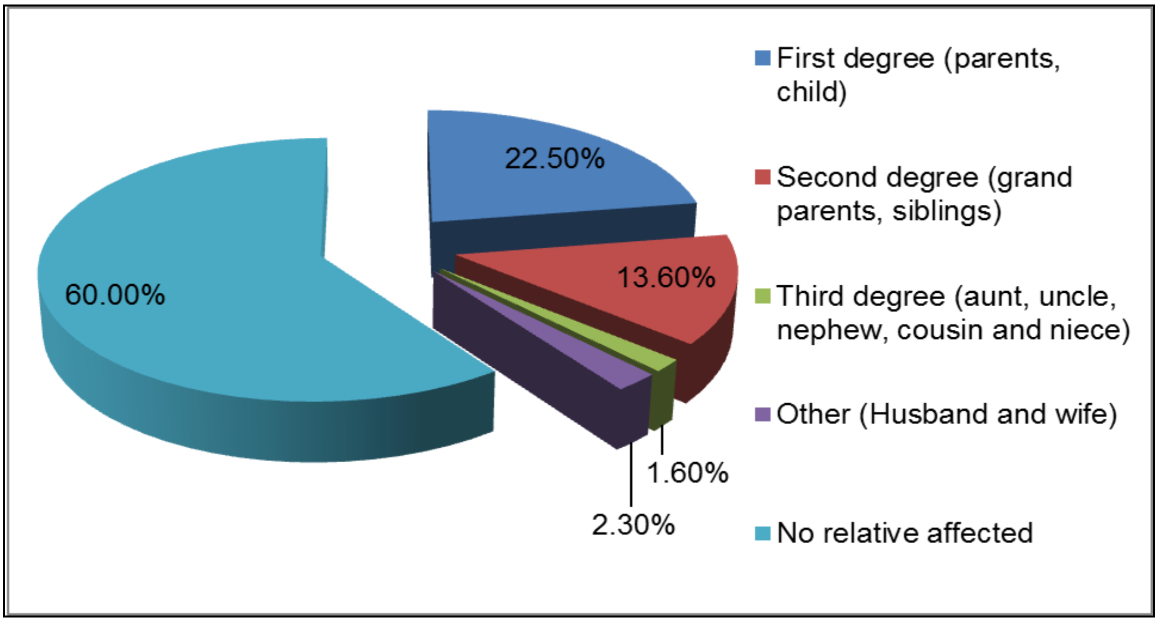

Figure 9. Familial clustering of podoconiosis, East and West Gojam zones, northern Ethiopia

4.2.6. Shoe-wearing, foot-washing and walking experience

The median ages of first use of shoes and socks in the area were 22 and 23 years, respectively. About 40% of the patients said that they had one pair of shoes. More men than women owned more than one pair of shoes (61.1% vs. 50.5%; $\chi^2 = 11.6$ $p = 0.001$). Most study participants suggested that they needed three pairs of shoes per year.

The types of shoes worn by the study participants at the time of interview were covered hard plastic (33.3%) followed by canvas (20.9%) and *berebaso/gilet* (open sandals locally made from tyres) (13.2%). During the interview, 23.6% of the respondents were observed to be barefoot of whom most (65.3%) were women. Men were more likely to wear open, non-protective shoes. There was no statistically significant association between gender and use of protective shoes ($p = 0.92$).

Based on patients' estimates, the average one-way walking time to the nearest water source for washing feet was 19 minutes (SD = 15.7). The average one-way walking time to the nearest field and nearest market were 20 minutes (SD = 14.9) and 54.5 minutes (SD = 50.1), respectively. On average, the respondents travelled to their nearest field and to market nine (SD = 10.9) and four (SD = 3.9) times per month, respectively.

On observation, 46.8% of patients had clean feet, 25.1% had dirty feet, 13.9% had cracked feet and 13.9% had both dirty and cracked feet. The reported average frequency of foot washing was seven times a week. There was no statistically significant difference between men and women in the frequency of foot washing ($p = 0.12$) and foot washing with soap ($p = 0.33$) (**Table 5**).

Table 5 Shoe wearing and foot washing experience of patients

Characteristics	Category	Male	Female	Total
Average age at first shoes	Mean (SD)	25.4 (12.6)	24.9 (13.6)	25.2 (13.1)
Average age at first socks	Mean (SD)	25.6 (12.7)	22.4 (15.2)	24.3 (13.9)
Number of pairs of shoes owned (*n* = 1,168), *n* (%)	None	44 (7.3)	87 (15.4)	131 (11.2)
	One pair	218 (36.1)	236 (41.8)	454 (38.9)
	Two pairs	237 (39.2)	169 (26)	406 (34.8)
	Three pairs	83 (13.7)	58 (10.3)	141 (12.1)
	Four Pairs	18 (3.0)	13 (2.3)	31 (2.7)
	More than four pairs	4 (0.7)	1 (0.2)	5 (0.5)
Number of pairs of shoes needed (*n* = 1,177), *n* (%)	One pair	25 (4.1)	26 (4.6)	51 (4.3)
	Two pairs	171 (28.0)	171 (30.2)	342 (29.1)
	Three pairs	210 (34.4)	179 (31.6)	389 (33.1)
	Four pairs	151 (24.7)	142 (25.1)	293 (24.9)
Times when patients do not wear shoes (*n* = 1,170), *n* (%)	During farming	145 (24.1)	50 (8.8)	195 (16.7)
	During non-farming work	132 (22.0)	52 (9.2)	184 (15.7)
	At home	153 (25.5)	200 (35.2)	353 (30.2)
	I am usually barefoot	100 (16.6)	160 (28.2)	260 (22.2)
	I am always barefoot	71 (11.8)	106 (18.7)	177 (15.1)
Feet cleanliness at the time of interview (*n* = 1,287), *n* (%)	Clean and intact	331 (50.2)	274 (43.4)	605 (46.8)
	Dirty	147 (22.3)	177 (28)	324 (25.1)
	Cracked	80 (12.1)	99 (15.7)	179 (13.9)
	Dirty and cracked	99 (15.0)	80 (12.7)	179 (13.9)
Average frequency of foot washing per week	Mean (SD)	6.8 (2.1)	6.9 (2.2)	6.8 (2.1)
Use soap for washing feet (*n* = 1,302), *n* (%)	Yes	407 (61.9)	424 (65.9)	831 (63.8)
	No	250 (38.1)	219 (34.1)	469 (36.0)
Average frequency of foot washing with soap per week	Mean (SD)	5.2 (2.9)	5.1 (3.1)	5.2 (3.0)
SD - standard deviation				

4.2.7. Social stigma

Approximately 13% of patients mentioned that they had experienced one or more forms of social stigmatization at school, church, or in the market place. The various forms of stigmatization and the locations at which these were experienced are described in **Table 6**. There was a statistically significant difference between men and women in exclusion from marriage and shunning within marriage (0.8% vs. 3.6%, X^2 = 12.7, p < 0.0001), but there was no statistically significant difference between men and women for any other experience of stigma.

Table 6. Types of stigma experienced by study subjects in East and West Gojam zones, northern Ethiopia.

Type of stigma (*n* = 1303)	**Places**					
	School	**Church**	**Marriage**	**Market**	**Feast/ Holiday Gathering**	**Non-specific**
School drop - out	17 (1.3%)					
Forced exclusion		25 (1.9%)	22 (1.7%)		40 (3.1%)	
Not buying their products				26 (2%)		
Shunning	14 (1.1%)	33 (2.5%)	18 (1.4%)		29 (2.2%)	
Pointing at them	5 (0.4%)	25 (1.9%)	2 (0.2%)		10 (0.8%)	
Pinching nose	3 (0.2%)	19 (1.5%)	0 (0%)		13 (1%)	
Insulting						19 (1.5%)
Total	**39 (3.0%)**	**102 (7.8%)**	**42 (3.2%)**	**26 (2.0%)**	**92 (7.1%)**	**19 (1.5%)**

4.2.8. Physical and productivity impairments

We assessed patient perception of the effect of podoconiosis on physical activity and economic productivity. Many (60.1%) said that their movement was impaired by podoconiosis and 26.9% said their movement was frequently impaired by episodes of ALA. More than half (55.0%) of women claimed their household chores were affected by podoconiosis, and 30.9% that chores were affected by ALA. Similar proportions of men said their daily activities were impaired by podoconiosis (59.5%) and ALA (23.6%).

Many participants (36.8%) believed that podoconiosis reduced the energy with which they could work, 38.2% stated that it reduced their working hours, and 35.0% stated that it increased work absenteeism. Several patients thought that their productivity had declined (24.6%), and 16.6% believed that this meant they could not earn as much income as podoconiosis-free individuals in their community. The coping strategies adopted by patients to mitigate the physical impairment caused by podoconiosis included: working only occasionally (44.9%), avoiding physically demanding tasks (32.4%), working shorter hours (21.9%) or completely stopping work (8.0%). Almost all (96.4%) patients said they had experienced a decline in their income following the development of podoconiosis. When asked to rate their income compared to their healthy neighbours, 78.0% said they were poorer.

4.3. Chapter summary

A cross-sectional household survey was conducted in Debre Eliyas and Dembecha *woredas* (districts) in East and West Gojam zones, respectively. The survey covered all 17,553 households in 20 *kebeles* (administrative subunits) randomly selected from the two *woredas*. A detailed structured interview was conducted on 1,704 cases of podoconiosis identified in the survey. The prevalence of podoconiosis in the population aged 15 years and above was found to be 3.3% (95% CI, 3.2% to 3.6%). 87% of cases were in the economically active age group (15-64 years). More male as compared to female patients were married (84.6% vs. 53.6%, X^2 = 157.1, p < 0.0001) while more female as compared to male patients were divorced (22.5% vs. 3.6%, X^2 = 102.3, p < 0.0001).

On average, patients sought treatment five years after the start of the leg swelling. Most subjects had second (42.7%) or third (36.1%) clinical stage disease, 97.9% had mossy lesions, and 53% had open wounds. On average, patients had five episodes of acute adenolymphangitis (ALA) per year and spent a total of 90 days per year with ALA. The median age of first use of shoes and socks were 22 and 23 years, respectively. More men than women owned more than one pair of shoes (61.1% vs. 50.5%; X^2 = 11.6, p = 0.001). At the time of interview, 23.6% of the respondents were barefoot, of whom about two-thirds were women.

Less than half of the study subjects believed podoconiosis could be prevented (37.5%) or controlled (40.4%) and many (41.3%) did not know the cause of podoconiosis. Two-fifths of the study subjects had a relative affected with podoconiosis. Approximately 13% of the respondents had experienced one or more forms of social stigmatization. The coping strategies adopted by patients to mitigate the physical impairments caused by podoconiosis were: working only occasionally (44.9%), avoiding physically demanding tasks (32.4%), working fewer hours (21.9%) or completely stopping work (8.0%). Most study subjects (96.4%) had noticed a decline in their income following the development of podoconiosis, and 78% said they were poorer than their healthy neighbours.

This study showed high prevalence of podoconiosis and associated morbidities such as ALA, mossy lesions and open wounds in northern Ethiopia. The predominance of cases at an early clinical stage of podoconiosis indicates the potential for reversing the swelling and calls for disease prevention interventions. Moreover, the study shows that podoconiosis has strong psychosocial, physical and economic impacts on patients in the East and West Gojam zones of northern Ethiopia. Concerns related to familial clustering, poor understanding of the causes and prevention of podoconiosis all add to the physical burden imposed by the disease. Strategies that may ease the impact of podoconiosis include delivery of tailored health education on the causes and prevention of disease, involving patients in intervention activities, and development of alternative income - generating activities for treated patients.

5. Chapter 5- Individual correlates of podoconiosis

The previous chapter detailed the baseline survey which showed the magnitude of podoconiosis and patients' perceptions surrounding the disease. The baseline survey also enabled us to broadly categorize the study area into different levels of podoconiosis endemicity. Next, we conducted a case-control design study with the goal of understanding the individual level covariates for developing podoconiosis at areas with varying levels of disease endemicity as defined by the baseline survey. For this purpose, a new house-to-house podoconiosis prevalence survey followed by in-depth interviews of cases and controls was conducted. In addition to comparing cases with controls, basic differences were assessed by comparing controls residing in different areas. The present chapter describes the methods and processes of the case-control study and describes the findings with emphasis on the most important individual level covariates for development of podoconiosis.

5.1. Methods

A conceptual framework that illustrates the relationship between individual level correlates for podoconiosis was developed based on current understanding **(Figure 10**). At an individual level the factors were classified into four main categories: socio-demographic, behavioural, history of the disease and history of foot-soil exposure. Indeed, some of the factors are inter-related (indicated by arrows) and one factor cannot be the sole reason for the development of the disease. In addition, some factors may be both a risk factor for and a result of, the development of the disease.

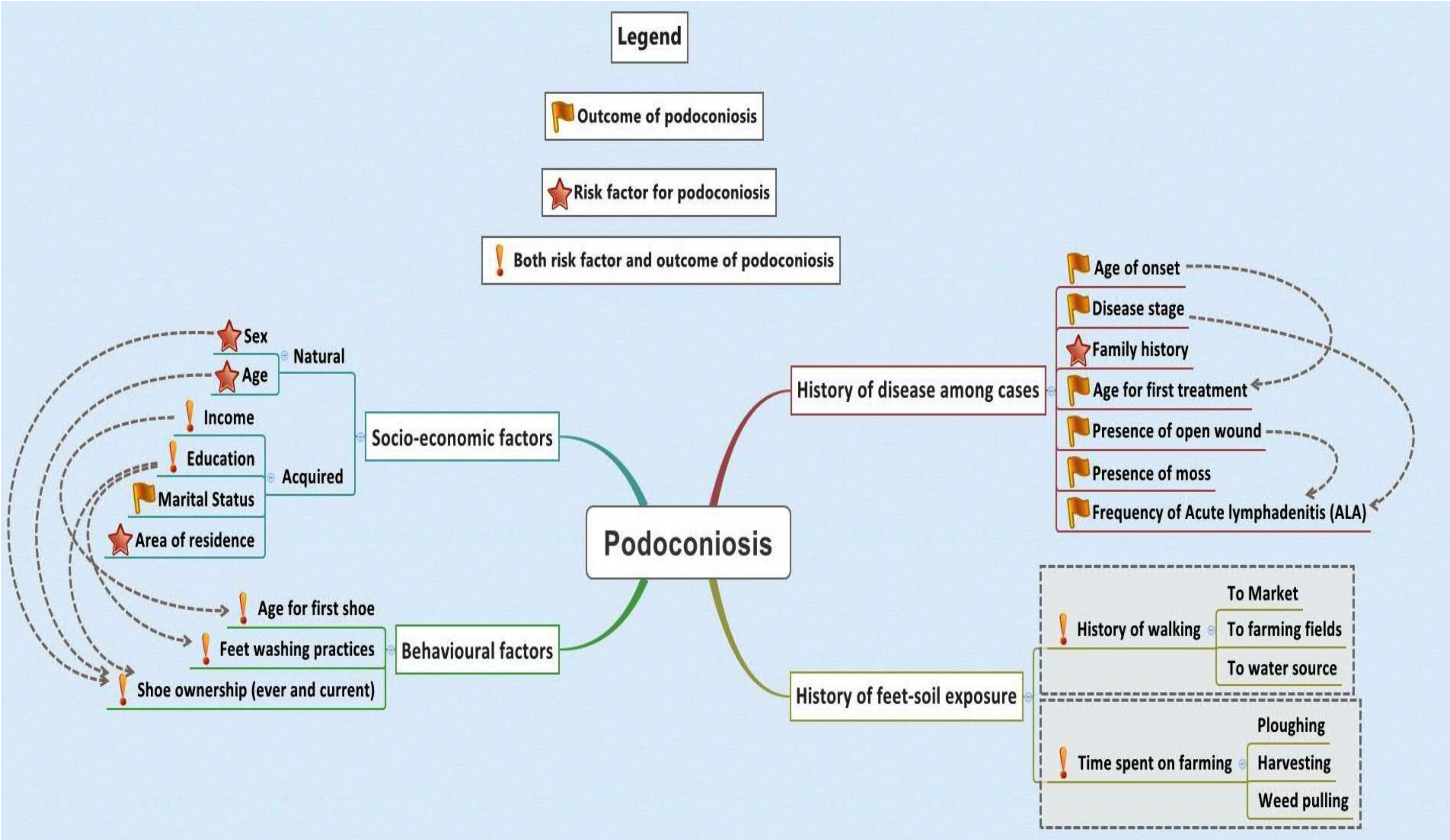

Figure 10. Conceptual framework describing the potential relationships between individual level correlates and podoconiosis.

5.1.1. Study area

The study was conducted in East Gojam zone, a zone with more than 2.1 million inhabitants in northern Ethiopia. The previous chapter (chapter 4) showed the prevalence of podoconiosis in East Gojam zone to be 3.3%. Based on Price's environmental and behavioural risk factors for podoconiosis (Price 1974; Price 1984; Price and Bailey 1984) (i.e., altitude above 1000 m asl, annual rainfall above 1000 mm, and land farmed and lived on by people who do not wear shoes consistently and daily), we identified six rural *kebeles* (the smallest administrative units in Ethiopia with an average population of 5000 people) as study areas. The six *kebeles* were Gedamawit Zuria, Gidimbel Tsyhon, Zhigamera Yeted, and Woleke from Gozamn and Sinan *woredas* (government administrative unit, similar to a district), and Qerer and Yewlana Akababiwu from Machakel w*oreda* (See **Figure 11**). All six *kebeles* lay between 2135 and 3142 m asl. Since no published report existed on the prevalence of podoconiosis in these *kebeles*, we interviewed the District Health Office heads and head of the International Orthodox Christian Charities' Podoconiosis Project in Debre Markos to ascertain an estimate of podoconiosis cases from these *kebeles*. We also followed up reports of cases from these *kebeles* by the local health extension workers for three months. Both the interviews and follow-up reports suggested that Qerer and Yewlana Akababiwu had the largest number of podoconiosis cases, and were provisionally classified as "high" endemicity. Gidimbel Tsyhon, Zhigamera Yeted, and Woleke had "medium" endemicity, whilst Gedamawit Zuria had very few cases, and hence was classified as "low" endemicity. This provisional classification of the study areas was validated by a house-to-house survey of podoconiosis conducted in all 7202 households in 83 villages within the six *kebeles*. The survey showed the *kebele* level prevalence of podoconiosis to be above 5%, 1-5%, and below 1% in the ‘high’, ‘medium’ and ‘low’ endemicity *kebeles*, respectively. The presence of a spatial pattern in the distribution of podoconiosis was supported by village level prevalence values (**Figure 11**).

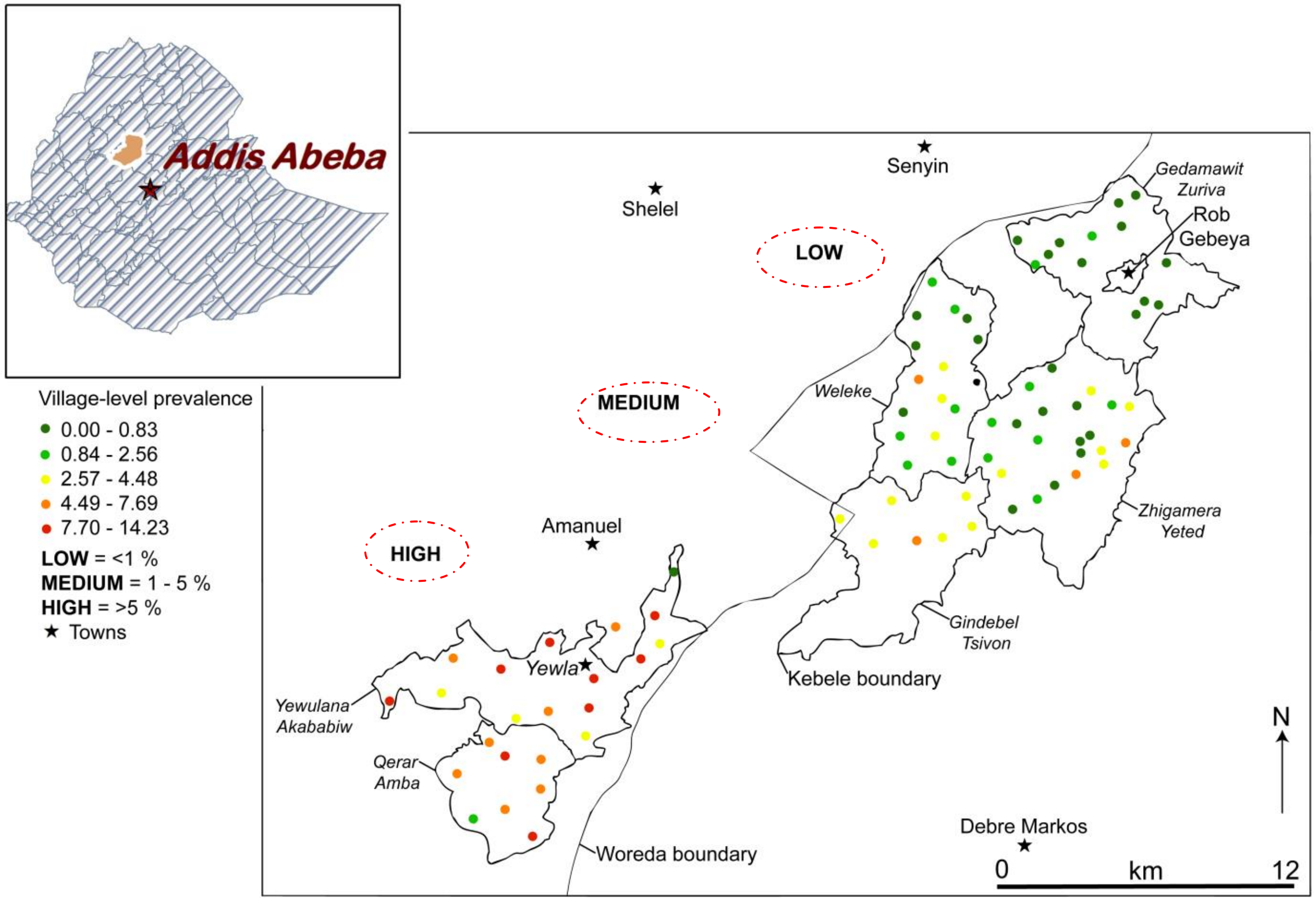

Figure 11. Study area used for individual level correlates and spatial patterns of village level podoconiosis prevalence in east Gojam province in Ethiopia.

5.1.2. Study design, sample size, and data collection procedures

In the present study individuals with podoconiosis living in areas with three different levels of podoconiosis prevalence were compared with podoconiosis-free controls from the same areas. Therefore, a case-control study was carried out, with cases identified initially through local census. A case was defined as an individual clinically confirmed to have podoconiosis by a trained HEW or nurse. A control was an individual living in the household closest to the case, and clinically demonstrated not to have podoconiosis (Desta, Ashine et al. 2007).

A minimum sample size calculation was used to estimate the sample size required to identify a given difference between means (Bernard 2005), assuming that the mean age of first wearing shoes was 22.9 years (SD = 15.9 years) among cases (Alemu, Tekola Ayele et al. 2011): 261 cases and 261 controls in each area were estimated to give 80% power (Z_β = 0.84) to detect a difference in first shoe use of 4 years with 95% confidence level (Z_α = 1.96). The statistical formula used was:

$$n = \frac{2\sigma^2 (Z_\beta + Z_{\alpha/2})^2}{\text{difference}^2}$$

Where:

n=Sample size in each group (assumes equal sized groups)

σ=Standard deviation of the outcome variable

Zβ=Represents the desired power (typically .84 for 80% power)

Difference= Effect Size (the difference in means)

Zα=Represents the desired level of statistical significance (typically 1.96)

Data were collected by health extension workers (HEWs) and nurses who were trained to identify and examine podoconiosis cases at the IOCC Podoconiosis Project. First, the HEWs who lived with the community conducted house-to-house visits in the six selected kebeles to identify podoconiosis cases. During the house-to-house visits, the HEWs asked the head of the household whether there was a podoconiosis affected individual using locally known terminologies and by displaying a picture of podoconiosis affected leg. When the head of the household confirmed that there is a household member with podoconiosis or swollen lower leg, the HEWs conducted in depth interview regarding the onset and progression of the disease (Appendix 6). Next, they conducted physical examination of the feet and legs according to a clinical staging system developed for podoconiosis (Appendix 6) and exclude cases with leprosy or filarial lymphoedema. When an individual(s) fulfil(s) the criteria outlined for podoconiosis during patient history taking and physical examination, the individual's name, age, sex, and address was recorded and passed to the field nurses. Following this, the nurses confirmed identified cases and interviewed only one patient from every household with one or more podoconiosis cases. In households where more than one podoconiosis case was encountered, the oldest individual was selected. After enrolling and interviewing a podoconiosis case, a control was recruited from the nearest unaffected household. All interviewed individuals had lived in the area for at least ten years to ensure they were not misclassified for area of residence (refer to **Table 7** below for case and controls selection criteria). The data collection tool was a structured questionnaire that included questions about socio-demographic characteristics, shoe wearing habits and current practices; foot washing practices, time spent walking and clinical history, and clinical examination of podoconiosis patients. The tool was translated into Amharic and pre-tested in Debre Markos town.

Table 7 - Case and control definition and selection criteria

Characteristics	Case	Control
Definition	An individual diagnosed by a trained nurse and a health extension worker (HEW) to have podoconiosis. Diagnosis was made when an individual in endemic areas fulfils all of the following diagnostic criteria: history of burning sensation on the feet when the swelling started; visible bilateral swelling that started from feet and progressed upwards; at least with stage I of the five validated clinical stages of podoconiosis (Appendix 6); and no known clinical signs and symptoms of leprosy or lymphatic filariasis (Appendix 6).	An individual with no past or current history, signs and symptoms of podoconiosis as diagnosed by a trained nurse and HEW.
Household	Any household with podoconiosis cases	The nearest household to an identified podoconiosis case
Permanent resident	A person that has lived in the area at least for ten years	A person that has lived in the area at least for ten years
Age	The oldest podoconiosis case in the household; minimum age 15 years	The oldest person without podoconiosis in the household; minimum age 15 years
Sex	Can be either male or female	Can be either male or female
Note: Podoconiosis diagnosis was made by excluding other differential diagnosis. A standard training material developed by Prof Gail Davey was used to train nurses and HEW (**Appendix 6**).		

5.1.3. Data analysis

Data were entered, cleaned and analysed using IBM SPSS version 17 and R version 2.15. Univariate, multivariate and correlation analyses were undertaken and their significance was tested using the chi-square (X^2) test, *t*- test and ANOVA. The level of confidence was set at $\alpha = 0.05$. Bivariate and multivariate analyses were applied to several variables. The chi-square (X^2) test was used to compare disease status (i.e., being a podoconiosis case or control) for the categorical variables (sex, marital status, education, shoe-wearing history, shoe-wearing at time of interview and foot cleanliness by observation,). The *t*-test and ANOVA were used for the continuous variables (age, income, age at first wearing shoes, and time spent farming and walking) for comparing study subjects by disease status, sex and area of residence (i.e. 'high', 'medium' and 'low' endemicity). A forward stepwise conditional logistic regression analysis was applied to all variables, except age, which was excluded due to the large positive correlation between age of the individual and age at first wearing shoes ($r = 0.8$). The median age of onset for podoconiosis among study subjects was 30 years. Therefore, we used 30 years of age as a threshold for categorizing individuals as those starting footwear before or after the average age of onset for podoconiosis. A composite indicator to assess foot-soil contact was calculated for each study subject. This indicator summarized the product of time taken and frequency of travel to the nearest field, the furthest field, the nearest water source and the regular market.

5.2. Results

5.2.1. Socio-demographic characteristics

A total of 7202 households were visited and 611 individuals affected by podoconiosis (331 men and 280 women) were identified in 463 households. In total, 460 cases and 707 controls were included, giving a total of 1167 study subjects: 255 cases and 258 controls from ‘high’ endemicity *kebeles*, 193 cases and 195 controls from ‘medium’ endemicity *kebeles* and 12 cases and 254 controls from the ‘low’ endemicity *kebeles*. The *kebele* level prevalence was: ‘low’ for Gedamawit Zuria (0.5%); ‘medium’ for Woleke (3.3%), Gidimbel Tsyhon (4.2%) and Zhigamera Yeted (2.8%); and ‘high’ for Qerer (8.5%) and Yewlana Akababiwu (9.7%). The few cases identified in the ‘low’ endemicity area may have been the result of travel to nearby ‘medium’ or ‘high’ endemicity areas, since they were identified in villages close to the *kebele* boundaries. The female-to-male ratio was 1.1:1 (243/217) among cases, 0.6:1 (270/437) among controls, and 0.8:1 (513/654) among all study subjects. On average, controls were younger than cases (mean age difference = 10 years, $t = 10.9$, $p < 0.0001$).

On average, a case earned 62 birr (~ $3) per month less than a control ($t = -4.4$, $p <$ 0.0001). Affected women earned less than affected men ($t = 3.2$, $p = 0.001$). There was a statistically significant difference in the proportion of cases and controls that had ever gone to school: fewer cases than controls had ‘ever’ gone to school (27.9% vs. 40%, $X^2 = 17.9$, $p < 0.0001$). **Table 8** shows the socio-demographic characteristics of all study subjects. Marital status was classified into married and unmarried (single, divorced, separated or widowed), and cases and controls were compared. Unmarried people had three times greater odds of disease than married people (Odds ratio (OR) = 3.4, 95% CI = 2.6 to 4.6, $p < 0.0001$). Stratified analysis by sex among cases showed that affected women had greater odds of being unmarried than affected men (OR = 3.7, 95% CI = 2.4 to 5.5, $p < 0.0001$) (**Table 8**).

Table 8 Socio-demographic characteristics of cases and controls

Characteristics	Category	Cases			Controls		
		Men (*n* = 217)	**Women** (*n* = 243)	**Total** (*n* = 460)	**Men** (*n* = 437)	**Women** (*n* = 270)	**Total** (*n* = 707)
Endemicity of area (*n* = 1167)	'High'	111 (51.2)	144 (59.3)	255 (55.4)	127 (29.1)	131 (48.5)	258 (36.5)
	'Medium'	97 (44.7)	96 (39.5)	193 (42.0)	141 (32.3)	54 (20)	195 (27.6)
	'Low'	9 (4.1)	3 (1.2)	12 (2.6)	169 (38.7)	85 (31.5)	254 (35.9)
Age distribution (*n* = 1167)	Mean (± SD)	52.29 (± 16.5)	50.76 (± 15.8)	51.48 (± 16.1)	43.79 (± 14.2)	37.56 (±13.6)	41.41 (±14.3)
	Median (Min-Max)	55 (14 - 80)	50 (11 - 85)	52 (11 - 85)	42 (14 - 80)	35 (15-90)	40 (14 - 90)
Age group distribution (*n* = 1167)	< 15 years	1 (0.5)	2 (0.8)	3 (0.7)	1 (0.2)	0	1 (0.1)
	15 - 64 years	152 (70.0)	188 (77.4)	340 (73.9)	391 (89.5)	260 (96.3)	651 (92.2)
	> 64 years	64 (29.5)	53 (21.8)	117 (25.4)	45 (10.3)	10 (3.7)	55 (7.8)
Have ever gone to school (*n* = 1161)	Yes	96 (44.2)	32 (13.2)	128 (27.9)	236 (54.1)	45 (16.9)	281 (40)
	No	121 (55.8)	210 (86.8)	331 (72.1)	200 (45.8)	221 (83.1)	421 (60)
Level of education (*n* = 408)	Informal	80 (36.9)	20 (62.5)	100 (77.5)	190 (80.9)	12 (27.3)	202 (72.4)
	Primary	14 (14.4)	10 (31.3)	24 (18.6)	32 (13.6)	21 (47.7)	53 (19)
	Secondary	3 (3.1)	2 (6.3)	5 (3.9)	13 (5.5)	8 (18.2)	21 (7.5)
	College/diploma	0	0	0	0	2 (4.5)	2 (0.7)
	University	0	0	0	0	1 (2.3)	1 (0.4)
Occupation (*n* = 1164)	Farmer	193 (88.9)	125 (51.4)	318 (69.1)	414 (94.7)	171 (63.3)	585 (82.7)
	Housewife	0	64 (26.3)	64 (13.9)	0	64 (23.7)	64 (9.1)
	Retired	5 (2.3)	17 (7.0)	22 (4.8)	5 (1.1)	7 (2.6)	12 (1.7)
	Unemployed	6 (2.8)	13 (5.3)	19 (4.1)	5 (1.1)	4 (1.5)	9 (1.3)
	Merchant	1 (0.5)	11 (4.5)	12 (2.6)	2 (0.5)	5 (1.9)	7 (1)
	Student	5 (2.3)	2 (0.8)	7 (1.5)	5 (1.1)	4 (1.5)	9 (1.3)
	Others	5 (2.3)	11 (4.5)	16 (3.5)	6 (1.4)	14 (5.2)	20 (2.8)
Marital status (*n* = 1167)	Single	25 (11.5)	11 (4.5)	36 (7.8)	18 (4.1)	17 (6.3)	35 (5.0)
	Married	173 (79.7)	126 (51.9)	299 (65)	410 (93.8)	201 (74.4)	611 (86.4)
	Divorced	3 (1.4)	26 (10.7)	29 (6.3)	4 (0.9)	20 (7.4)	24 (3.4)
	Separated	3 (1.4)	10 (4.1)	13 (2.8)	2 (0.5)	11 (4.1)	13 (1.8)
	Widowed/er	13 (6.0)	70 (28.8)	83 (18)	3 (0.7)	21 (7.8)	24 (3.4)
Income distribution	Mean (± SD)	323.17 (± 213.3)	255.32 (± 198.2)	288.79 (± 208.3)	351.29 (± 238.6)	349 (± 212.1)	350 (± 229.5)
	Median(Min - Max)	300 (0 - 1000)	200 (0 - 1000)	250 (0 - 1000)	300(0 - 1500)	300 (0 -1100)	300 (0 -1500)

5.2.2. Covariates for controls living in varying podoconiosis endemic areas

The socio-demographic and other characteristics of controls living in the three different levels of podoconiosis endemicity were compared to assess the existence of basic differences among these groups (**Table 9**). Comparing the average income, there was no statistically significant difference between controls living in 'high' and 'low' endemicity areas (mean difference = 21.8, $t = 1.2$, $p = 0.231$), whereas a significant difference in income was observed after adjusting for sex. In general, controls living in the 'medium' endemicity area earned less than controls living in 'high' or 'low' endemicity areas. There was no difference in marital status among controls by area of residence. The age distribution showed women living in the 'low' endemicity area to be older than women in 'high' and 'medium' endemicity areas ($f = 15$, $p < 0.001$), but there was no significant difference among men living in different areas ($f = 3.9$, $p = 0.084$). Differences in travel time and frequency to market were observed by area of residence, whereas no differences were found in 'ever' going to school or use of protective shoes. More female controls were interviewed in endemic areas, where more affected women were also identified. In these areas, however, fewer farmers and more housewives were found.

Table 9. Univariate and multivariate analysis of covariates for controls living in podoconiosis 'high, 'medium' and 'low' endemic areas

Variable	Category	'High'	'Medium'	'Low'	High vs Medium	High vs Low	Medium vs Low
					OR (95% CI), *p value*	**OR (95% CI), *p value***	**OR (95% CI), *p value***
Sex	Male	127 (49.2%)	141 (72.3%)	169 (66.5%)	1	1	1
	Female	131 (50.8%)	54 (27.7%)	85 (33.5%)	2.69 (1.81 - 4.01), $p < 0.0001$*	2.05 (1.44 - 2.93), $p < 0.0001$*	0.76 (0.51 - 1.15), $p = 0.190$
Marital status	Married	215 (83.3%)	171 (87.7%)	225 (88.6%)	1	1	1
	Unmarried	43 (16.7%)	24 (12.3%)	29 (311.4%)	1.04 (0.59 - 1.84), $p = 0.891$	1.18 (0.69 - 2.02), $p = 0.53$	1.26 (0.68 - 2.31), $p = 0.463$
Occupation	Farmer	169 (65.8%)	179 (91.8%)	237 (93.3%)	1	1	1
	House wives	54 (21.0%)	6 (3.1%)	4 (1.6%)	9.53 (3.99 - 22.74), $p < 0.0001$*	18.93 (6.73 - 53.28), $p < 0.0001$*	1.99 (0.55 - 7.14), $p = 0.293$
	Non-farmer	34 (13.2%)	10 (5.1%)	13 (5.1%)	3.60 (1.73 - 7.52), $p = 0.001$*	3.67 (1.88 - 7.16), $p < 0.0001$*	1.02 (0.44 - 2.38), $p = 0.966$
'Ever' go to school	Yes	85 (33.5%)	86 (44.3%)	110 (43.3%)	1	1	1
	No	169 (66.5%)	108 (55.7%)	144 (56.7%)	1.18 (0.78 - 1.78), $p = 0.434$	1.22 (0.83 - 1.79), $p = 0.317$	1.09 (0.72 - 1.65), $p = 0.680$
'Ever' own shoe	Yes	105 (40.7%)	92 (47.2%)	167 (65.7%)	1	1	1
	No	153 (59.3%)	103 (52.8%)	87 (34.3%)	1.02 (0.687 - 1.52), $p = 0.914$	2.50 (1.73 - 3.62), $p < 0.0001$*	3.06 (1.96 - 4.78), $p < 0.0001$*
Wore protective shoe	Protective	36 (14.0%)	22 (11.3%)	52 (22.9%)	1	1	1
	Non-protective	221 (86.0%)	172 (88.7%)	175 (77.1%)	0.64 (0.35 - 1.14), $p = 0.129$	1.57 (0.97 - 2.53), $p = 0.068$	2.65 (1.52 - 4.61), $p = 0.001$*
Observed feet cleanliness	'Clean and intact'	178 (69.0%)	116 (59.5%)	160 (63.0%)	1	1	1
	'Dirty'	62 (24.0%)	25 (12.8%)	57 (22.4%)	1.74 (1.02 - 2.96), $p = 0.042$*	0.99 (0.65 - 1.51), $p = 0.952$	0.59 (0.35 - 1.01), $p = 0.056$
	'Cracked'	13 (5.0%)	14 (7.2%)	15 (5.9%)	0.79 (0.35 - 1.79), $p = 0.578$	0.80 (0.37 - 1.75), $p = 0.578$	1.26 (0.58 - 2.72), $p = 0.557$
	'Dirty and cracked'	5 (1.9%)	40 (20.5%)	22 (8.7%)	0.09 (0.03 - 0.23), $p < 0.0001$*	0.24 (0.09 - 0.66), $p = 0.006$*	2.43 (1.37 - 4.32), $p = 0.003$*

Table 9. Continued

Variable	Category	'High'	'Medium'	'Low'	High vs Medium	High vs Low	Medium vs Low
		Mean (SD)	**Mean (SD)**	**Mean (SD)**	**t, mean difference, *p value***	**t, mean difference, *p value***	**t, mean difference, *p value***
Age distribution	Male	42.17 (12.56)	42.39 (14.53)	46.18 (14.86)	- 0.13, - 0.22, $p = 0.896$	-2.51,-4.00, $p = 0.013$*	-2.26,-3.79, $p = 0.024$*
	Female	34.65 (10.60)	34.93 (11.42)	43.73 (16.61)	-0.16,-0.28, $p = 0.879$	-4.91,-9.08, $p < 0.0001$*	-3.41,-8.80, $p < 0.0001$*
Average monthly income	Male	474.55 (215.18)	232.27 (175.81)	356.52 (253.18)	9.8, 242.27, $p < 0.0001$*	4.09, 118.03, $p < 0.0001$*	-4.74, -124.24, $p < 0.0001$*
	Female	357.87 (197.75)	233.45 (190.92)	400.75 (225.41)	3.39, 124.42, $p = 0.001$*	-1.34,-42.88, $p = 0.181$	-3.86,-167.29, $p < 0.0001$*
Average age for first shoes	Male	27.28 (10.73)	28.00 (11.75)	31.34 (13.15)	-0.36, -0.72, $p = 0.717$	-1.99, -4.06, $p = 0.048$*	-1.94, -3.34, $p = 0.054$
	Female	22.66 (13.11)	31.50 (12.02)	32.88 (16.19)	-0.94, -8.84, $p = 0.354$	-3.16,-10.22, $p = 0.002$*	0.39, -1.38, $p = 0.907$
Frequency of feet washing per week	Male	8.05 (2.41)	7.21 (2.40)	6.90 (1.42)	2.84, 0.84, $p = 0.005$*	5.09, 1.14, $p < 0.0001$*	1.37, 0.30, $p = 0.172$
	Female	9.21 (3.33)	8.63 (3.35)	8.98 (3.67)	1.08, 0.58, $p = 0.280$	0.49, 0.24, $p = 0.624$	-0.56, -0.35, $p = 0.575$
Average distance to regular market	Male	96.21 (42.74)	135.12 (57.29)	36.94 (24.45)	-6.09, -38.91, $p < 0.0001$*	14.67, 59.27, $p < 0.0001$*	18.85, 98.18, $p < 0.0001$*
	Female	78.62 (46.52)	161.63 (47.36)	27.64 (20.69)	-10.52, -83.01, $P < 0.0001$*	10.61, 50.98, $p < 0.0001$*	18.69, 133.99, $P < 0.0001$*
Frequency of travel to regular market	Male	3.29 (1.59)	3.68 (2.09)	6.31 (2.82)	-1.63, -0.38, $p = 0.104$	-10.46, -3.01, $p < 0.0001$*	-9.09, -2.63, $p < 0.0001$*
	Female	3.86 (2.22)	3.42 (2.22)	6.47 (2.19)	1.37, 0.44, $p = 0.173$	-8.77, -2.60, $p < 0.0001$*	-7.59, -3.05, $p < 0.0001$*
Average time spent on farming	Male	9.67 (2.09)	10.68 (1.53)	10.47 (1.79)	-4.36, -1.02, $p < 0.0001$*	-3.37, -0.81, $p = 0.001$*	1.01, 0.21, $p = 0.277$
	Female	8.40 (3.94)	5.71 (3.71)	4.44 (2.48)	3.99, 2.69, $p < 0.0001$*	7.31, 3.96, $p < 0.0001$*	2.19, 1.27, $p = 0.031$*
Note: all variables were adjusted for sex							

5.2.3. Covariates for both cases and controls

Each variable was assessed using univariate logistic regression analysis. Next, forward conditional logistic regression analysis was applied to all covariates except age (age and age of first wearing shoes were correlated, $r = 0.8$). This was a stepwise regression analysis starting from one covariate and then adding the most significant variables at each step. The variables that were in the final model were: sex, marital status, current shoe ownership, wearing non-protective shoes, state of feet at the interview, wearing of shoes before the age of 30 years, time walked to regular market and frequency of travel to the regular market. Of all these covariates, sex, marital status, wearing non-protective shoes, having 'cracked' feet, not wearing shoes before age 30 (the average age of onset of podoconiosis), and travel time to regular market remained strongly associated with disease status (**Table 10**).

Table 10. Univariate and multivariate analyses of covariates for cases and controls

Variable	Category	Case (%)	Control (%)	Univariate analysis	Multivariate analysis[∞]
				Crude Odds ratio (95%CI), *p value*	Adjusted OR (95%CI), *p value*
Sex	Men	217 (47.2)	437 (61.8)	1	1
	Women	243 (52.8)	270 (38.2)	1.81(1.43 to 2.29), $p < 0.0001$*	3.01 (1.73 to 5.25), $p < 0.0001$*
Marital status	Married	299 (65.0)	611 (86.4)	1	1
	Unmarried[¥]	161 (35.0)	96 (13.6)	3.43 (2.57 to 4.57), $p < 0.0001$*	5.31 (2.59 to 10.87), $p < 0.0001$*
'Ever' went to school	Yes	128 (27.9)	281 (40)	1	
	No	331 (72.1)	421 (60)	1.73 (1.34 to2.23), $p < 0.0001$*	NA
'Ever' owned shoes	Yes	245 (53.4)	364 (51.5)	1	
	No	214 (46.6)	343 (48.5)	0.93 (0.73 to 1.17), $p = 0.528$	NA
Currently owns shoes (of 'ever' owned shoes)	Yes	223 (90.3)	354 (97.5)	1	1
	No	24 (9.7)	9 (2.5)	4.23 (1.93 to 9.27), $p < 0.0001$*	3.32 (1.07 to 10.33), $p = 0.039$*
Wearing protective shoes during interview	Yes	88 (19.3)	110 (16.2)	1	1
	No	367 (80.7)	568 (83.8)	0.81 (0.59 to 1.10), $p = 0.176$	0.39 (0.24 to 0.65), $p < 0.0001$*
State of feet at interview	Clean and intact	176 (38.5)	454 (64.2)	1	1
	Dirty	103 (22.5)	144 (20.4)	1.85 (1.36 to 2.51), $p < 0.001$*	1.44 (0.73 to 2.83), $p = 0.295$
	Cracked	68 (14.9)	42 (5.9)	4.18 (2.74 to 6.37), $p < 0.001$*	6.04 (2.74 to 13.32), $p < 0.0001$*
	Dirty and cracked	110 (24.1)	67 (9.5)	4.24 (2.98 to 6.01), $p < 0.001$*	1.65 (0.85 to 3.21), $p = 0.140$
Wore shoes before age 30	Yes	88 (36.1)	231 (64.2)	1	1
	No	156 (63.9)	129 (35.8)	3.17 (2.26 to 4.45), $p < 0.0001$*	3.53 (2.22 to 5.62), $p < 0.0001$*

Table 10. Continued

Variable	Category	Case	Control	Univariate analysis t, mean difference, *p value*	Multivariate analysis∞ t, mean difference, *p value*
Age distribution	Mean (± SD)	51.5 (±16.1)	41.4 (± 14.3)	11.18, 10.07, $p < 0.0001$*	NA
Average monthly income	Mean (± SD)	288.8 (± 208.3)	350.66 (± 229.5)	-4.39, -61.86, $p < 0.0001$*	NA
Average age for first shoes	Mean (± SD)	38.7 (± 15.47)	28.8 (± 13.1)	8.41, 9.84, $p < 0.0001$*	NA
Average months spent on farming activities/ year	Mean (± SD)	7.84 (± 4.3)	9.04 (± 3.3)	-4.60, -1.20, $p < 0.0001$*	NA
Time walked to regular market (mins)	Mean (± SD)	109.7 (± 67.2)	83.75 (± 60.6)	6.49, 25.99, $p < 0.0001$*	1.009 (1.005 to 1.013), $p < 0.0001$*
Frequency of travel to regular market/month	Mean (± SD)	3.43 (± 3.6)	4.58 (± 2.6)	-6.04, -1.15, $p < 0.0001$*	0.95 (0.89 to 1.01), $p = 0.102$

∞**Note**: all variables were adjusted for: sex, marital status, 'ever' went to school, 'ever' owned shoes, currently owns shoes, wearing protective shoes, foot cleanliness, income, had shoes before age 30, months spent on farming, time spent walking to and frequency of traveling to the regular market.
¥ unmarried included: single, divorced, separated, and widowed;
NA = variable was not included in the final regression model;
Data are number (%) or mean (SD) or median (Minimum - Maximum)

5.2.4. Shoe wearing and foot washing history

There was no statistically significant difference in 'ever' owning shoes between cases and controls (53.4% of cases and 51.5% of controls had 'ever' worn shoes, $p = 0.528$). Among those that had 'ever' owned shoes, 223 (90.3%) of cases and 354 (97.5%) controls owned some type of shoe at the time of the interview (X^2 *comparing proportions* = 15.1, $p < 0.0001$). People in 'high' and 'medium' endemicity areas were less likely than people in 'low' endemicity areas to have 'ever' owned shoes (OR = 0.49, 95% CI = 0.37 to 0.67, $p < 0.0001$), and the same pattern was seen among controls. Affected men had greater odds than affected women to have 'ever' owned shoes (OR = 3.7, 95% CI = 2.5 to 5.4, $p < 0.0001$). The most common type of shoes owned by the cases were: closed plastic shoes (60.7%), canvas shoes (31.3%), tyre sandals (26.8%) and plastic sandals (18.3%). Shoes owned by controls were: closed plastic (59.9%), closed leather (48.0%), canvas (32.5%) and sandals (29.4%). During the interview 322 (70.8%) cases and 521 (76.8%) controls were observed to be barefoot. The types of shoes that the study subjects wore were classified into protective (wearing closed shoes) and non-protective (barefoot or wearing open shoes). At interview, 367 (80.7%) cases (of whom 322 were barefoot) were classified as 'not protected' compared to 568 (83.8%) controls (of whom 521 were barefoot). This difference was not statistically significant ($X^2 = 1.7$, $p = 0.18$). More affected men than women owned shoes (69.9% vs. 38.7%, $X^2 = 44.8$, $p < 0.0001$) and wore shoes classified as protective (26.0% vs. 13.3%, $X^2 = 11.8$, $p = 0.001$). The gender difference also existed in the control group where male controls used protective shoes more than female controls (21.7% vs. 7.6%, $X^2 = 23.5$, $p < 0.0001$).

The mean age at first wearing shoes was 38.68 years (SD = 15.5) for cases and 28.84 years (SD = 13.1) for controls. This ten year difference was statistically significant ($t = 8.2$, $p < 0.0001$). Overall, there was no statistically significant association between age of first wearing shoes and the level of podoconiosis endemicity in the area of residence ($f = 1.8$, $p = 0.165$). However, the average age of first wearing shoes was higher among controls living in 'low' than other endemicity areas. There was a large correlation between the age of study subjects and the age at first wearing shoes ($r = 0.8$, $p < 0.001$). Moreover, for study subjects that owned shoes during the interview, the duration of shoe wearing (i.e., the number of years from first shoe wear to the time of the interview) was assessed. This was found to be less than 30 years for the majority of the study subjects that owned shoes, indicating that age of onset of shoe wearing has decreased in recent years for both cases and controls (**Figure 12**). However, the number of years since podoconiosis onset (mean = 19.8, SD = 12.5) was larger than the duration of shoe wearing (mean = 12.9, SD = 9.7), showing that, in general, cases started wearing shoes after the onset of the disease. Moreover, the age of first wearing shoes for cases and the age of onset of podoconiosis produced a large positive correlation ($r = 0.6$, $t = 12.5$, $p < 0.0001$).

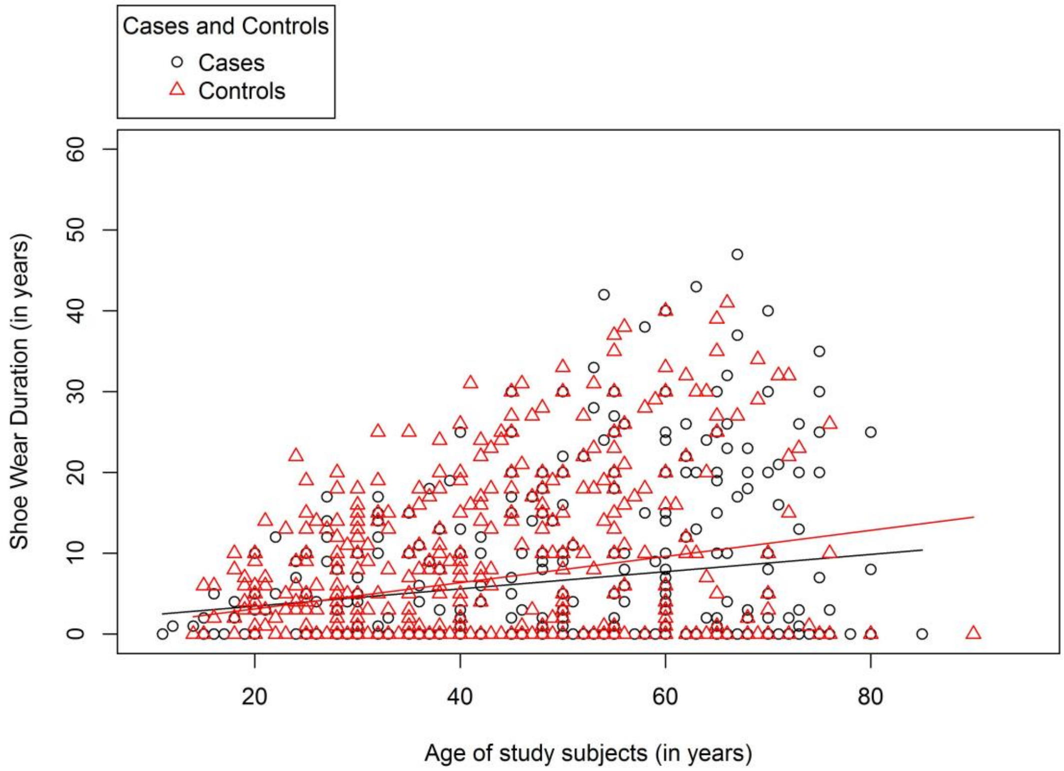

Figure 12. Duration of shoe wearing (up to the date of interview) among cases and controls who owned shoes.

Among cases, average monthly income and age of first wearing shoes produced a small negative correlation (*r* = -0.3, *t* = -4.1, *p* < 0.0001) (**Figure 13**). After adjusting for income, age of first wearing shoes and level of education were negatively correlated (*r* = -0.5, *t* = -8.1, *p* < 0.001).

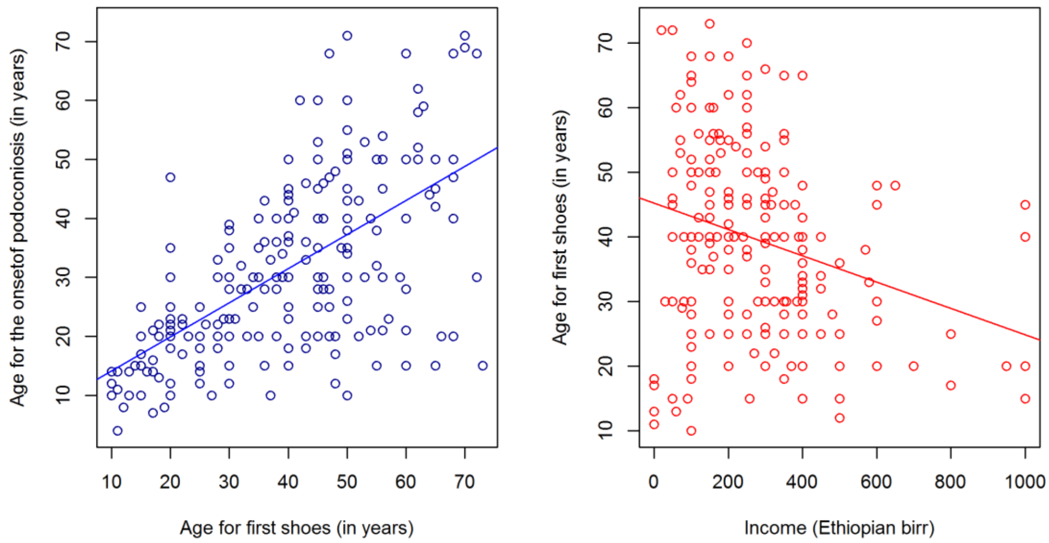

Figure 13. Average age of first wearing of shoes compared with income and age of onset of podoconiosis among cases.

The most common activities for which shoes were not worn included working inside the house (52.4% of cases and 62.1% of controls), and activities in the field, including ploughing (35.4% of cases and 55.8% of controls), planting (45.1% of cases and 61.5% of controls), and harvesting (37.8% of cases and 49.5% of controls).

Almost all of the cases and controls, 99.6% and 99.9% respectively, were able to get enough water to wash their feet. There was no significant difference in accessing piped water between cases and controls living in 'high' endemicity areas (47.6% vs. 52.4%, X^2 = 0.1, p = 0.788), but piped water was more common (49.1%) in 'low' endemicity areas while well water was more common (39.1%) in 'high' endemicity areas. There was no significant difference between cases and controls in the frequency of foot-washing per week; both groups said they washed eight times per week on average. Similarly, both groups said they used soap on average four times per week while washing their feet. Comparing foot-washing practices for people living in ‘high’, ‘medium’ and ‘low’ endemicity areas: frequency of foot-washing was higher in ‘high’ endemicity areas than in ‘medium’ or ‘low’ endemicity areas (mean (SD) = 8.7 (3.0) vs. 7.6 (2.6) and 7.6 (2.6) f = 23.3, $p < 0.0001$), but there was no difference between cases and controls living in the ‘high’ endemicity areas (mean (SD) = 8.7 (3.1) vs. 8.6 (2.9) $f = 0.08$, $p = 0.782$). The results were the same for washing with soap.

The cleanliness of interviewees’ feet was observed during interview and categorised into four groups as ‘clean and intact’, ‘dirty’, ‘cracked’, ‘dirty and cracked ’. The odds of study subjects being cases were two times greater among those with dirty feet (OR = 1.9, 95% CI = 1.4 to 2.5, $p < 0.0001$), four times greater among those with cracked feet (OR = 4.2, 95% CI = 2.7 to 6.4, $p < 0.0001$), and four times greater among those with both dirty and cracked feet (OR = 4.2, 95% CI = 2.9 to 6.0, $p < 0.0001$). These associations remained significant after adjusting for age, sex, ‘ever’ shoe ownership, and frequency of foot-washing. After adjusting for sex and disease status, level of education was found to be significantly associated with frequency of foot-washing ($t = 2.7$, $p = 0.008$).

5.2.5. Foot-soil exposure

More than 97.0% of cases and controls had not lived outside their home *kebeles* in the previous year. Of the 338 (29.0%) participants that had travelled for social purposes, such as attending funerals, 223 (66.0%) were controls and 115 (34.0%) were cases (X^2 = 5.69, p = 0.017). There was no statistically significant difference between cases and controls in the frequency or time taken to travel to the nearest and furthest field or water source. On the other hand, there was a statistically significant difference between cases and controls in the time taken and frequency of travel to the most commonly used market. The one way journey to the usual market took on average 109.74 minutes (SD = 67.2) for cases and 83.8 minutes (SD = 60.6) for controls. This 26 minute average difference was statistically significant (t = 6.5, p = 0.0001). Similarly, the monthly frequency of travel to the market was significantly different (t = -6.0, p = 0.0001); cases travelled less frequently on average than controls (3.4 (SD = 3.6) vs. 4.6 (SD = 2.6)). Comparing only controls, the average time to regular market was longer for controls living in the 'high' and 'medium' endemicity areas, and controls in these areas travelled less frequently to market places. A composite indicator that summarized the product of time taken and frequency to the nearest field, the furthest field, the nearest water source and the regular market was calculated for each study subject. This composite indicator showed no significant difference in travel time between cases and controls (t = 0.03, p = 0.97).

Each year, cases spent approximately 60 fewer days in farming activities than controls (t = -4.6, p < 0.0001). The time spent on specific farming activities such as ploughing, harvesting and weed-pulling showed the same significant difference. On the other hand, there was no significant difference in time spent in any of the farming activities by area of endemicity, either between cases and controls (f = 0.7, p = 0.485) or amongst the controls (f = 2.3, p = 0.100).

5.2.6. Disease history among cases

Comparing male and female cases, there was no statistically significant difference in: average age of disease onset (30 years for both), speed of progression to current stage, age when treatment was first sought, occurrence and frequency of acute adenolymphangitis (ALA), weather related/seasonal variation for occurrence of ALA, or number of days without work due to ALA. More than half of all cases had stage two podoconiosis and leg circumference between 26 and 36 cm, and more than a quarter had mossy lesions on at least one foot. We found no statistically significant association between disease clinical stage and frequency of ALA (p = 0.066). However, presence of an open wound was significantly associated with ALA both with (t = - 2.6, p = 0.009) and without (t = -2.1, p = 0.037) adjustment for disease clinical stage. Few of the cases (15.0%) had received treatment for podoconiosis. Age at first treatment was compared with income, age at disease onset and age at first wearing shoes, as shown in the scatter matrix (**Figure 14**). Age at first treatment was most closely correlated with age at onset.

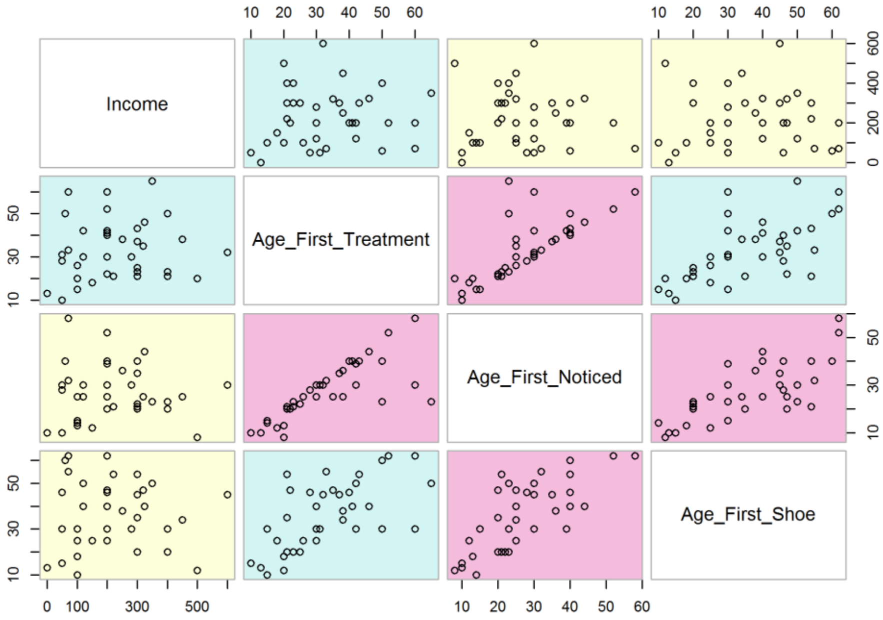

Figure 14. Scatter matrix showing cases that were treated for podoconiosis§.

§Note: First noticed swelling and first treatment *r* = 0.9, age at first wearing shoes and income *r* = -0.04, age at first wearing shoes and first noticed *r* = 0.2, age at first wearing shoes and first treatment *r* = 0.2, first noticed swelling and income *r* = -0.1, income and first treatment *r* = 0.01.

More than half of the cases (54.8% of men and 52.1% of women) had a family member affected by podoconiosis (**Figure 15**). The degree of relationship between cases and their podoconiosis-affected family members was classified as first degree (parents and children), second degree (grandparents, grandchildren and siblings), third degree (aunt, uncle, nephew, cousin and niece) or 'other' (husband or wife). The majority of the cases (61.4%) had podoconiosis-affected first degree relatives, followed by second degree relatives (51.8%) and third degree relatives (41.6%). There was clustering of podoconiosis cases within households. Of the 463 households that were found to have cases during the household census, 321 (69.3%) had one affected member and 142 (30.7%) had two or more.

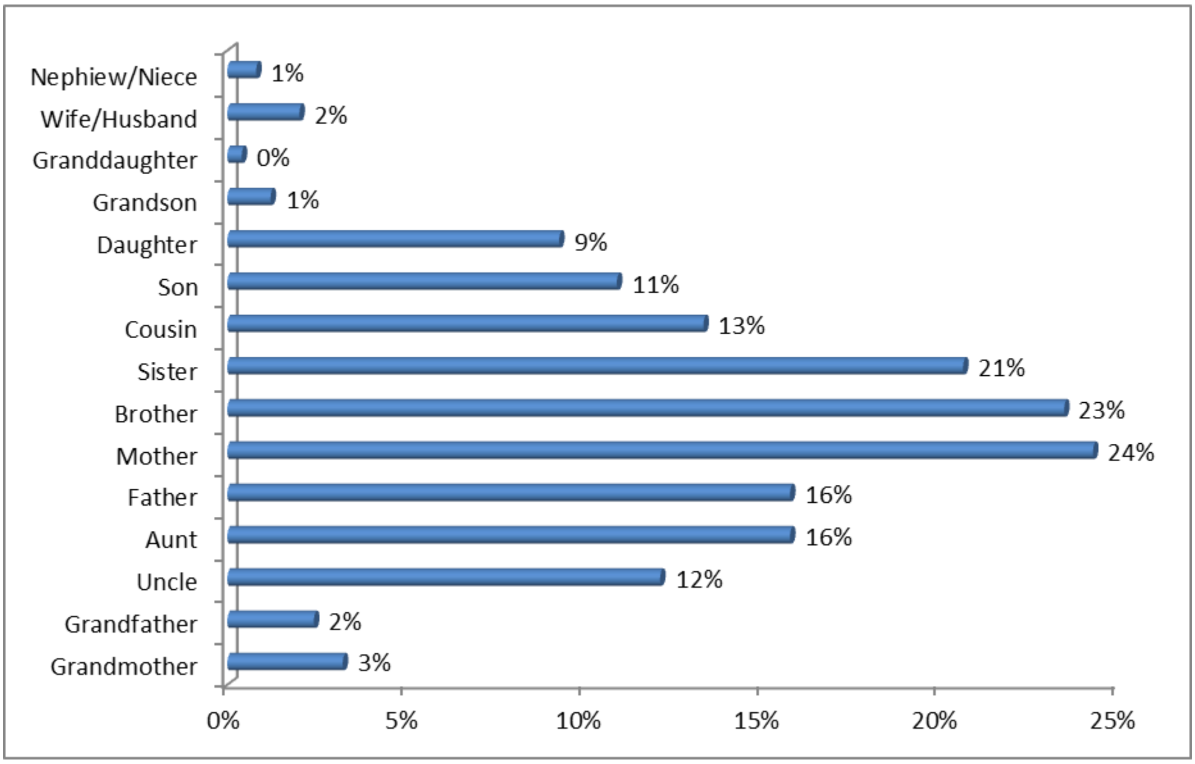

Figure 15: Cases with podoconiosis affected family members

5.3. Chapter summary

Previous studies have suggested that podoconiosis arises from the interplay of individual and environmental factors. Here, our aim was to understand the individual level correlates of podoconiosis by comparing 460 podoconiosis-affected individuals and 707 unaffected controls. This was a case-control study carried out in six *kebeles* (the lowest governmental administrative unit) in northern Ethiopia. Each *kebele* was classified into one of three endemicity levels: 'low' (prevalence < 1%), 'medium' (1–5%) and 'high' (> 5%). A total of 142 (30.7%) households had two or more cases of podoconiosis. Compared to controls, the majority of the cases, especially women, were less educated (OR = 1.7, 95% CI = 1.3 to 2.2), were unmarried (OR = 3.4, 95% CI = 2.6 to 4.6) and had lower income ($t = 24.4$, $p < 0.0001$). On average, cases started wearing shoes ten years later than controls. Among cases, the age of first wearing shoes was positively correlated with age of onset of podoconiosis ($r = 0.6$, $t = 12.5$, $p < 0.0001$). Among all study participants the average duration of shoe wearing was less than 30 years. Between both cases and controls, people in 'high' and 'medium' endemicity *kebeles* were less likely than people in 'low' endemicity areas to 'ever' have owned shoes (OR = 0.5, 95% CI = 0.4 to 0.7). Late use of shoes, usually after the onset of podoconiosis, and inequalities in education, income and marriage were found among cases, particularly among females. There was clustering of cases within households, thus interventions against podoconiosis will benefit from household-targeted case tracing. Most importantly, we identified a secular increase in shoe-wearing over recent years, which may give opportunities to promote shoe-wearing without increasing stigma among those at high risk of podoconiosis.

6. Chapter 6 - Environmental correlates of podoconiosis

A comprehensive understanding of the occurrence of podoconiosis needs investigation of both the individual-level and environmental level correlates. The case-control study described in chapter 5 has enabled us to identify the major individual-level correlates of podoconiosis. To complete the picture and meet the third objective of the research project, which aimed to discern the environmental correlates of podoconiosis, a range environmental covariates that are potentially associated with podoconiosis had to be studied. Building on existing evidence showing the contributions of soil properties, altitude, and precipitation in podoconiosis, we expanded our study with an aim to further the comprehensive investigation of environmental covariates by using state of the art soil property and spatial analysis techniques and involving a multidisciplinary team from epidemiology, geology, spatial statistics and genetics. The study narrows down the focus on specific soil properties, and enhanced the direction for future biomedical investigations aimed at identifying the exact etiology of podoconiosis, as described in detail in this chapter.

6.1. Methods

6.1.1. Study area

The study was conducted in the Gozamen and Machakel districts of the East Gojam zone in northern Ethiopia. Twelve *kebeles* (representing the lowest administrative units) with 147 villages, over an area of 900 km^2, were covered in the study (**Figure 16).**

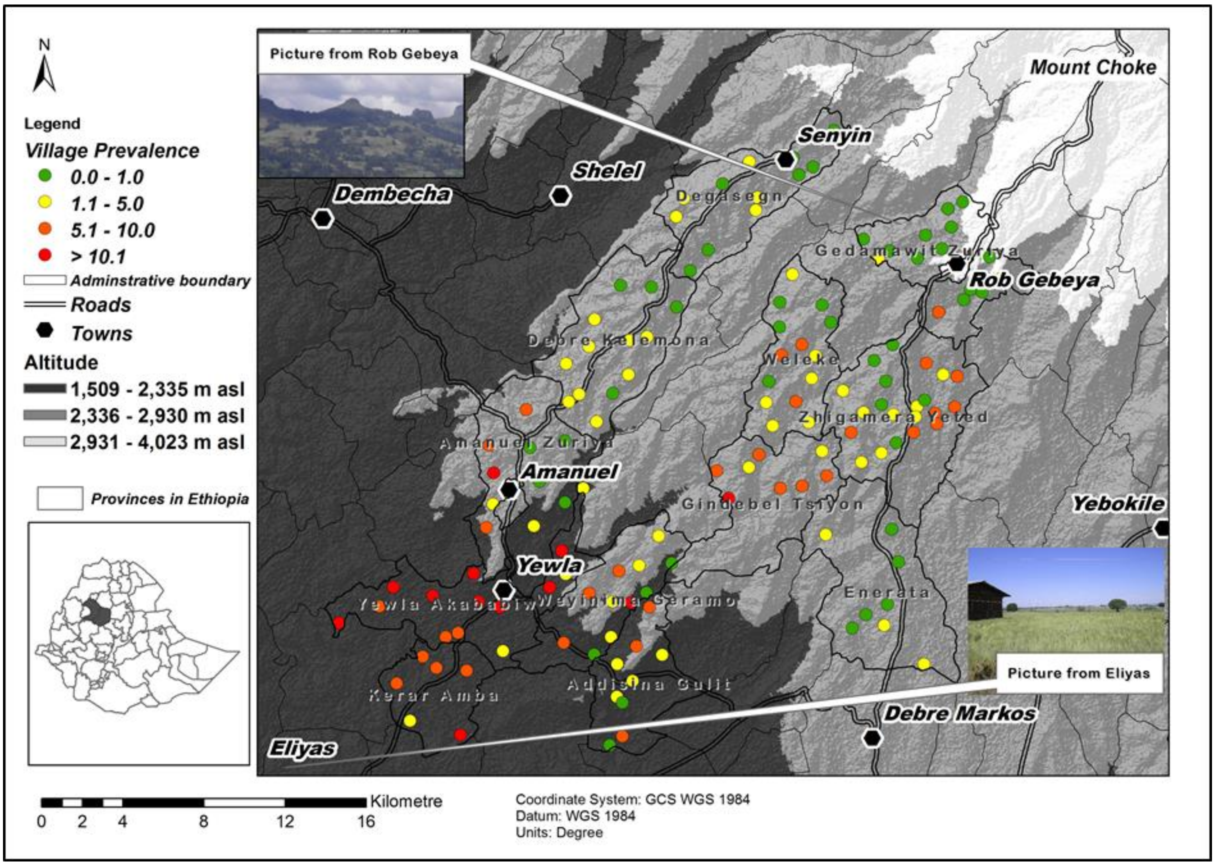

Figure 16. Spatial distribution of podoconiosis prevalence and elevation in East Gojam zone of northern Ethiopia

6.1.2. Data sources and preparation

6.1.2.1. Case data

Podoconiosis case data were collected by Health Extension Workers (HEWs) who were trained to identify podoconiosis cases in their catchment *kebeles*. Following the training, the HEWs visited each household and recorded: the number of household members, the number of podoconiosis affected cases, the sex and age using a standardised checklist (Molla, Tomczyk et al. 2012). Based on presence or absence of podoconiosis - affected cases in a house, the households were classified as case or control households. Village level prevalence was calculated based on the number of adult (> 15 years old) cases in all households and the adult (age >= 15 years) population within the same village. The data were entered into a spread sheet and imported into the R statistical program version 2.15.

6.1.2.2. Soil data

The soil samples were taken from villages randomly selected from six of the twelve *kebeles*. An initial control or case household was selected randomly and then every third household in the village was included for soil sampling. Soil samples were collected from selected households, and from traverses connecting main *kebeles* and towns in the study area. At each selected household, the person collecting the soil located the closest field farmed regularly by the family, or the next closest field that the barefoot farmers would directly be exposed to. At each sample site, the GPS coordinates and altitude at the centre of the field were recorded. Next, the data collector walked 10 paces towards the house and 1/3-filled the labelled sample bag with soil (~2.5 kg) by removing the top 5 cm of soil using a plastic soil scoop. From this sampling site the collector walked 20 paces away from the house, and another 1/3 of the bag was filled with soil. Approximately 5 kg of homogenised soil was taken from two points within the field at the sample site, and stored in sample bags that were labelled with the identification number used in the epidemiological survey. Additional soil samples were collected from traverses, within a household field or frequently used path, with sampling sites selected for every 100 m vertical descent or 1 km road distance from the point of maximum altitude (Mount Choke). In total soil samples from 86 sample sites, within 31 villages, were included in the analysis. The soil samples were analysed for a range of geochemical and mineralogical characteristics (listed in **Table 11**), using instruments based at the Natural History Museum, London (LeBlond, Cuadros et al. 2014).

Table 11. Description of the soil characteristics

Soil characteristic	**Method used**
Organic/inorganic carbon (C), hydrogen (H) and nitrogen (N)	CHN (Carbon Hydrogen, and Nitrogen) analyser
Major oxides (Al_2O_3, CaO, Fe_2O_3, K_2O, MgO, MnO, Na_2O, P_2O_5, SiO_2 and TiO_2) and trace elements (As, Ba, Cd, Co, Cr, Cu, Ni, Pb, Sb, Sc, Sr, Y, V and Zr)	Digestion and inductively coupled plasma (ICP) - atomic emission spectroscopy (AES) / mass spectrometry (MS) Soil chemical content measured as weight percent (wt%) plus loss on ignition (LOI). Chemical composition and elements will together add up to 100%.
Soil minerals: Crystalline (quartz) and amorphous components (volcanic glass), clays (smectite, kaolinite) and mica and chlorite.	X-ray diffraction: fixed and scanning geometry were employed. Random powders, oriented mounts and glycolated samples were analysed
Particle size, cumulative volume of the following cut-off sizes: 1 μm (in aerodynamic diameter), 2 μm, 5 μm, 10 μm, 20 μm, 100 μm, 500 μm, 1000 μm and 2000 μm.	Laser diffraction, using both water and de-flocculant (Na pyrophosphate) as a dispersant

6.1.2.3. Spatial data

Podoconiosis prevalence and soil characteristic data were geo-referenced based on GPS coordinates recorded in the field during the soil sampling collection and coordinate data obtained from the Ethiopian Mapping Agency. Detailed topographic information and a geological map of the study area (with 1:50,000 and 1:250,000 scale, respectively) were also obtained from the Ethiopian Mapping Agency and Ethiopian Geological Survey respectively. Precipitation and temperature data, with a spatial resolution of 1 km, compiled monthly over a period of 50 years (from 1950-2000), were extracted to the village level in ArcGIS from an online meteorological source (http://www.worldclim.org). In addition, digital elevation model (DEM) data were downloaded with a spatial resolution of 30 m from the NASA Global ASTER data repository (http://asterweb.jpl.nasa.gov/gdem.asp). Percentage slope was calculated using the DEM in ArcGIS. Similarly, the DEM was used to calculate the water flow direction and water flow accumulation. The slope and water flow accumulation data take into consideration steepness and direction, both of which are important for influence soil deposition.

6.1.3. Data analysis

This study investigated environmental factors, such as soil characteristics, that have been previously associated with podoconiosis using a variety of statistical models and theories. Geology, altitude and precipitation had been previously linked to disease in Africa, including Ethiopia, (Price 1974a, 1976a, 1974b, 1976b). These secondary factors influence both the process of soil formation and the characteristics of the soil. The geochemical and mineralogical characteristics of the soil samples were determined and used as primary environmental predicators representing multiple areas with varying level of podoconiosis prevalence. These primary and secondary covariates were linked to predict the soil characteristics within the study area. The flowchart below (**Figure 17**) summarizes the exploratory analysis conducted.

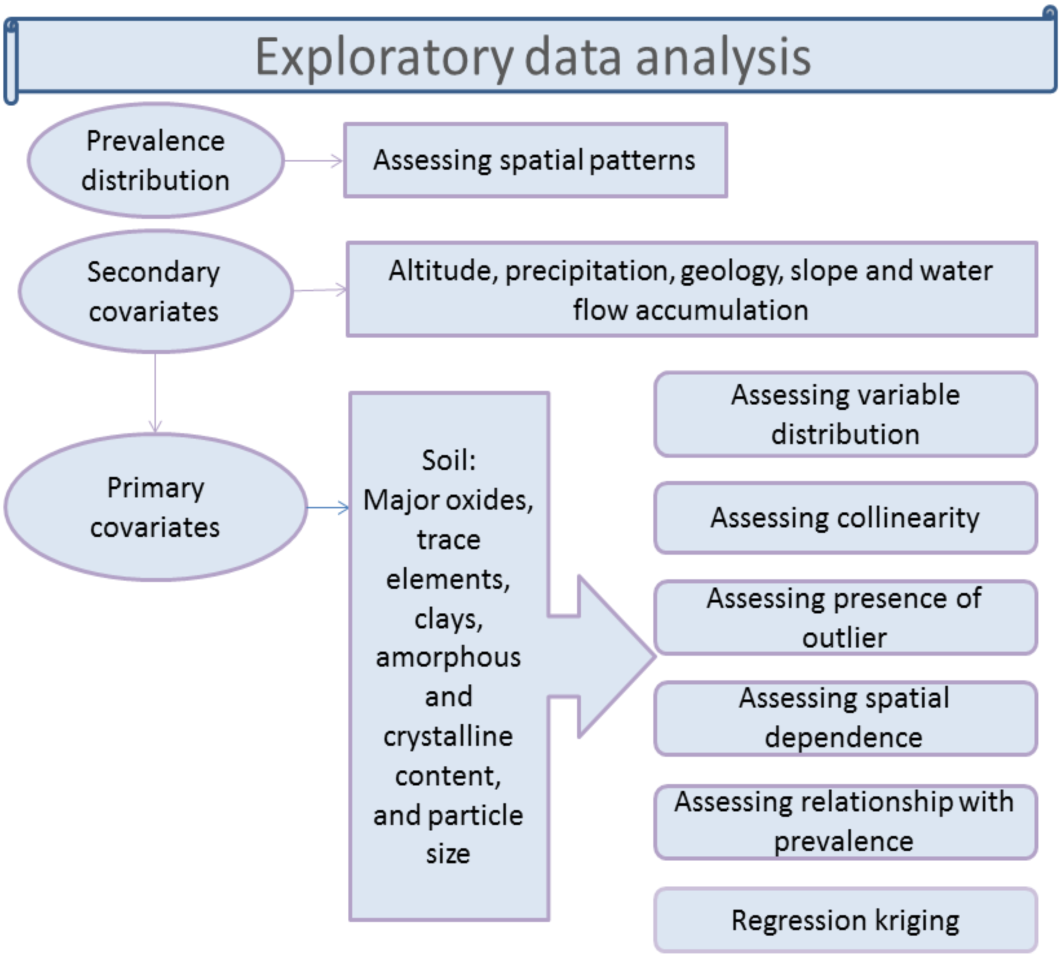

Figure 17: Exploratory data analysis flowchart for environmental covariates

6.1.3.1. Analysis and interpolation of soil characteristics

The primary variable of interest was podoconiosis prevalence. The prevalence data were explored for the presence of a spatial pattern in the 147 villages. A variogram (which shows spatial dependence or spatial correlation between pairs of points in space) was estimated and fitted with an exponential model in the geoR R package. Spline interpolation was used to characterise the spatial distribution of prevalence in the study area. Spline interpolation takes as input point data values and produces a smooth, spatially continuous surface which passes through the sampled data points in the area of interest (Dubrule 1983). Similarly, the clustering of podoconiosis prevalence was mapped in ArcGIS spatial statistics tool (Hot Spot Analysis (Getis-Ord Gi*)). This tool calculates *z*-scores and *p*-values to identify statistically significant spatial clusters of high values and low values (**Figure 16**).

Geology, altitude, precipitation and temperature influence soil formation and were, therefore, classified as secondary covariates in this study. These secondary covariates were explored for the presence of spatial patterns, and were not analysed in combination with the primary environmental predictors (soil covariates), because the secondary covariates lead to formation of the soil that comes in direct contact with individuals. The altitude, geology, precipitation, slope and water flow accumulation were subsequently used for interpolation of soil covariates.

The soil characteristics, determined from geochemical analysis, were considered primary environmental predictors as podoconiosis arises from direct contact with the soil. Exploratory data analysis was undertaken to determine which of the soil variables, or combination of variables, should be taken forward for regression kriging and subsequent analysis in relation to podoconiosis prevalence. Kriging is a spatial interpolation technique that predicts the value of the variable of interest at an unobserved location as a weighted average of values in neighbouring locations (Dubrule 1983). As an initial step, the assumption of normality was tested for each soil variable using histogram plots and measures of central tendency (mean, median, standard deviation, skewness and kurtosis). During the second step, pairwise correlation coefficients were calculated to assess relationships between individual soil characteristics. For variables with non-normal distributions, the non-parametric Spearman's Rank correlation coefficient was used. Where the correlation coefficient between two soil characteristics was >0.6 the variables were classified as correlated. Based on the correlation analysis, in tandem with careful consideration of geological understanding, several soil characteristics were omitted from further consideration. This procedure ensured (1) collinearity within the variables was minimised and (2) the soil characteristics which were carried forward for further analysis were geologically relevant.

The third step focused on identifying and managing outliers. Statistical outliers were defined as measurement values widely dispersed from the majority for a specific soil measured property. The distribution of the soil variables measurements were presented in box and whisker plot as well as in Cleveland plot, to visually identify measurement values that are extremely different from the majority of the values for each soil property. Soil variables which contained statistical outliers were transformed for better visualization and outliers were removed from the data.

Figure 18a presents a box and whisker plot where extremely high or extremely low values were plotted beyond the upper (95th) and lower (5th) percentile. The horizontal axis represents the name of soil property measured, and the vertical axis represents the measurement values of the soil variable. Figure 18b presents multiple Cleveland plots stacked together, for different soil properties. The distribution of measured values for each soil property is compared with the same variable. The vertical axis represents the soil measurement values for each variable in order of where the soil samples were taken from. And the horizontal value showed how each measurement value deviates from the whole measurement values for a soil property variable. Therefore, the plot shows distribution of measurement values for each soil property independent of the other soil properties. Each variable was assessed individually; for example, although the quantities of Fe_2O_3 (iron oxide) determined in the soil samples (from chemical analysis) included outliers in a box plot (**Figure 18a**), the Cleveland plot showed measurements were similar to the majority (**Figure 18b**). Therefore, all the measurement values for Fe_2O_3 were retained. On the other hand, variables such as Zr (zirconium) and Cr (chromium) included, respectively, one and two measurement values that were widely dispersed from the majority. Those were designated statistical outliers and removed from further analysis (**Figure 18b**).

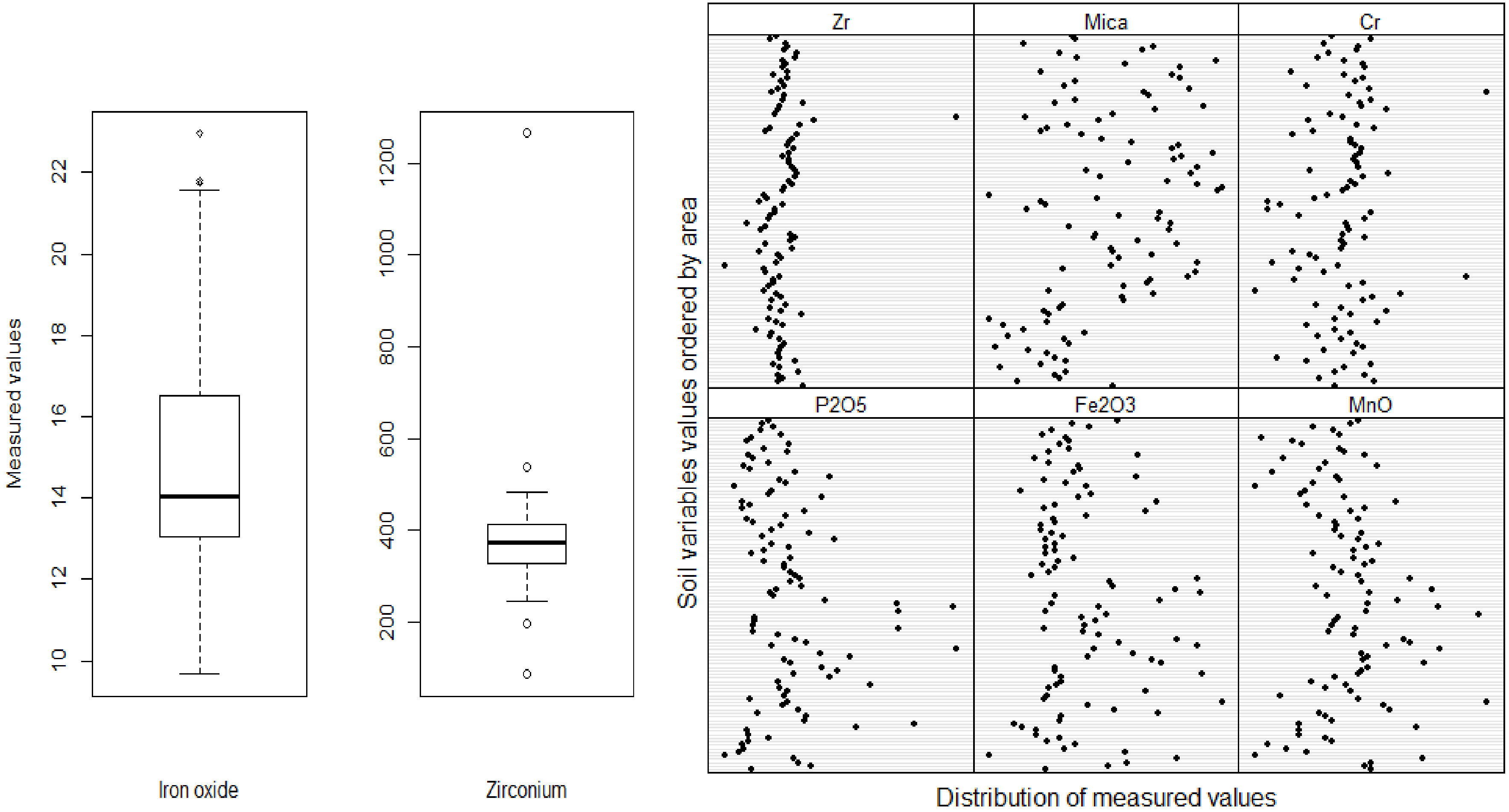

Figure 18a) Box plot and b) Cleveland plot showing distribution of soil chemical analysis measurement values.

During the fourth step, spatial patterns in each of the remaining covariates were assessed using a plot to show soil measurement values spatial distribution and variables that exhibited a distribution unrelated to the disease were removed. For instance, the measurement values for P_2O_5 showed higher concentrations in the area where more household soil samples were taken**.** This could be because household samples represented more farmed soil and hence soil with fertilizer than traverse soil samples. Similarly, the higher concentrations of MnO (Manganese oxide), Sb (antimony/ stibium), and Sc (scandium) around the summit of Mount Choke may merely be due to the effect of volcanic ash from Mount Choke. For instance, Sb (Miravet, Lopez-Sanchez et al. 2007), MnO (Miura and Hariya 1997) and Sc have been shown to be associated with volcanic rocks (Fryklund Jr and Fleischer 1963).

Finally, univariate analysis excluded the remaining variables with 95% confidence interval $p > 0.500$ and AIC (Akaike Information Criterion - a measure of the quality of a model) > 85.50 which is the median AIC value.

The techniques involved in soil characterisation are highly labour intensive, and so fewer soil samples were analysed (86 data points within 31 villages) than the number of villages for which prevalence was available (147 villages). In addition, due to the varied geology of the region, soil characteristics were assumed to be inherently heterogeneous with significant variation within small areas. Collecting multiple soil samples within each village was anticipated to address this variation. This produced multiple soil measurements recorded for the same disease prevalence value of a village.

In this study, regression kriging was used to interpolate each soil variable as a combined function of (i) regression with a set of related covariates and (ii) spatial interpolation of the residuals of the regression through kriging (Hengl, Heuvelink et al. 2007). Covariates assessed for regression kriging were: geology, slope, altitude, precipitation, and water flow accumulation. The geology of the area was selected because the underlying geology represents the parent material from which soil is formed over time. Altitude, slope, precipitation and water flow accumulation were included due to their influence on weathering (for example, water flow accumulation is related to soil deposition rates). The covariates used for regression kriging of each of the soil characteristics were selected using linear regression models and correlation coefficients.

Residual variograms (from the residuals of the best fitting linear regression model), were estimated and variogram models fitted for each soil characteristic variable, prior to the application of regression kriging. From the kriging results, predictions with a kriging error smaller than a predefined threshold (taken as the mean of the kriging standard error) were retained for each soil characteristic variable and those with an error larger than the threshold were omitted from further analysis. The omission of sample points with kriging error larger than the median will not be appropriate for small kriging standard error throughout. However, the soil sample distribution was not regularly distributed in space, producing large errors for few of the sample points. This ensured that further analysis used only soil characteristic values which were predicted with a high degree of accuracy, since the soil sample sites were not distributed regularly in space.

The output raster variables were the predicted values of each soil characteristic variable, based on geo-statistical interpolation of the soil sample data, which used covariate information to increase the accuracy of the prediction. The predicted soil variables were overlaid onto the village level disease prevalence data points, and then interpolated soil values were extracted for each village.

6.1.3.2. Analysis of podoconiosis prevalence based on soil characteristics

The relationship between the interpolated soil variables and podoconiosis prevalence was assessed using univariate regression analysis. Variables that did not exhibit a statistically significant association with the outcome (p >0.05) were omitted from further analysis. Since the prevalence data were over-dispersed, a generalized linear model (GLM) of the Quasi-Poisson family was used for the multivariate analysis. Multivariate regression analysis was applied to the remaining variables and the output was checked for multi-collinearity using the Variance Inflation Factor (VIF; a VIF greater than 10 indicates multi-collinearity between variables). Soil variables with a VIF greater than 10 were removed prior to the multivariate analysis and the process repeated until the remaining soil variables had a VIF less than 10.

The final multivariate regression model was evaluated for goodness-of-fit, coefficient of determination (r^2) and residual diagnostics. The goodness-of-fit was tested by examining the residual deviance and by comparing the residual deviance to a Chi-squared (X^2) distribution. For an acceptable model fit, the ratio of residual deviance to degrees of freedom of the residuals was expected to be close to 1. Comparing the distribution of the residuals with a Chi-squared distribution should give a value close to zero. Residual diagnostics were also checked using plots of the residual and predicted values, and Quantile-Quantile (QQ) plots of the fitted and empirical value distributions. Finally, the residuals were evaluated for autocorrelation using residual variograms and spatial plots.

6.2. Results

6.2.1. Spatial pattern of podoconiosis prevalence and environmental covariates

The sample variogram of podoconiosis prevalence exhibited clear spatial autocorrelation and was fitted well by an exponential model **(Figure 19).** Crude exploratory interpolation indicated an increase in the prevalence of podoconiosis from the north-east (at the summit of Mount Choke) towards the south-west of the study area (**Figure 19**).

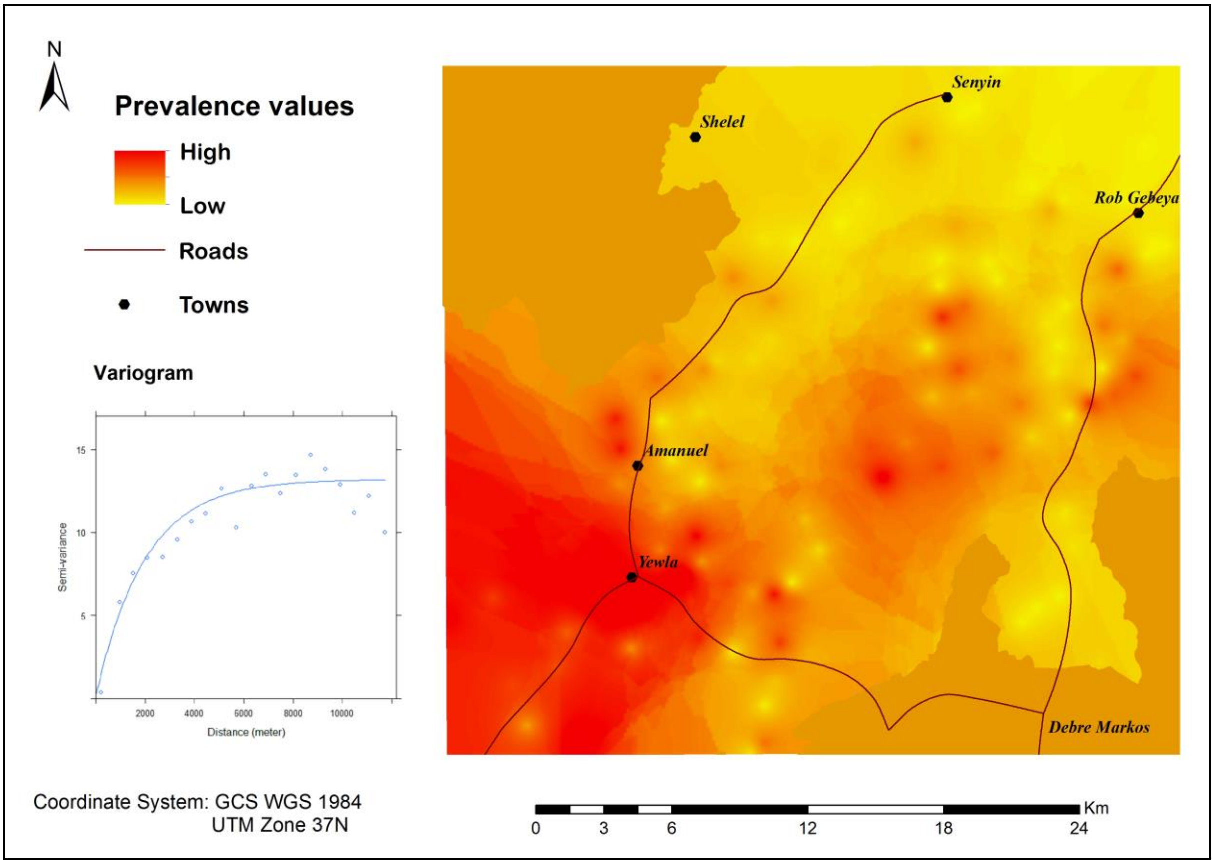

Figure 19. Variogram with exponential model fitted and Spline interpolation of prevalence distribution.

The increase in podoconiosis prevalence from the north-east to the south-west (**Figure 19**) was matched by a decrease in altitude and precipitation in the same direction (see **Figure 16** for altitude). The altitude in the study area ranged from 2000 to 4000 m asl and the mean annual precipitation ranged from 1000 to 1200 mm. In addition, the underlying geology of the study area included igneous deposits that were classified into eight types (reflecting the variation in deposit characteristics) and varying values of prevalence were recorded within the same deposit type (**Figure 20**).

The observed variation in altitude, precipitation and geology were not, however, analysed further in direct association with podoconiosis. This is because, in addition to the previously stated indirect effect of these factors on the development of podoconiosis (which we do account for by predicting soil properties), 1) the lowest altitude (2100 m asl) in the study area is higher than most places where podoconiosis has previously been recorded (Price 1974); and 2) the lowest mean precipitation value in the study area (997 mm) was high compared with previously suggested levels of precipitation when considering the previous associations made with podoconiosis (>1000 mm; (Price 1974)).

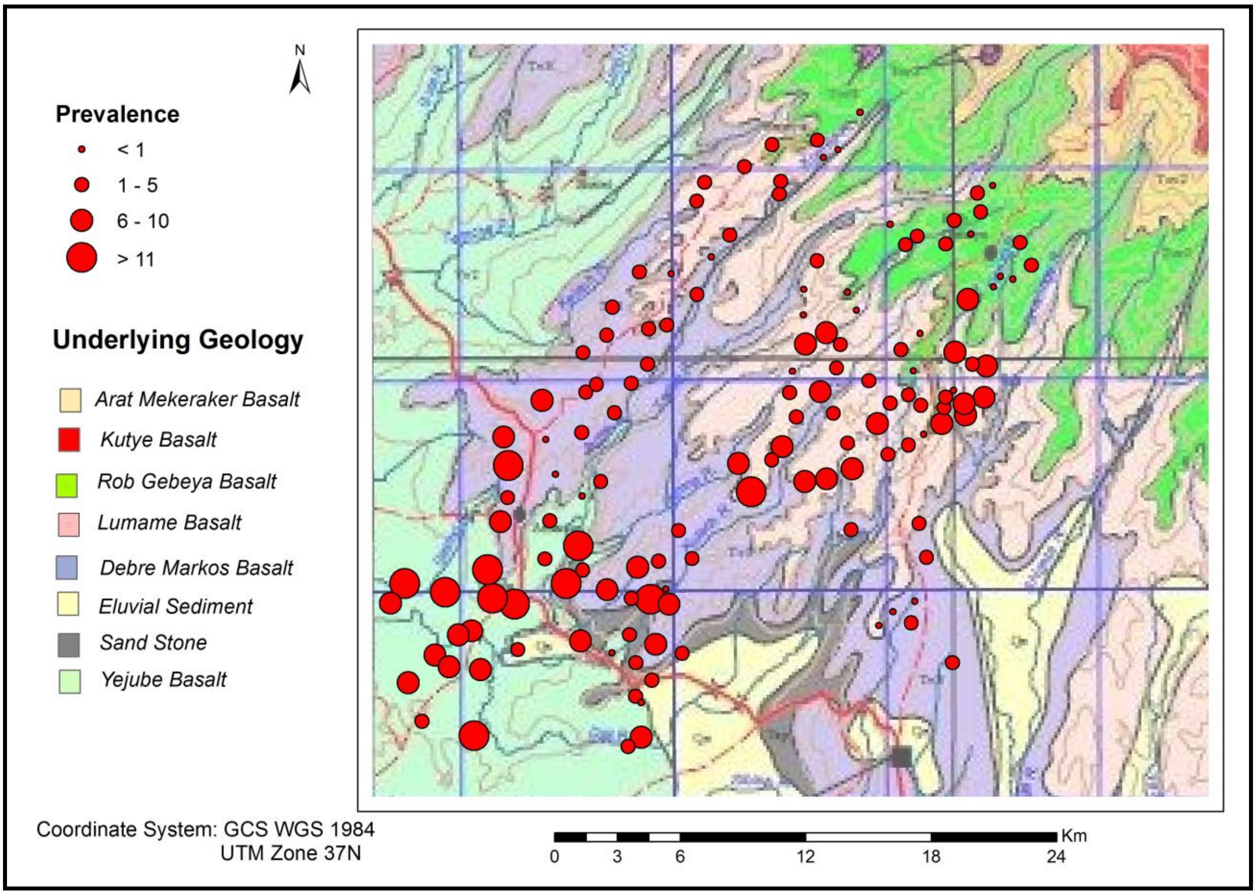

Figure 20. Underlying geology and podoconiosis prevalence distribution sampled at 147 villages within East Gojam, northern Ethiopia.

6.2.2. Relationship between podoconiosis and environmental covariates

A supplementary material with results of the exploratory analysis that included correlation matrixes with correlation coefficient, histogram plots with measures of central tendency; and spatial plots for soil characteristics measurement values is annexed (**Appendix 6**). Most of the soil variables were not normally distributed, and multiple variables were significantly correlated. Thus, MgO, Na_2O, CaO, K_2O and TiO_2 were removed from the soil chemical oxide group; Cu, Ni, Y and Sr from the trace elements (**Figure 21**); inorganic carbon, nitrogen and hydrogen from the organic content group; iron oxide, amorphous silica and feldspars from the mineralogical data. Soil particle size less than 1 μm and less than 2 μm prepared in water were correlates (r = 0.9). Therefore, particle size less than 2 μm was dropped from the analysis. Univariate analysis that showed relationship between soil characteristics and prevalence prior to interpolation excluded: Al2O3, soil particle size analysed using de-flocculant (Na pyrophosphate), organic carbon, As, Pb, V and Cd (**Table 12**). The soil variables that were maintained for further analysis at the end of step-by-step variable selection were: Fe_2O_3, soil particle size less than 1 μm prepared in water, quartz, smectite, kaolinite, mica, chlorite and Zr.

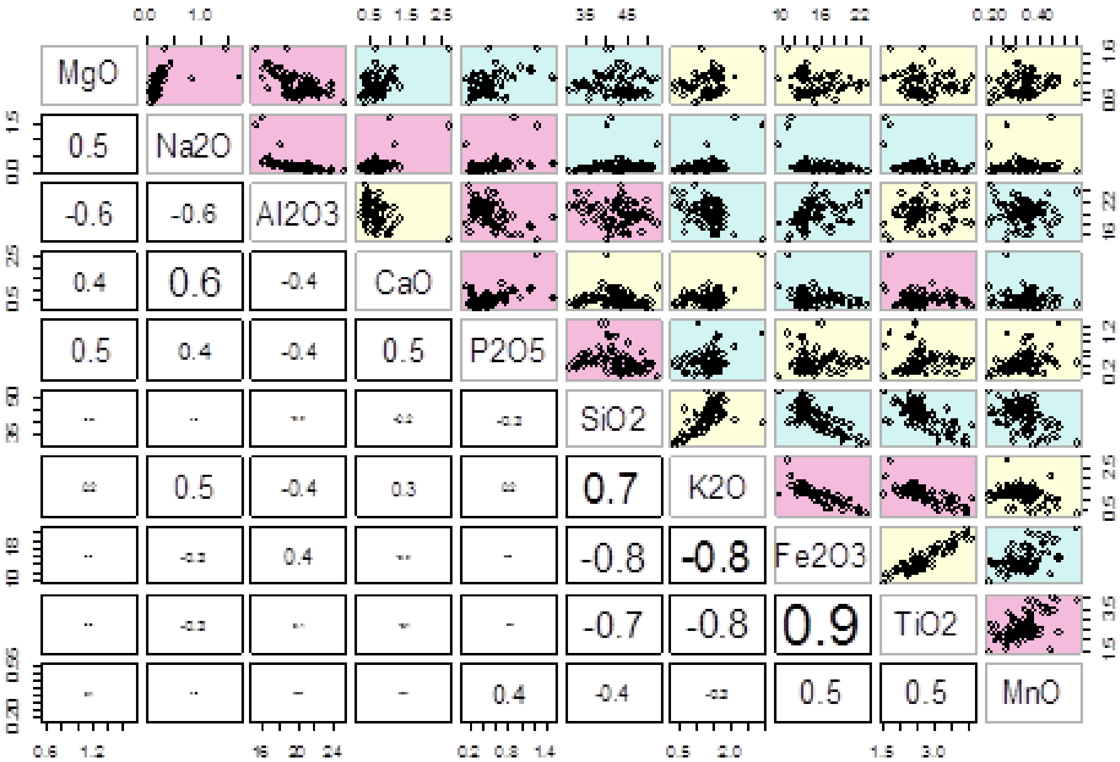

Figure 21. Spearman’s Correlation matrix of soil chemical oxides.

Table 12. Univariate analysis for soil characteristics

Soil Characteristics	Univariate analysis					
					CI	
	AIC	Estimate	*p* – value	OR	2.5%	97.5%
Al2O3†	86.45	0.11	0.520	1.12	0.85	1.49
Fe2O3	65.02	-0.73	0.001	0.48	0.29	0.70
Particle size <1microns- analysis by water	83.11	-0.27	0.055	0.76	0.57	0.99
Particle size <2microns- analysis by de-flocculant †	87.05	0.01	0.800	1.01	0.95	1.07
Particle size <10microns-analysis by de-flocculant †	86.74	0.01	0.545	1.01	0.97	1.05
Organic carbon †	87.01	0.08	0.745	1.09	0.65	1.83
Quartz	85.42	0.04	0.212	1.05	0.98	1.13
Smectite	85.37	0.32	0.200	1.38	0.86	2.34
Kaolinite	85.11	-0.05	0.168	0.95	0.88	1.02
Mica	75.28	0.11	0.003	1.12	1.05	1.21
Chlorite	57.82	-1.14	0.0003	0.32	0.15	0.55
As †	87.11	0.001	0.970	1.00	0.94	1.07
Pb †	87.10	-0.007	0.931	0.99	0.84	1.17
Sb †	87.11	-0.002	0.979	1.00	0.85	1.19
V †	87.08	0.001	0.851	1.01	0.99	1.03
Cd †	86.10	0.66	0.354	1.00	0.99	1.01
Ba	52.41	-0.04	0.0003	0.96	0.94	0.98
Zr	64.50	0.03	0.0003	1.03	1.01	1.05
Cr	77.23	0.02	0.012	1.02	1.01	1.04

† variables removed; Variables were retained based on the 50th percentile of the AIC (< 85.50) and *p* – value < 0.500.
AIC – Akaike Information Criterion ; CI – Confidence Interval; OR – Odds Ratio

Geological deposit types identified in the study area were: Eluvial Sediment (sedimentary origin), Choke shield volcano (differentiated into: Kutye Basalt, Arat Mekeraker Basalt and Rob Gebeya Basalt) and the flood basalt deposits (differentiated into: Lumame Basalt, Debre Markos Basalt, Sandstone and Yejube Basalt; **Figure 20**). Geological deposit types were not considered as covariates in the soil characteristic regression kriging, as they did not adequately capture the spatial heterogeneity of the soil within the study area. The majority of the soil variables showed significant correlations (according to *p*-values from linear regression) with altitude and precipitation. Since altitude and precipitation were highly correlated (r = 0.9), altitude was selected for regression kriging and further analysis (**Table 13**).

Table 13. Relationship between soil and covariates.

Soil Variable	Slope	WFA [¥]	Altitude	Precipitation	Remark
Quartz	$\beta = 0.03$ $p = 0.837$	$\beta = 0.12$ $p = 0.514$	$\beta = -0.01$ $p = 0.002$	$\beta = -0.05$ $p < 0.001$	slope ~ WFA $r = -0.7$
	$r = -0.04$ $p = 0.742$	$r = 0.05$ $p = 0.655$	$r = -0.27$ $p = 0.013$	$r = -0.35$ $p < 0.001$	
Mica	$\beta = 0.11$ $p = 0.622$	$\beta = -0.26$ $p = 0.328$	$\beta = -0.01$ $p = 0.122$	$\beta = -0.03$ $p = 0.127$	slope ~ altitude $r = 0.1$
	$r = 0.06$ $p = 0.567$	$r = -0.16$ $p = 0.132$	$r = -0.24$ $p = 0.026$	$r = -0.20$ $p = 0.066$	
Smectite	$\beta = -0.01$ $p = 0.605$	$\beta = 0.003$ $p = 0.892$	$\beta = -0.0004$ $p = 0.378$	$\beta = -0.03$ $p = 0.593$	slope ~ precipitation $r = 0.1$
	$r = 0.02$ $p = 0.853$	$r = -0.07$ $p = 0.533$	$r = -0.12$ $p = 0.268$	$r = -0.01$ $p = 0.944$	
Kaolinite	$\beta = 0.04$ $p = 0.8151$	$\beta = 0.15$ $p = 0.485$	$\beta = -0.001$ $p = 0.6913$	$\beta = -0.01$ $p = 0.6341$	altitude ~ precipitation $r = 0.9$
	$r = 0.05$ $p = 0.662$	$r = 0.08$ $p = 0.464$	$r = -0.01$ $p = 0.928$	$r = -0.02$ $p = 0.834$	
Particle size < 1μm prepared in water	$\beta = 0.05$ $p = 0.301$	$\beta = -0.17$ $p = 0.008$	$\beta = 0.003$ $p = 0.006$	$\beta = 0.01$ $p = 0.003$	WFA ~ precipitation $r = -0.2$
	$r = 0.11$ $p = 0.297$	$r = -0.26$ $p = 0.016$	$r = 0.20$ $p = 0.061$	$r = 0.30$ $p = 0.005$	
Fe_2O_3	$\beta = -0.01$ $p = 0.878$	$\beta = 0.01$ $p = 0.843$	$\beta = 0.004$ $p < 0.001$	$\beta = 0.02$ $p < 0.001$	WFA ~ altitude $r = -0.1$
	$r = -0.0001$ $p = 0.999$	$r = 0.04$ $p = 0.697$	$r = 0.47$ $p < 0.001$	$r = 0.48$ $p < 0.001$	
Zr	$\beta = -4.329$ $p = 0.045$	$\beta = 6.460$ $p = 0.013$	$\beta = -0.15206$ $p < 0.001$	$\beta = -0.8210$ $p < 0.001$	
	$r = -0.201$ $p = 0.064$	$r = 0.175$ $p = 0.107$	$r = -0.579$ $p < 0.001$	$r = -0.649$ $p < 0.001$	

Note: β - regression coefficient ; r = correlation coefficient; p = *p - values*
[¥] Water flow accumulation

Interpolated soil characteristics were extracted for 108 villages for which disease prevalence values were available (this excluded locations where the kriging standard error was greater than the mean). Univariate and multivariate regression analysis was carried out to analyse the relationships between interpolated soil characteristics and prevalence data for the 108 villages.

Table 14 shows univariate and multivariate associations between disease prevalence and soil characteristics. Multivariate analysis indicated that particle size, Fe_2O_3, Zr and kaolinite were not significantly associated with disease prevalence. However, particle size was retained in the multivariate model as previous evidence has suggested a role in disease causation (Price 1990). Multi-collinearity assessment estimated that Fe_2O_3 had a VIF greater than 10, so this variable was eliminated and multivariate analysis continued with the remaining soil characteristic variables; soil particle size <1 *µm* (analysed using water as a dispersant), and quartz, mica and smectite. All variables apart from soil particle size <1 *µm* were found to be significantly associated with prevalence with a VIF <5 in the final multivariate model (**Table 14**).

Table 14. Univariate and multivariate regression of prevalence of podoconiosis on soil properties, (*n* = 108).

Univariate analysis						Multivariate analysis				
Soil variable	**Estimate**	***p* – value**	**OR**	**CI**		**Estimate**	***p* - value**	**OR**	**CI**	
				2.5%	**97.5%**				**2.5%**	**97.5%**
Quartz	0.18	$p < 0.001$ ***	1.2	1.12	1.30	0.14	$p = 0.001$ **	1.2	1.1	1.3
Mica	0.09	$p < 0.001$ ***	1.1	1.07	1.12	0.09	$p < 0.001$ ***	1.1	1.1	1.1
Fe_2O_3	-0.62	$p < 0.001$ ***	0.5	0.46	0.63	NA[≠]				
Particle Size < 1μm	0.04	$p = 0.526$	1.0	0.92	1.17	-0.15	$p = 0.058$	0.9	0.7	1.0
Zirconium	0.02	$p < 0.001$ ***	1.02	1.02	1.03	NA[¥]				
Smectite	0.88	$p = 0.022$ *	2.4	1.11	4.94	1.04	$p = 0.007$ **	2.8	1.3	5.7
Kaolinite	-0.09	$p = 0.002$ **	0.9	0.86	0.97	NA[¥]				

Note: Number of villages included = 108
CI = confidence interval, OR = Odds Ratio
≠ Fe_2O_3 excluded: VIF > 10;
¥ Particle size, zirconium, and Kaolinite excluded *p*-values greater than 0.050

The final model included smectite (*OR* = 2.76, 95% *CI*: 1.35, 5.73; $p = 0.007$), quartz (*OR* = 1.16, 95% *CI*: 1.06, 1.26; $p = 0.001$) and mica (*OR* = 1.09, 95% *CI*: 1.05, 1.13; $p < 0.001$), each of which displayed positive correlations with podoconiosis prevalence in the study area. The model presented in *Equation 1* represents the relationship between the logarithm of the podoconiosis case count ($\log \tilde{y}$) and the three soil minerals. The regression model used village level adult population offset (as denominator), therefore the coefficients of each soil variable are rate ratios:

$$\log \tilde{y} = -8.24 + 0.14\ \text{quartz} + 0.09\ \text{mica} + 1.04\ \text{smectite} \qquad \textit{Equation 1}$$

Hence, keeping all other factors constant, the podoconiosis case count ($\tilde{y}$) for each soil variable becomes:

Podoconiosis case count alone = $\exp^{-8.24} = 2.64*10^{-4}$

Podoconiosis count considering increase in quartz

$= \exp^{-8.24+0.14} = \exp^{-8.24} * \exp^{0.14} = 3.04*10^{-4}$

Podoconiosis count considering increase in mica

$= \exp^{-8.24+0.09} = \exp^{-8.24} * \exp^{0.09} = 2.89*10^{-4}$

Podoconiosis count considering increase in smectite

$= \exp^{-8.24+1.04} = \exp^{-8.24} * \exp^{1.04} = 7.5*10^{-4}$

$$\tilde{y} = 2.64*10^{-4} + 3.04*10^{-4}\ \text{quartz} + 2.89*10^{-4}\ \text{mica} + 7.5*10^{-4}\ \text{smectite} \qquad \textit{Equation 2}$$

Note that *Equation* 2 does not present the mathematical addition of the factors for the development of podoconiosis. The *Equation* presents the effect of each soil variable on podoconiosis count when all other variables are considered constant. Therefore, based on the model, when the percentage of smectite in the soil increases by 1% (for instance a rise from 1% to 2% in the value across its full range), the podoconiosis case count almost trebles (*Equation 2*). Similarly, the increase in the podoconiosis case count will be 9.47% for mica and 15.15% for quartz. This assumption, based on the calculations, holds true when all other factors contributing to the development of podoconiosis (such as genetic susceptibility, an individual's behaviour in terms of foot washing, and shoe wearing practices) are held constant.

The coefficient of determination for the model was 40% ($r^2 = 0.4$) which indicates that the covariates in the final multivariate regression model accounted for approximately 40% of the variation in the outcome variable. The model's goodness-of-fit was tested by examining the residual deviance and comparing the deviance with a chi-square distribution. The residuals deviance test of the model gave a value of 6.8, while comparison of the residuals with a Chi-squared distribution gave zero (8.86×10^{-89}). The Q–Q plot (**Figure 22a**) confirmed that the empirical data were sufficiently close to the theoretical reference line, indicating a reasonably good model fit. The plots for the spatial distribution of the quasi-Poisson regression residuals (**Figure 22b**) showed the presence of spatial patterns.

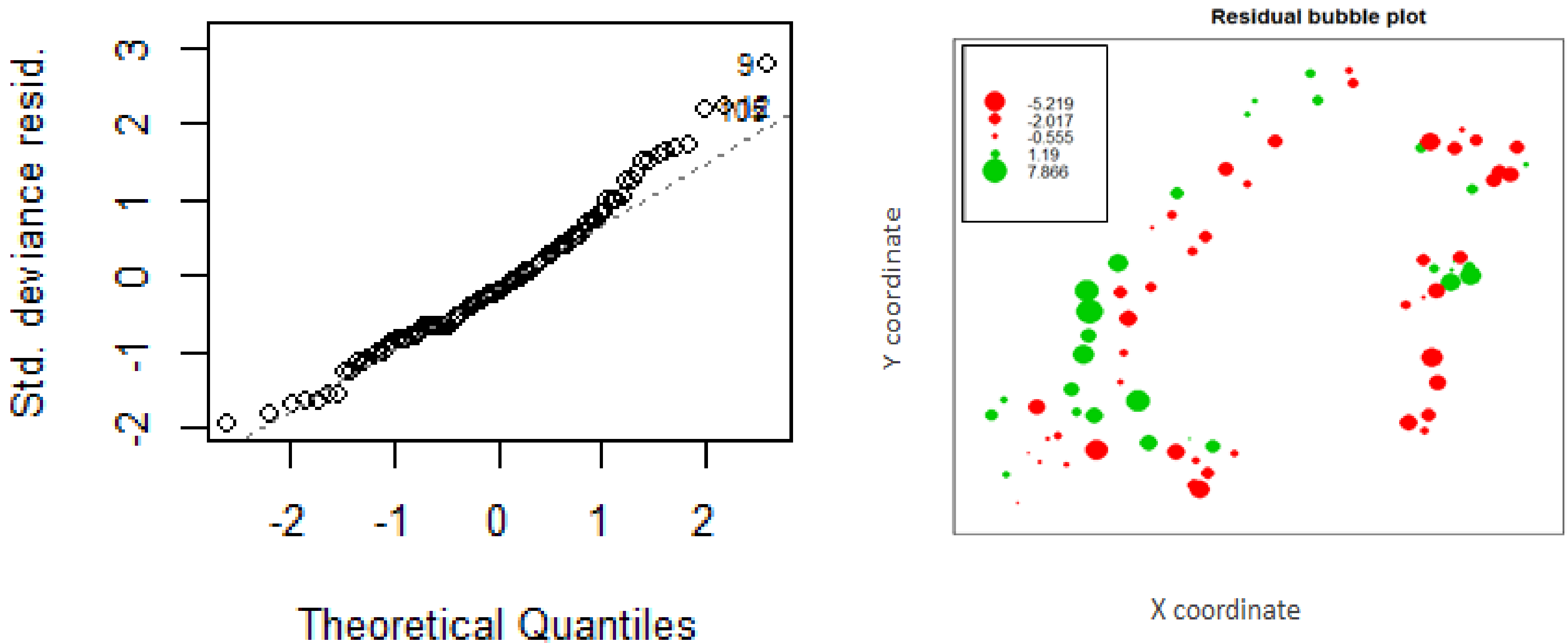

Figure 22. a) Normal Q - Q plot and b) Residual bubble spatial plot for residual diagnostics.

6.3. Chapter summary

Previous studies pointed to the need for comprehensive exploration of the range of soil characteristics, including chemical composition (major and trace elements) and soil particle size, in podoconiosis endemic areas. Understanding these soil properties in-depth will be a basic pillar for enhancing the knowledge gap in the actual pathogenesis of podoconiosis.

In the present study, we undertook an exploratory analysis to explain observed podoconiosis prevalence with a range of potential covariates including soil characteristics, underlying geology groups, altitude, precipitation, slope and water flow accumulation and thus developed a model including only the most significant environmental level correlates of podoconiosis.

The study was conducted in 12 *kebele* (administrative units) of northern Ethiopia. Geo-located prevalence data and soil samples were collected by a team of trained community health workers, geologists and a geographer. Secondary data including geological maps, a topographic map, meteorological data, and a digital elevation model were used. The soil data were analysed for a range of characteristics including soil chemical composition, mineralogy and particle size. Regression kriging of the soil variables with covariates was done. Statistical and spatial analyses were performed using ArcGIS and R statistical software packages. Exploratory univariate and multivariate analysis of podoconiosis distribution in relation to environmental covariates was conducted. Finally a model showing the relationship between variables was developed and tested.

Podoconiosis distribution showed spatial pattern along with variation in level of elevation and precipitation. Elevation, precipitation, and geology were analysed as secondary covariates while soil variables were analysed as primary covariates of podoconiosis. Stepwise exploratory analysis showed clay minerals (smectite, kaolinite and mica), quartz, iron oxide, zirconium and soil particle size <1 μm analysed in water to be associated with podoconiosis. The soil variables that remained in the final model were smectite, quartz and mica.

The findings of this study challenge some of the pre-existing assumptions that link podoconiosis with the presence of metallic oxides or trace elements within the soil (Price and Henderson 1978; Price and Henderson 1981; Frommel, Ayranci et al. 1993). Our study narrowed the focus into clay minerals, in particular smectite, and quartz (crystalline silica), as likely to be associated with the disease. The study exhibited a strong multidisciplinary approach, combining epidemiological, geological and geospatial methods. Our findings contributed to the growing research on the aetiology of podoconiosis, and provide new ground for further exploration of podoconiosis aetiology using biomedical and toxicology studies.

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7. Chapter 7 - Discussion and conclusion

7.1. Baseline survey

7.1.1. Discussion

Amhara region, where this study was conducted, is the second largest region in Ethiopia. This study is the largest of all household surveys of podoconiosis in Ethiopia conducted over the past ten years. It documented not only the magnitude and clinical presentation of podoconiosis, but also the extensive effects of podoconiosis-related psychological, physical and economic impairments on patients. The study has also confirmed the existence of substantial misconceptions surrounding causes, prevention, control and the familial nature of podoconiosis.

Men and women were equally affected by podoconiosis, as found in the Wolaita study (1:0.98) (Destas, Ashine et al. 2003) but in contrast to that in Gulliso (1:2.6) (Alemu, Tekola Ayele et al. 2011) and Ocholo (0.24:1) (Mengistu, Humber et al. 1987) studies. The prevalence of podoconiosis in the present study area (3.3%) was higher than the recent reports for Gulliso *woreda* in western Ethiopia (2.8%) (Alemu, Tekola Ayele et al. 2011) but lower than that reported among long-term residents in Ocholo village in southern Ethiopia (5.1%) (Mengistu, Humber et al. 1987), among resettlement scheme residents in Illubabor, western Ethiopia (9.1%), among residents in Gera and Didessa towns in southern Ethiopia (8-10%) (Kloos, Bedri Kello et al. 1992), among residents in Midakegn district, central Ethiopia (Geshere Oli, Tekola Ayele et al. 2012) , and in Wolaita, southern Ethiopia (5.5%) (Destas, Ashine et al. 2003). The prevalence falls within the earliest national estimate of 0.4% to 3.7% across fifty-six markets (Oomen

1969). The prevalence of podoconiosis found in the present study was greater than the previous estimates in Gojam of 2.4% based on market counts by Oomen (Oomen 1969) and 2.3% based on school enquiries by Price (Price EW 1974) nearly four decades ago in Debre Markos, the capital of East Gojam zone. These studies had limitations since they were based on market counts of cases and school enquiry of students from villages and were therefore likely to underestimate the overall prevalence. Nevertheless, the absence of decline in prevalence of podoconiosis after four decades clearly reflects that podoconiosis has remained neglected in the Amhara region.

This study reinforces recent evidence from Gulliso indicating the enormous burden imposed by ALA among podoconiosis patients (Alemu, Tekola Ayele et al. 2011). The frequency of attacks, duration of pain and number of bed days due to ALA were all considerable. Physical examination of the interviewees reporting ALA at the time of interview confirmed the widespread frequency of the problem. Although the present study did not compare the financial status of patients with unaffected people in the area, previous studies have shown the large economic burden imposed by podoconiosis [25]. This burden arises because of the concentration of the disease in the productive age group as seen in this study and the effect of ALA hampering productivity (Destas, Ashine et al. 2003; Tekola, Mariam et al. 2006).

The findings of this study are broadly consistent with others in southern and south-western Ethiopia and north-western Cameroon that have documented the social and economic impact of podoconiosis in endemic areas (Wanji, Tendongfor et al. 2008; Tekola, Bull et al. 2009; Alemu, Tekola Ayele et al. 2011). Functional impairments such as inability to move or to do daily occupational work or household chores hamper patients' physical capabilities. As with other debilitating diseases such as lymphatic filariasis, functional impairment worsens the burden of the disease (Ramaiah, Kumar et al. 1997) and can affect economic productivity of patients. Patients reported that they worked fewer hours, stopped work or were only able to work with reduced energy. They also perceived their productivity and income to have decreased more since becoming affected with podoconiosis than their healthy neighbours. Similarly, experiences from families of lymphatic filariasis patients show that the economic loss due to the disease may push an already poor family to near destitution (Perera, Whitehead et al. 2007). The interconnection of lymphatic filariasis with poverty acts beyond the household level, and contributes to poverty at national level, reducing the likelihood of achieving the Millennium Development Goal related to poverty reduction (Molyneux 2003; Durrheim, Wynd et al. 2004). Likewise, economic analysis of productivity loss due to podoconiosis indicated enormous economic losses in southern Ethiopia (Tekola, Mariam et al. 2006), and the subjective reports of this study suggested that similar losses occur in other podoconiosis-endemic areas of Ethiopia. This productivity loss due to podoconiosis cannot be addressed with mere treatment of the disease. Alternative income generating activities that are less physically demanding are needed.

Nearly half of the patients interviewed had misconceptions about the cause of podoconiosis. Less than half of patients believed podoconiosis could be prevented (37.5%) or controlled (40.4%). Among individuals who said that podoconiosis could be prevented, some believed that avoiding physical contact with patients might be helpful. Some suggested that control might be possible by avoiding contact with patients (assuming podoconiosis was infectious) or by using holy water (assuming the cause was supernatural). Avoidance of contact may partly explain the high divorce rates among the study subjects. Previous studies in the southern and northern parts of Ethiopia and north-western Cameroon have also observed multiple misconceptions about the cause of podoconiosis including witchcraft or contact with podoconiosis patients among the community (Wanji, Tendongfor et al. 2008; Yakob, Deribe et al. 2008; Tomczyk, Tamiru et al. 2012). These misconceptions have an effect on the individual, the community and on podoconiosis programs and interventions. Like other debilitating diseases such as leprosy and lymphatic filariasis, patients with podoconiosis may find it difficult to be accepted by communities because of exclusion from community events and marriage (Suma, Shenoy et al. 2003; Luka 2010). The belief that podoconiosis is contagious could make communities avoid contact with patients and health professionals unwilling to provide health care (Yakob, Deribe et al. 2008; Yakob, Deribe et al. 2010). Myths about the causes, prevention and treatment of podoconiosis may mean that patients look for alternative ways to treat the disease, avoid seeking treatment, or be less likely to adopt shoe wearing and foot hygiene (Tomczyk, Tamiru et al. 2012).

Intervention must target these knowledge gaps through education directed not only to people with podoconiosis but also to the general community. Involving patients that have witnessed improvement through adherence to treatment, as experienced by an intervention program in the southern part of Ethiopia needs to be scaled up to other endemic areas (Davey and Burridge 2009). Delivery of podoconiosis care and support must also be integrated with national neglected tropical disease initiatives such as those focusing on the importance of hygiene.

Approximately two-fifths of participants had a family member affected with podoconiosis. The study found that more patients stated that they had an affected first degree (parent or child) or second degree (grandparent or siblings) relative than a more distant affected relative. However, this may be affected by recall bias or because of loose family ties beyond first and second degree relatives. Participants assumed that podoconiosis clustering within families meant that it could not be prevented or controlled. Previous studies in southern Ethiopia have shown widespread beliefs about the familial nature of podoconiosis (Yakob, Deribe et al. 2008; Tekola, Bull et al. 2009). Segregation analysis (Davey, Gebrehanna et al. 2007) and more recently a genome-wide association study (Tekola Ayele, Adeyemo et al. 2012) have demonstrated genetic susceptibility to podoconiosis. A recent study in southern Ethiopia has explored the influence of beliefs about heritability on behaviour, and suggests that those who think podoconiosis is heritable are less likely to endorse prevention of disease by use of shoes (Ayode, McBride et al. 2012). Similar consequences of beliefs about heritability are seen in the present study, with 8.7% of respondents giving this as a reason for thinking that podoconiosis could not be prevented or treated. Participants in another study in southern Ethiopia used more biologically-based terms such as ‘bone’, and ‘blood’ (Tekola, Bull et al. 2009) to describe familial clustering than did the present study participants. A more detailed study is needed to understand better the extent of existing understanding about familial clustering and stigma in north Ethiopia. Even though familial clustering of podoconiosis is a source of stigma against patients, the benefits of targeting and prioritizing high risk groups for intervention should be taken into account (Tekola Ayele, Adeyemo et al. 2012).

Observing that podoconiosis clusters in families, and believing that it cannot be prevented or treated are important sources for social and psychological distress among affected people. Intense stigmatization of podoconiosis patients has been shown to be widespread by previous studies (GebreHanna 2005; Wanji, Tendongfor et al. 2008; Yakob, Deribe et al. 2008; Tekola, Bull et al. 2009; Yakob, Deribe et al. 2010; Tora, Davey et al. 2011). In this study, podoconiosis patients' experience "enacted" stigma in the form of isolation from community events such as feasts and church ceremonies. This may lead to "internalising" (accepting) the stigma (Weiss 2008). Tora *et al* explored the psychological effect of stigma, documenting how stigmatised patients opt for avoidant types of coping which in turn separates patients further from non-patients and aggravates stigma-induced stress (Tora, Davey et al. 2011). These observations demonstrate the need for further investigation to measure the extent of psychological trauma and the mental health status of podoconiosis patients. In addition to exacerbating emotional distress, stigma may delay treatment seeking and affect adherence to treatment as seen in this study and previous research (Perera, Whitehead et al. 2007; Weiss 2008).

Based on the findings, the potential opportunities and challenges for primary and secondary prevention of podoconiosis in Gojam were reviewed. Primary prevention consists of avoiding prolonged skin to soil contact by wearing protective shoes and socks. Secondary prevention requires regular foot hygiene, and the use of antiseptic soaks and emollients. Early evidence of effectiveness of this treatment in reducing leg circumference and disease stage and in improving quality of life has recently emerged from a small, uncontrolled follow-up study by Sikorski *et al*. (Sikorski, Ashine et al. 2010). Since most cases of podoconiosis in the present study were in the early stages of 2 and 3, secondary prevention is potentially possible in this area.

The study also revealed several challenges to primary and secondary prevention. First, there were serious deficiencies in protection against the soil with footwear. Suboptimal shoe-wearing behaviour was reported even among those owning shoes, and observation at the time of interviews confirmed a substantial proportion of barefoot respondents. The types of shoes worn by most patients were not considered protective. Although men owned more pairs of shoes than women, there were similar low levels of shoe-wearing and foot-washing practice among men and women resulting in almost equal prevalence of disease. However, more advanced stages were seen among women. The similar average age of onset of leg swelling and age of first shoe wearing indicate prolonged contact with the soil and delay in protection.

Secondly, there was substantial continuous contact with irritant soil. In addition to daily work as subsistence farmers, the frequency of travel and walking distances to and from water sources, markets and fields considerably increased the duration of contact with the soil. Limited access to water (average round trip of 40 minutes) may explain poor foot hygiene as patients prioritize water for drinking and cooking before washing their feet. The average time spent travelling to get water in Gojam was greater than in Gulliso, western Ethiopia (average round trip of 20 minutes) and also greater than the

WHO recommended maximum (30 minutes round trip) (WHO 2010). This will constitute a considerable challenge for primary and secondary prevention of podoconiosis in Gojam.

Thirdly, the long interval between onset of swelling and seeking treatment indicates an important delay in accessing secondary prevention to control disease progression. Most of the podoconiosis cases in this study were found in the highland areas away from the towns where most health centres are based. There was no podoconiosis treatment in Amhara Region before the establishment of the IOCC podoconiosis prevention and treatment centre in June 2010. The patients who visited health centres for treatment may not have received appropriate treatment, forcing them to try other forms of support including traditional medicine. Previous studies have demonstrated health professionals' misconceptions surrounding podoconiosis and stigmatizing attitudes towards patients, so patients who attended formal health facilities may not have received treatment (Yakob, Deribe et al. 2010).

Fourthly, limited knowledge and misconceptions about the disease by the patients themselves may also act as a barrier against primary and secondary prevention by delaying treatment seeking behaviour (Yakob, Deribe et al. 2008). In Wolaita, adopting avoidant coping strategies led to patient isolation and reduced access to health care (Tora, Davey et al. 2011). Similarly, linking ALA to a range of experiences including *mitch* (exposure to the sun inducing inflammation) resulted in poor treatment seeking and resorting to traditional medicine for a significant proportion of the patients.

7.1.2. Conclusion

The prevalence of podoconiosis in Gojam was almost identical to that described in the 1970s by Price and Ooman (Oomen 1969; Price 1974) indicating that the disease has been almost entirely neglected. Significant challenges remain in increasing protective shoe-wearing practices, improving access to water for washing, and encouraging earlier treatment seeking. However, given that early stages of disease were predominantly observed, if treatment were offered, it is likely to be effective.

Moreover, this study showed that in North Ethiopia, podoconiosis has strong psychosocial, physical and economic impacts on the lives of patients. Concerns related to familial clustering, and poor understanding of the causes, prevention and control of the disease add to the disease burden. The high prevalence and profound consequences of podoconiosis in this area call for health education about the causes, prevention and control of podoconiosis to be integrated into national Neglected Tropical Disease initiatives. The extent of psychological distress due to stigma needs further exploration and carefully tailored interventions. The familial nature of the disease may enable targeted intervention, so families of the affected are given priority in resource-constrained areas (Tekola Ayele, Adeyemo et al. 2012). The economic disadvantages that result from physical impairment due to podoconiosis may be averted by introducing alternative income generating activities.

7.2. Individual level correlates

7.2.1. Discussion

The discussion was organised according to the conceptual framework (**Figure 10**). Sex, age, area of residence and family history were classified as potential risk factors for the development of podoconiosis. Income, education level, age for first shoe, feet washing practices, previous and current shoe ownership, history of farming and history of walking were classified as both risks for, and outcomes of, podoconiosis. Marital status and history of the disease among cases were classified as outcomes of podoconiosis.

This study compared podoconiosis cases and controls living in three areas categorised by podoconiosis prevalence into 'high', 'medium' and 'low' endemicity. In addition, disease history was explored among cases. Mean age of cases and controls was well above the average age for the development of podoconiosis reported by earlier studies, which is usually after the second decade of life (Alemu, Tekola Ayele et al. 2011; Geshere Oli, Tekola Ayele et al. 2012; Molla, Tomczyk et al. 2012; Tekola Ayele, Alemu et al. 2013). Therefore, it is unlikely that the controls in this study would become cases.

Sex ratio among case in our study did not show difference between men and women for the development of the disease, similar to findings in East and West Gojam of northern Ethiopia, Wolaita of southern Ethiopia and Pawe of north western Ethiopia (Birrie, Balcha et al. 1997; Destas, Ashine et al. 2003; Molla, Tomczyk et al. 2012). However, other studies have shown that females have increased odds of being affected (Mengistu, Humber et al. 1987; Alemu, Tekola Ayele et al. 2011), while another study showed males had increased odds of being affected (Kloos, Bedri Kello et al. 1992).

Sex ratio among cases in our study did not show difference between men and women. However, the men to women ratio in the controls (1.6:1) showed male preponderance that produced statistically significant association. This may be because by including the oldest person in the control household, men who are the main household heads were more likely to be included in the study. This might have driven the observed differences in income, education, marital status, current shoe ownership, and observed shoe type between cases and controls. However, history of age for the first shoe wear, the most important predictor of podoconiosis status found in the study, is less likely to be affected

The ability of this study to determine risk factors for podoconiosis is limited since we included prevalent cases rather than incident cases. Podoconiosis takes many years to develop, making it labour-intensive and costly to include and follow incident cases. However, by including controls living in proximity with cases, we partially controlled for potential environmental, social and behavioural confounding factors.

Low income is both a prior risk for, and a potential outcome of, podoconiosis. Cases earned less each month than controls, and additionally female cases earned less than male cases. Income did not vary significantly by level of podoconiosis endemicity. We assessed average household income as a proxy indicator to compare the level of poverty among study subjects to evaluate relative economic inequality rather than defining level of poverty. However, we acknowledge that reported income may be biased because it is based on estimations made by the study subjects, and a measure of wealth index composed of expenditure and income would be more informative. In addition, we cannot be sure whether the poverty level reported during the study preceded occurrence of podoconiosis or was a consequence of the disease. A similar relationship, however, between poverty and disease status has been demonstrated in other NTDs, including lymphatic filariasis (Perera, Whitehead et al. 2007; Hotez, Fenwick et al. 2009; WHO 2010). Previous studies have indicated that most podoconiosis-affected people are in the ‘productive’ age group (Destas, Ashine et al. 2003; Tekola, Mariam et al. 2006; Alemu, Tekola Ayele et al. 2011; Molla, Tomczyk et al. 2012). A study on productivity loss due to podoconiosis in Southern Ethiopia showed that the majority of cases worked fewer days than individuals free of podoconiosis, and hence lost 45.0% of total productive work days (Tekola, Mariam et al. 2006). We also found income disparity by gender, with female cases earning less than male cases similar to the southern Ethiopian study (Tekola, Mariam et al. 2006). Higher levels of ‘ever’ owning shoes and wearing more ‘protective’ shoes among men may also result from gender disparity in income, as has also been found in previous studies (Alemu, Tekola Ayele et al. 2011; Tekola Ayele, Alemu et al. 2013).

Fewer cases went to school or were married than controls. Neither marital status nor ‘ever’ going to school differed in areas with different levels of podoconiosis prevalence. The influence of podoconiosis on marriage has previously been reported in other studies (GebreHanna 2005; Ayode, McBride et al. 2012; Molla, Tomczyk et al. 2012). We also found that a significantly higher proportion of female cases were unmarried compared to male cases or female controls. Stigma-related mate selection and marriage assessment may result in female cases having increased odds of being unmarried compared to male cases, possibly due to differences in access to resources (Tora, Davey et al. 2011). The lower levels of education we found among cases have also been noted in previous studies (Alemu, Tekola Ayele et al. 2011; Tora, Davey et al.

2011; Molla, Tomczyk et al. 2012), and may result from a range of factors. Firstly, since most of the cases are poor, limited financial access may lead to less school enrolment. Secondly, stigma related to podoconiosis may force students to discontinue their education (Ayode, McBride et al. 2012; Molla, Tomczyk et al. 2012). Thirdly, impaired mobility due to podoconiosis and frequent morbidity from ALA may affect schooling (Molla, Tomczyk et al. 2012; Molla, Tomczyk et al. 2012). The relationship between podoconiosis and education is bidirectional, so higher levels of education may lead to positive behaviours (earlier age at first shoe wearing and more frequent foot-washing).

Most of the cases were in the second stage of podoconiosis and had a podoconiosis-affected first or second degree relative. The stage of podoconiosis was consistent with that found in northern and southern Ethiopia (Tekola Ayele, Mariam et al. 2008; Molla, Tomczyk et al. 2012). Familial clustering of podoconiosis, where biologically closer relatives were more affected than remote relatives, supports the hypothesis that genetic factors may influence susceptibility to podoconiosis (Davey, Gebrehanna et al. 2007; Tekola Ayele, Adeyemo et al. 2012). The fact that approximately one out of three podoconiosis- affected households had at least two podoconiosis-affected individuals implies that podoconiosis intervention programs could use the location of affected index cases to trace additional affected individuals and target resources (Tekola Ayele, Adeyemo et al. 2012).

During the interview, the majority of both cases and controls were observed either to be barefoot or to be wearing non-protective shoes. Prolonged barefoot-walking in podoconiosis-endemic areas has long been observed to be associated with podoconiosis (Price 1976; Price 1984; Davey 2008). In the present study we explored having ‘ever’ owned shoes, current shoe ownership, and age at first wearing shoes. Cases and controls did not differ significantly in terms of ‘ever’ shoe ownership. On the other hand, controls owned more pairs of shoes, but these were of less protective types than those owned by cases. It appears that controls were more able to buy shoes because of their higher income. The majority of the cases started wearing shoes after disease onset, and wore more protective shoes. The increased current protective shoe ownership among cases may reflect proactive responses to disease development. Among cases, men were more likely to have ‘ever’ owned shoes and to wear more protective shoes, when compared to women. A previous study in western Ethiopia showed that men owned better quality shoes than women (Alemu, Tekola Ayele et al. 2011), and other studies in northern and southern Ethiopia showed more women than men to be barefoot (Ayode, McBride et al. 2012; Molla, Tomczyk et al. 2012).

The average age at first wearing shoes for both cases and controls was larger than that reported by a previous study in northern Ethiopia (Molla, Tomczyk et al. 2012). The difference may partly be because the current study was conducted in rural *kebeles* whereas the earlier baseline survey covered both rural and urban *kebeles*. A study in southern Ethiopia showed differences between rural and urban residents in physical and financial access to treatment including starting to wear shoes (Tora, Davey et al. 2012). On average, cases started wearing shoes when they were in their late 30s (mean = 38.7, SD = 15.5), hence ten years later than controls. Age at first wearing shoes was positively correlated with age of onset of podoconiosis, suggesting that most cases might have started wearing shoes after the development of podoconiosis as observed in other studies in western and northern Ethiopia (Alemu, Tekola Ayele et al. 2011; Molla, Tomczyk et al. 2012).

This study showed that shoe wearing has generally increased over the past three decades among both cases and controls. In addition, the age at which the subject first wore shoes was highly correlated with the subject's age, which indicates that the age at which subjects first wore shoes became younger as shoe wearing increased. The trend in average health and health-related indicators of Ethiopia for the past three decades showed an improvement in most indicators including higher Gross Domestic Product (GDP) and increased adult literacy rates (Abraha and Nigatu 2009). Changes in shoe wearing practices preceded health promotion activities linked to podoconiosis treatment facilities in the area and are, therefore, are possibly related to these secular changes (Tomczyk, Tamiru et al. 2012).

The study compared walking, farming and foot-washing practices between cases and controls. Months spent on different farming activities each year, one-way average times walked and frequency of travel to fields, water sources and regular market visits were assessed. The average one-way walking time to farmed fields and water sources was not different for cases and controls. However, cases travelled for longer and less frequently to market. As observed in previous studies (Molla, Tomczyk et al. 2012), this may be a result of slower walking due to the physical impairment imposed by podoconiosis or an 'avoidant' coping mechanism against stigmatization that drives patients away from the nearest markets where other community members visit (Tora, Davey et al. 2011). A composite indicator for the time travelled and frequency of travel per month showed that there was no difference between cases and controls living in different areas. Cases who were farmers spent less time on farming activities than controls, whereas there was no difference by area of endemicity for controls. This suggests that podoconiosis-affected individuals become less able to farm and hence less productive due to the disease (Tekola, Mariam et al. 2006; Molla, Tomczyk et al. 2012).

Foot-washing practices did not vary significantly between cases and controls. It is possible that study subjects provided ‘socially acceptable’ (false) responses, or that cases improved their washing practices after development of the disease. During interview, cases were observed to have more dirty and cracked feet. We acknowledge that observed reports of “cracked” and “dirty’’ feet among cases may be affected by interviewer subjectivity. However, it is important to recognise (even qualitatively), as long-standing cracked feet may increase the risk of soil particles penetrating through the skin (Filon, D'Agostin et al. 2009), triggering podoconiosis.

7.2.2. Conclusion

To summarise, this study showed socio-demographic and behavioural differences between podoconiosis-affected cases and unaffected controls, and between female and male cases in northern Ethiopia. The study used a matched case-control design, where controls were taken from the nearest household to cases although not of the same age or sex. Therefore, during the analysis, covariates were adjusted for sex and age. Cases were observed to earn less, be less educated and were less likely to be married, when compared with controls. These disparities were more pronounced among female than male cases. Shoe wearing practices, particularly starting to wear shoes after the average age of development of podoconiosis, was significantly more common among individuals affected with podoconiosis than controls. It is acknowledged that genetic and environmental variation modifies the level of susceptibility to podoconiosis (Price 1972; Price 1974; Price 1974; Price 1976; Price 1976; Price 1984; Davey, Gebrehanna et al. 2007; Tekola Ayele, Adeyemo et al. 2012); however, we believe that addressing the individual level correlates identified in this study may influence the occurrence and associated burden of podoconiosis. Most importantly, the observed secular increases in shoe-wearing over recent years may indicate opportunities to promote shoe-wearing without increasing stigma among those at high risk.

7.3. Environmental level correlates

7.3.1. Discussion

Several previous studies have evaluated environmental factors, including soil properties in endemic areas, to further knowledge about podoconiosis. However, they failed to give a complete picture for several reasons. First, some of the findings were based on subjective assessments. For instance, the association of red soil and podoconiosis was established based on Price's visual observation of red soil and higher disease prevalence within a 25 km radius (Price 1974). Later, Price explained that the redness was considered to be due to iron oxide content; based on records of soil studies that classified the soil in Price's study area as tropical lateritic or 'ferrisol' soils (Price 1974). Second, the sample sizes used in previous studies were small. For instance, a comparative study that postulated association of podoconiosis with elements within the soil such as silicon and aluminium included lymphatic tissues of 38 individuals in Ethiopia and 17 in Cameroon (Price and Henderson 1978; Price, McHardy et al. 1981). Although the soils in these disease endemic areas were analysed, exploration of the association between soil types and disease prevalence was absent. Third, analysis of soil properties did not reproduce the results in multiple studies. For instance, Frommel *et al*. (in 1990s) suggested the role of trace elements such as zirconium; however, Price *et al*. (1980s) emphasised the role of silicon and aluminium although the finding of statistically significant differences in Al/Si ratio in the tissues of cases and controls from Ethiopia was not later reproduced in a study conducted in Cameroon (Price and Henderson 1978; Price, McHardy et al. 1981; Frommel, Ayranci et al. 1993). More recently, Harvey *et al.* suggested that the effects of the amorphous silica commonly found in podoconiosis-endemic areas are not comparable with those of crystalline silicates, and that amorphous silica is unlikely to cause podoconiosis (Harvey, Powell et al. 1996). These conflicting findings highlight the need for a comprehensive exploration of soil characteristics, including those that have been previously linked to the disease, to fully elucidate the potential causes of podoconiosis. Understanding these soil properties will be fundamental to solving the longstanding puzzle of the pathogenesis of podoconiosis.

In this study an exploratory analysis was done to explain observed podoconiosis prevalence with a range of potential covariates including soil characteristics, underlying geology groups, altitude, precipitation, slope and water flow accumulation. From this we have developed a model that identifies the environmental factors that correlate significantly with podoconiosis.

This study identified preliminary associations between prevalence of podoconiosis and soil characteristics in a study site in Ethiopia. It begins to fill the research gap left by previous work which either did not directly assess soil composition in the areas where study participants lived (Price, McHardy et al. 1981), or which assessed soil composition taken from areas dichotomized into endemic or non-endemic based on expert opinion and without prevalence data (Price and Henderson 1978). In addition, recent developments in soil chemical analysis techniques and advances in geospatial and statistical methods enabled us to explore environmental correlates more extensively than was possible previously.

We found that the prevalence of podoconiosis was positively associated with the quantities of smectite, mica and quartz (crystalline silica) measured in the soil. The correlation between podoconiosis and smectite was stronger than that between podoconiosis and other phyllosilicates (kaolinite, chlorite and mica) or quartz. Smectite is a name given to group of clay minerals classified as a 2:1 phyllosilicate, with a structure in which two tetrahedral silicate sheets sandwich a central octahedral silicate sheet. In general, 2:1 phyllosilicates have large surface areas (due to their reduced crystallite size), are able to undergo isomorphous substitution (ion exchange within its structure) and often have elevated surface reactivity. The presence of 2:1 phyllosilicates in soils typically results in the deposits displaying distinctive characteristics such as high cation exchange capacity and shrink-swell properties. Smectite has considerable properties of water absorption and expansion, and is able to modify water flow (Odom 1984).

The biological properties of smectites have mostly been investigated in relation to gastrointestinal and dermatological therapeutic effects. Smectites are known as dermatological protectors for their ability to adhere to the skin, form a protective film and absorb greases and toxins (Carretero 2002; Carretero and Pozo 2010) . However, these properties of adherence and water absorption might potentially, through establishment of an external water gradient influencing permeability of the stratum corneum, increase transdermal uptake of potential toxins (Saroha, Singh et al. 2013). Release and transdermal uptake of a range of ions bound to pelotherapy clays has been demonstrated (Tateo, Ravaglioli et al. 2009), so it is possible that ionic species adsorbed to clays of endemic areas are exchanged across the skin of the lower leg and foot.

Other studies have investigated the effects of clays on infection. Montmorillonite, a specific mineral within the smectite group that typically results from the weathering of volcanic ash, was noted in the 1970s to have a higher infection potentiation effect than kaolinite and illite. (Rodeheaver, Pettry et al. 1974). On the other hand, recent studies have demonstrated bactericidal effects of hydrated clay in which cell death occurs by "exchange of soluble clay constituents toxic to the bacteria". Williams *et al.* noted that expandable clay minerals, particularly illite-smectite, had the most pronounced antibacterial properties (Williams, Metge et al. 2011) due to extreme pH and Fe concentration, while Otto and Haydel recently demonstrated powerful antibacterial activity of illite-smectite rich clay mixtures (Otto and Haydel 2013) due to Cu^{2+} and Zn^{2+} ions. Closer examination of the mechanism of action through linear regression demonstrated antibacterial activity to be positively correlated with concentration of Cu^{2+} and Zn^{2+} ions, negatively correlated with Fe^{3+} and no correlation with pH. Further investigation of the role of clay mineral types in infection may improve our understanding of the pathogenesis of episodes of super-infection and ALA (frequent complication of podoconiosis) (Fuller 2005; Molla, Tomczyk et al. 2012; Ferguson, Yeshanehe et al. 2013).

Mica, quartz, and the element zirconium were also significantly associated with increased prevalence of podoconiosis. In the past, a number of researchers have independently observed the presence of clay minerals such as mica, kaolinite and smectite in the soil samples they analysed (Price and Henderson 1978; Price, McHardy et al. 1981; Price and Bailey 1984; Frommel, Ayranci et al. 1993). Price *et al.* found amorphous silica and aluminium oxides in the lymph nodes of podoconiosis cases and postulated that these minerals, particularly silica, may be involved in the pathogenesis of podoconiosis (Price, McHardy et al. 1981; Price and Bailey 1984). Frommel *et al.* suggested that the high level of soil trace elements such as Zr found in podoconiosis-endemic areas was responsible for the development of podoconiosis (Price and Henderson 1978; Price and Henderson 1981; Frommel, Ayranci et al. 1993). Examination of more recent studies and additional literature suggests that amorphous silica and zirconium are unlikely to be toxic. For example, amorphous silica is considered less toxic in the human body than quartz (a form of crystalline silica ubiquitous in the environment). The ability of quartz to induce an inflammatory response and fibrosis has been demonstrated in the pathogenesis of lung silicosis (Cassel, Eisenbarth et al. 2008; Lacasse, Martin et al. 2009; Steenland and Ward 2013). Quartz is listed as a Group 1 carcinogen by the international Agency for Research on Cancer (IARC 2012). Finally, animal models have shown lymphatic fibrosis and blockage comparable to that found in podoconiosis on injection of crystalline silica suspension into the lower limbs of rabbits (Fyfe and Price 1985; Harvey, Powell et al. 1996).

Multiple studies corroborate that zirconium is unlikely to have a pathologic role in the human body (Couture, Blaise et al. 1989; Emsley 2001). Our finding of elevated zirconium in podoconiosis-endemic areas may suggest that this element plays another role, such as in facilitating dryness and cracking of skin on the feet. A recent study in Ethiopia showed that podoconiosis cases had lower stratum corneum hydration than unaffected controls, resulting in skin dryness and cracking which, in turn, may facilitate the ingress of mineral particles or microorganisms through the skin barrier (Ferguson, Yeshanehe et al. 2013). The ability of zirconium to accumulate in skin is supported by a study that detected high quantities of zirconium in the stratum corneum after application of aluminium-zirconium tetrachlorohydrex, a common ingredient in antiperspirants (Cullander, Jeske et al. 2000). Adding zirconium to commonly used aluminium chloride antiperspirants increases antiperspirant efficacy (Benohanian 2001), and application of non-emollient antiperspirants was also shown to reduce sweat moisture in feet (Knapik, Reynolds et al. 1998). It is therefore possible that zirconium in the soil plays a role in dehydration and cracking of the skin of the feet, thereby predisposing to podoconiosis.

In the present study, the proportions of soil particles with size less than 1 μm, prepared both in water and in dispersants, were not significantly associated with prevalence of podoconiosis. Previous studies suggested that soil particle size less than 5 μm may be relevant for the development of podoconiosis (Price 1990). In addition, observation of soil particles as large as 7 μm in inguinal lymph node and 25 μm in dermis of prolonged barefoot people in podoconiosis endemic areas (Blundell, Henderson et al. 1989) is likely due to a more compromised (cracked) skin in podoconiosis cases (Molla, Tomczyk et al. 2012; Ferguson, Yeshanehe et al. 2013; Molla, Le Blond et al. 2013). Experimental studies have also shown that particle size as small as 1 μm can penetrate intact skin with motions such as wrist bending (Tinkle, Antonini et al. 2003) signifying that fine particles can potentially penetrate the intact skin of the foot. More importantly, the well-known fine size of clay minerals (< 2 μm) (Guggenheim and Martin 1995) such as smectite and mica that were found to be associated with podoconiosis in the present study, and previous suggestion of a more important role of small particles in the development of podoconiosis (Price 1990), supports the hypothesis that fine soil particles may be more responsible for the development of podoconiosis than coarse particles.

Our model captured 40% of the variation in podoconiosis prevalence. The regression residuals indicate that the development of podoconiosis depends on aetiological factors other than purely environment factors. Genetic susceptibility has been shown to be another key aetiological factor (Tekola Ayele, Adeyemo et al. 2012) , as have shoe-wearing practices (Tekola Ayele, Adeyemo et al. 2012; Molla, Le Blond et al. 2013). This study has limited capability to capture individual behaviours and genetic variations that are also likely to have been important factors in spatial autocorrelation (Burnett, Ma et al. 2001; Molitor, Jerrett et al. 2007). However, exploring the role of environmental factors, particularly soil composition, is essential in order to understand the development of podoconiosis in areas where the majority of the people go barefooted.

7.3.2. Conclusion

In conclusion, the findings of this study challenge some of the pre-existing assumptions that link podoconiosis occurrence with the presence of metallic oxides or trace elements within the soil (Price and Henderson 1978; Price and Henderson 1981; Frommel, Ayranci et al. 1993). Our study narrows the focus to clay minerals, in particular smectite, and quartz (crystalline silica). Our findings contribute to the growing research on the aetiology of podoconiosis, and provide new starting points for further exploration of podoconiosis aetiology using biomedical and toxicological studies.

7.4. On - going and future studies

Validation of the current model

This study involved novel interdisciplinary approaches by modelling epidemiological, geological and spatial data to understand the individual and environmental level correlates of podoconiosis. The final model found in the study should be validated and the methodological approaches should be refined in other podoconiosis endemic areas.

Spatial prediction and modelling of soil particles with podoconiosis prevalence

The purpose of the current study was to explore and explain the correlates of podoconiosis in areas with varying podoconiosis prevalence. The final model developed in the analysis was not used to predict prevalence of podoconiosis in another area. There is another on-going study that is developing podoconiosis national risk map based on elevation. In the future, a more refined model that applies Bayesian analysis should be developed to quantify the level of uncertainty in the model and to predict (extrapolate) the levels of prevalence and risk for developing podoconiosis taking into consideration the distribution of primary covariates, particularly soil.

Biomedical experiments

Cellular responses to the clay minerals (smectite and mica) and quartz (crystalline silica) identified in this study are being tested *in - vitro*. Additional experiments using patient tissue samples will be advantageous to identify the soil particle composition *in - situ*. Most importantly, patient tissue samples will be useful in understanding the toxic or inflammatory responses of the cell to soil particles, which will shed light onto the etiological significance of the soil particles identified.

Multilevel modelling

Multi-level modelling in which individual and environmental factors are analysed at the same time were deemed important (Mauny, Viel et al. 2004) because the causes of a disease at individual level (causes for cases) might not be the same as causes at population level (causes of incidence) (Rose 2001). For instance, studies in the rural highlands of Ethiopia, where podoconiosis is prevalent, indicated presence of collective norms and practices that go beyond financial access and may result in feet-to-soil exposure regardless of shoe ownership (Ayode, McBride et al. 2012; Ayode, McBride et al. 2013). However, multilevel modelling has its own drawbacks that include the need to choose limited predictors to avoid model complexity and grouping of individuals is theory based that does not show the actual demarcation (Diez-Roux 2000). The intertwined nature of individual and environmental correlates of podoconiosis needed in-depth, comprehensive investigation prior to multilevel modelling. The predictors identified in this individual and environmental correlates studies can be used as inputs for multilevel modelling.

7.5. Podoconiosis correlates study, an example of an Environment Wide Association Study (EWAS)

This study of individual and environmental correlates of podoconiosis was presented as an example of an Environment Wide Association Study (EWAS). EWAS, a term adopted from Genome-Wide Association Study (GWAS), had recently been shown to be a comprehensive way for broader scale assessment of diseases, such as type 2 diabetes and metabolic syndrome, and associated environmental factors including life style (Patel, Bhattacharya et al. 2010; Lind, Risérus et al. 2013). Podoconiosis is another good candidate for EWAS due to the podoconiosis associated range of factors that include genetic susceptibility, area of residence and individual practices (Tekola Ayele, Adeyemo et al. 2012; Molla, Le Blond et al. 2013). The individual and environmental correlate study brought together multidisciplinary team that linked multiple factors to exhibit host-environment relationship.

Over all the study built on hierarchy of evidence starting from the understanding the podoconiosis burden (disease magnitude, clinical presentation, patients' perception, prevailing stigma) to investigating in-depth and linking together risk factors and their outcome at individual (socio-demographic, area of residence, history of foot-soil exposure, history of disease progression among cases, foot-washing and shoe-wearing practices) and environmental level (geology, precipitation, altitude, slope, water flow direction and accumulation, and soil properties analysis).

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8. Appendices

Appendix 1. Information and consent form

Information Sheet

My name is …………………, and I am working with Addis Ababa University. You are invited to take part in this research study, which we hope will yield valuable information on what exactly in the soil causes podoconiosis (elephantiasis). Before you decide whether to take part it is important for you to understand why we are collecting this information and what it will involve. Please take time to read this paper carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information.

Background to the study.

Although it is widely understood that podoconiosis occurs when susceptible people have long-term contact with red clay soils, this study will help us identify exactly which mineral or minerals in the soil trigger the problem. We hope that this will help us understand more about how to prevent and treat podoconiosis. With your permission, we intend to:

1. Ask you a series of questions about you and your family, the way you live and work, and in particular, the contact you have with the red soil. If you have podoconiosis, we will also ask questions related to the disease and how you have managed it.
2. Record information on the location of your house and the rocks, rivers and vegetation nearby.
3. Take a soil sample from the field nearest to your house. This will be analyzed for mineral content in the UK.
4. Take a water sample from the household water storage vessel.

We will not take any biological samples from you.

Possible harms. We do not anticipate any harm to you from asking the questions or collecting the soil and water samples. The questions will take a maximum of 30 minutes of your time.

Benefits. At the end of the questions, we will explain to you more about the condition and how to prevent and treat it. If appropriate, we will put you in touch with a treatment site if there is one nearby. We will also offer you a bar of soap as a token of thanks for your time in answering the questions.

Confidentiality. All information which is collected about you during the course of the research will be kept on a password protected database and is strictly confidential. Any information about you which leaves the research unit will have your name and address removed so that you cannot be recognized from it.

Autonomy. If you wish to discontinue the questionnaire or the sample collection at any time, you may, however, all the information you give us is highly valuable to the study. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you decide not to participate, the treatment you or your family receives in future at government or NGO treatment sites will not be affected.

If something goes wrong. If a problem arises, you can report it to one of the project staff, your *kebele* head, or the study co-ordinators at the address given below.

What will happen to the research? We anticipate that the results of this immediate study will be available next year, and we hope to publish the results. You will not be identifiable in any publication.

Who is organizing and funding the research? The research has been funded by the Wellcome Trust, a UK-based funding body dedicated to improving human and animal health through research. The research is organized jointly by researchers in Addis Ababa and the UK. The research has been reviewed by the Institutional Review Board of the Faculty of Medicine, Addis Ababa University and the National Ethical Review Committee in Ethiopia, and by Brighton & Sussex Medical School Ethics Committee.

Contact Address:	Yordanos Belayneh	or	IRB, School of Earth Sciences
Cell Phone:	0911- 869-869		Addis Ababa University

Reference ID | | | | |

Title of Project: **Comparative study to identify the environmental trigger of podoconiosis in Ethiopia.**

Lay Title: **Soil types and podoconiosis in Ethiopia.**

Investigators: Yordanos Belayneh, Dr Gail Davey, Dr Mohammed Umer, Dr Dagnachew Legesse, Dr Jenn Le Blond, Dr Javier Cuadros, Dr Peter Baxter

Healthy Volunteers' Consent Form

Please read this form and sign it once the above named or their designated representative has explained fully the aims and procedures of the study to you.

- I voluntarily agree to take part in this study.
- I confirm that I have been given a full explanation by the above named and that I have read and understand the information sheet given to me which is attached.
- I understand that the investigators will ask a series of questions about me and my work.
- I understand that the investigators will take samples of soil and water.
- I have been given the opportunity to ask questions and discuss the study with one of the above investigators or their deputies on all aspects of the study and have understood the advice and information given as a result.

- I agree to comply with the reasonable instructions of the supervising investigator and will notify him immediately of any unexpected unusual symptoms or deterioration of health.
- I authorise the investigators to disclose the results of my participation in the study but not my name.
- I understand that information about me recorded during the study will be kept in a secure database. If data is transferred to others it will be made anonymous. Data will be kept for 7 years after the results of this study have been published.
- I understand that I can ask for further instructions or explanations at any time.
- I understand that I am free to withdraw from the study at any time, without having to give a reason.
- I confirm that I have disclosed relevant medical information before the study.
- I understand that if something goes wrong I can report it to one of the project staff or the study coordinators at the address given below.

Health Volunteers' Consent Form

Name: …………………………………………………………………………………………

Address: ……………………………………………………………………………………..

Telephone number: ……………………………………………………………………….

Signature: …………………… **Date:** ……………………………….

Investigator Statement

I confirm that I have fully explained the purpose of the study and what is involved to:

(Name of participant)

…………………………………………………………………………………………….

I have given the above named a copy of this form together with the information sheet.

Investigators Signature: ……………………….. **Name**: ……………………………….

Contact Address: Yordanos Belayneh or IRB, School of Earth Sciences

Cell Phone: 0911- 869-869 Addis Ababa University

Appendix 2. Household census tool for baseline survey of podoconiosis

Registration Format (Debre Markos) *Kebele*: ____________ Date: ___________ Page: ___

	HH number	Head	HH members	Have you seen patients with podoconiosis?	Podo? (*show picture*)	How many?	First Name	Father's name	Sex	Age	Marital status[1]	Children (0-15 yrs)
#	##	M/F	##	1=yes 2=no	1=yes 2=no	#			1=M 2=F	##	#	#
1												
2												
3												
4												
5												

[1] 1=Single, 2= married, 3=divorced, 4=widowed, 5=separated

Appendix 3. Household census tool for podoconiosis cases and control identification

A. **Household Census** (heads residents for more than 10 years, others residents for 6 months)

Site ___________ *Kebele* ____________ Village___________ Date_____________

No	Resident (Household Members)	Relationship to Head	Sex (Male/Female)	Age (years)	Marital Status[2]	Years lived in the *kebele*	Podoconiosis Yes/No
1	Head	Same					
2							
3							
4							
5							
6							
7							
8							
9							
10							

[2] 1=Single, 2= married, 3=divorced, 4=separated, 5= widowed

Appendix 4. *Questionnaire for baseline survey among podoconiosis patients*

***Kebele*: ………** **Ketena: ………….** **Nurse: …………..** **Nurse code_____**

Consent

We would like to ask you some questions to understand the problem of podoconiosis in your area. We also want to examine your legs. We hope that this will help plan services for people with this condition.

Thank you for participating in this study.

1. Registration

1.1. Name: ……………………………………
1.2. Sex: 1. Male 2. Female
1.3. Your Age? _______years
1.4. Number of years lived in the *Kebele* ___________years

2. History of Disease and perceptions about podoconiosis

2.1. How old were you (age) when you first noticed your legs are swollen? ______years
2.2. How long after the swelling did you try to get treatment care? _____years
2.3. Where did you go first?

1. Health centre
2. Health post
3. Hospital
4. Podoconiosis treatment centre
5. Pharmacy/drug store
6. Traditional healer
7. Other (specify) _____________________________

2.4. When were you last sick with a painful swollen leg?

1. ___ wks ago 2. ___ mths ago 3. ___ years ago 4. never (*GO TO QUESTION 2.6*)

INTERVIEWER: MAY I HAVE A SHORT LOOK AT YOUR LEG?

2.5.1. HAS THE PERSON GOT ACUTE ATTACK DURING THE INTERVIEW?

1. Yes
2. No (Go to QUESTION.2.6.1)

2.5.2. IF YES to Q2.5.1: WHAT SIGNS AND SYMPTOMS DO YOU OBSERVE?

1. Oozing
2. Tenderness (pain on touch)
3. Hot (on touch)
4. Fever
5. Swollen lymph node
6. Other _______________

2.6.1. Did you look for help?

1. Yes
2. No (Go to QUESTION.2.6.3)

2.6.2. If YES to Q.2.6.1: Where did you seek help?

1. Health centre
2. Health post
3. Hospital
4. Podoconiosis treatment centre
5. Pharmacy/drug store
6. Traditional healer
7. Other (specify) _____________________________

2.6.3. Did you stay in bed?

1. Yes
2. No (Go to QUESTION.2.6.5)

2.6.4. If YES to Q.2.6.3: how long did you stay in bed?

____days

2.6.5. How often in the last 12 months did you have this problem?

________times *or*
Every ______months

2.6.6. Which time of the year is this problem worse?

1. All the time
2. Rainy and wet season
3. Hot and dry season
4. Other (please, specify) ___________________

2.6.7. What precipitates acute attack symptoms?

1. Hard (laborious) work
2. A little more than usual work
3. Long walk
4. Other (please, specify) ______________

2.6.8. How do you usually cope with (react towards) acute attack episodes?

1. Resort to less exertive work
2. Stay in bed
3. Other (specify):______________

2.7. Why do you think you have podoconiosis?(*NEVER READ ANSWERS. PROBE. CIRCLE ALL THAT APPLY*)

1. I am barefooted
2. I or my family are cursed
3. This is a familial problem (it runs through 'blood/bone' of our family)
4. I got it following contagion with an affected person (e.g. wore his/her shoes)
5. Following snake bite
6 Following exposure to condensation
7. I don't know
8. Other (SPECIFY) ___________________________

2.8. Did you experience any social stigmatization/discrimination because you have podoconiosis?(*READ B-F ONE BY ONE. IF THEY ANSWER YES, UNDERLINE THE POINTS MENTIONED IN THE BRACKET. PROBE FOR OTHER EXPERIENCES AND PUT THAT UNDER '7'*)

1. No. People treat me like anyone else.
2. Yes, schooling (drop out, shunning, pointing fingers, pinching nose)
3. Yes, church (exclusion, shunning, pointing fingers, pinching nose)
4. Yes, marriage (exclusion, shunning, pointing fingers, pinching nose)
5. Yes, market place (people are not interested to buy my products)
6. Yes, feasts (exclusion, shunning, pointing fingers, pinching nose)
7. Others (specify) _______________________________

2.9. Do you think podoconiosis can be prevented?

1. Yes
2. No -----CIRCLE AND GO TO Q2.11
3. I don't know----- CIRCLE AND GO TO Q2.11

2.10. If the answer to q2.9 was 'YES': How can podoconiosis be prevented? (*PLEASE DON'T READ THE ANSWERS. PROBE AND CIRCLE ALL THAT APPLY*)

1. Wearing shoes protective of exposure to soil regularly
2. Washing feet with soap and water regularly
3. Avoiding marriage with affected families
4. Avoiding contact with affected people
5. Other (please, specify) ______________________

2.11. Do you think progression of podoconiosis can be controlled at early stages of the condition/is it curable?

1. Yes
2. No -----CIRCLE AND GO TO Q2.13
3. I don't know----- CIRCLE AND GO TO Q2.13

2.12. If the answer to q2.11 was 'YES': How can podoconiosis be controlled at early stages? (*PLEASE DON'T READ THE ANSWERS. PROBE AND CIRCLE ALL THAT APPLY*)

1. Wearing shoes protective of exposure to soil regularly
2. Washing feet with soap and water regularly
3. Avoiding marriage with affected families
4. Avoiding contact with affected people
5. Other (please, specify) ______________________

2.13. If the answer to q2.12 was NO: Why do you think podoconiosis cannot be controlled (cured)? (*PLEASE DON'T READ THE ANSWERS. PROBE AND CIRCLE ALL THAT APPLY*)

1. It is familial (runs through 'blood/bone')
2. There is no drug for it
3. I have never seen a cured person
4. Others (please, specify) ____________

2.14. Examination

	2.14.1. Stage (1-5)	2.14.2. Moss (1=yes 2=no)	2.14.3. Wound (1=yes 2=no)	2.14.4. Type (water bag, nodular, mixed)	2.14.5. Greatest below-knee leg circumference (cm)
1. Right Leg					
2. Left Leg					

3. Background

3.1.1. Educational status:

1. Cannot read and write
2. Read and write

3.1.2. If the answer to Q3.1.1 is (2): What grade are you? ____

3.2. Main occupation

1. Farming
2. Weaving
3. Daily labourer
4. House wife
5. Other (please specify): _____________

3.3. Marital status

1.Married 2. Single 3. Divorced 4. Separated 5. Widowed

3.4. Family history *(NOTE: THIS IS A VERY SENSITIVE, YET RELEVANT SECTION. SO YOU SHOULD BE EXTRA POLITE AND EXPLAIN THAT ALL INFORMATION WILL BE KEPT CONFIDENTIAL. IN ADDITION MENTION THAT THIS INFORMATION WILL BE RELEVANT FOR TARGETTING DISEASE PREVENTION AND TREATMENT PROGRAMS*)

3.4.1. Does any member of <u>your family</u> (meaning relatives such as parents, grandparents, cousins, siblings or children) have podoconiosis?

1. Yes
2. No (Go to QUESTION.3.4.3)

3.4.2. If YES to Q3.4.1: How are you related? *(PROBE FOR OTHER CATEGORIES)*

	a. Number	b. Sex 1=Male, 2=Female	c. Still alive? 1= Yes 2= No
3.4.2.1 Grandparent?			
3.4.2.2. Parent?			
3.4.2.3. Sibling?			
3.4.2.4. Child?			
3.4.2.5. Other family? (specify)			

3.4.3. How many members of <u>your household</u> (together with you) are affected?

______

3.4.4. Is that person available for interview?

1. Yes 2. No

NOTE TO INTERVIEWER*: IF THE ANSWER IS 'YES', RECORD THE FOLLOW*

AND GIVE APPOINTMENT FOR NEXT DAY INTERVIEW BY A NURSE.

Name___________________

Age______

Sex: 1. Male 2. Female

3.4.5.1. Are any children in the house complaining of problems with feet?

1. Yes 2. No

3.4.5.2. If YES to Q.3.4.5.1: what are the signs and symptoms?

____

____

____

NOTE TO INTERVIEWER*: IF THE ANSWER IS 'YES', RECORD THE FOLLOWING*

AND GIVE APPOINTMENT FOR NEXT DAY INTERVIEW BY A NURSE.

Name___________________

Age______

Sex: 1. Male 2. Female

3.4.6. Why do you think there are multiple affected family members in your family (household)? (*CIRCLE ALL ANSWERS SPECIFIED*)

1. Because the disease is contagious
2. Because the disease runs through families ('blood/bone')
3. Because the family is cursed/any spiritual connection
4. Because the family is poor and cannot afford shoes
5. I don't know
6. Other (please, specify) ______________________

4. Wearing shoes

4.1.1. How old were you when you <u>first</u> got shoes? _____years

4.1.2. How old were you when you <u>first</u> got socks? _____years

4.2. *<u>INTERVIEWER</u>: OBSERVE AND DESCRIBE THE SHOES THE PERSON IS <u>NOW</u> WEARING?*

1. Hard plastic open
2. 'Barabaso'
3. Hard plastic covered
4. Leather
5. 'Shara'/canvass
6. Barefooted

4.3. When do you usually <u>not</u> wear shoes?

1. during farming
2. during non-farming work
3. At home
4. I am usually barefooted
5. I am always barefooted

4.4. How many pairs of shoes do you have? _____

4.5. How many pairs of shoes do you need/year? ______

5. Washing feet

5.1. Can you get enough water?

1. Yes (Go to Q.5.3) 2. No

5.2. If NO to Q.5.1: what is the problem?

1. Seasonal shortage
2. Distance
3. Other (please, specify): __________________________

5.3. How long (<u>in minutes</u>) do you go to the nearest water source (<u>1 way</u>)? ___ min

5.4. Did you wash your feet last night?

1. Yes
2. No

5.5. IF YES TO Q.5.4.INTERVIEWER: PLEASE OBSERVE AND DESCRIBE THE CLEANLINESS OF THE FEET

1. clean and intact
2. dirty
3. cracked
4. dirty and cracked

5.6. How many times/week do you wash your feet? ______times

5.7. After your feet started swelling, did your foot washing behaviour change?

1. Yes
2. No (go to Q.5.9)

5.8. If YES to Q.5.7: Do you wash your feet more often or less often?

1. More often
2. Less often

5.9. Do you use soap for your feet?

1. Yes
2. No

5.10. If YES to q.5.6: How many times/week do you wash your feet with soap?
______times

6. Distance walked

6.1. How long does it take to go to your nearest field? _______min/hrs

6.2. How many times do you go to your field each month? _____times

6.3. How long does it take to go to your nearest market? _________min
(INTERVIEWER: PLEASE CONVERT ALL TIMES INTO MINUTES)

6.4. How often do you go to market each month? ______times

6.5. ***ASK ANOTHER PERSON OF THE HOUSEHOLD: How many times last year was the person sick with acute attack? ____***

7. Disabling effects (functional impairment)

7.1 Over the past 30 days, has podoconiosis or acute attack of ALA hampered movement (walking, travelling to markets etc)? (MORE THAN ONE ANSWER POSSIBLE)

1. Yes, effect of the disease
2. Yes, effect of acute attacks
3. Uncertain
4. No

7.2 ASK WOMEN: Over the past 30 days, has podoconiosis or acute attack of ALA hampered any household chores (cleaning, cooking, child care etc)? (MORE THAN ONE ANSWER POSSIBLE)

1. Yes, effect of the disease
2. Yes, effect of acute attacks
3. No
4. Not applicable (*CIRCLE THIS IS THE RESPONDENT IS A MAN*)

7.3 ASK MEN: Over the past 30 days, has podoconiosis or acute attack of ALA hampered daily/occupational work? (MORE THAN ONE ANSWER POSSIBLE)

1. Yes, effect of the disease
2. Yes, effect of acute attacks
3. No
4. Not applicable (*CIRCLE THIS IS THE RESPONDENT IS A WOMAN*)

7.4. If either 7.2 or 7.3 is YES: What was the effect of the disease? (READ EACH ANSWER AND CIRCLE ALL THAT APPLY)

1. Worked less hours
2. Worked with less energy
3. Absence from work
4. Earned less income
5. Reduced productivity (e.g. harvest from agriculture)
6. Other (please, specify) ________________

7.5. How has podoconiosis affected your work life over a long period of time (many months or years)? (READ EACH ANSWER AND CIRCLE ALL THAT APPLY)

1. I work only occasionally
2. I work less hours
3. I resorted to less remunerative work
4. I avoided physically demanding tasks
5. I totally stopped work
6. Other (please, specify)________________

7.6. How do you rate your financial status compared to your fellow neighbours with the same occupation and family size?

1. about the same
2. I am poorer
3. I am better off

7.7. If the answer to q 7.6 was '2': Did your financial status worsen after your family became affected by podoconiosis?

1. Yes
2. No

We have finished the interview. Thank you for your time and participation!

INTERVIEWER: PROVIDE HEALTH EDUCATION NOW

Appendix 5. *Questionnaire for assessment of individual level correlates of podoconiosis*

B. Socio-Demographic Details (Head of Household and patients)

No.	Question	Answer	Skip
B01	Age		
B02	Sex		
B03	Did you ever go to school?	1. Yes 2. No	
B04	What is the highest level of school you completed?	1. Informal 2. Primary 3. Secondary 4. College/diploma 5. University 6. Other _____	
B05	What is your occupation?	1. Farmer 2. Housewife 3. Potter 4. Weaver 5. Merchant 6. Daily laborer 7. Unemployed 8. Other ____________________	
B06	What is your religion?	1. Protestant 2. Orthodox 3. Muslim 4. Catholic 5. Not affiliated to any 6. Other (specify)__________	
B07	What is your ethnicity?	1. Wolaita 2. Gamo 3. Sidama 4. Gurage 5. Amhara 6. Oromo 7. Tigre 8. Other (specify):________ 88.unknown	

		99. Not willing to answer	
B08	What was your first language	1. Wolaitegna 2. Gamogna 3. Sidamagna 4. Guragegna 5. Amharegna 6. Oromomegn 7. Tigregna 8. Other (specify):________ 88.unknown 99. Not willing to answer	
B09	What is your current marital status?	1. Single/never married 2. Married 3. Divorced 4. Separated 5. Widowed 99. Not willing to answer	
B10	What is your average monthly income (in *Birr*)?	1. _____ Birr 98. I don't know 99. Refused to answer	
B11	Do you live in this *Kebele* throughout the year?	1. Yes 2. No	If 'Yes' skip to **C01**
B12	How many months do you spend out of this *Kebele*?		
B13	Where and when do you go?	Explain ____________________________ ____________________________ ____________________________	

C. Use of Shoes.

No.	**Question**	**Answer**	**Skip**
C01	Have you ever owned a pair of shoes?	1. Yes 2. No	If 'No' skip to **C12**
C02	How old were you when you first owned a pair of shoes?	____ Years	
C03	How many of the years since this have you had a pair of shoes?	1. All the years. 2. Almost all the years. 3. More than half of the years. 4. About half of the years.	

		5. Less than half of the years. 6. Almost none of the years. 7. None of the years.	
C04	When you own a pair of shoes, how often do you use them?	1. Every day. 2. More than 5 days per week. 3. 2-5 days per week. 4. Every week, but less than 2 days per week. 5. Less often than weekly.	
C05	On a shoe-wearing day, how much of the day do you wear shoes?	1. All day. 2. More than half the day. 3. About half the day. 4. Less than half the day. 5. Only a few hours.	
C06	For which of these activities do you wear shoes? (**multiple answers possible**)	1. Walking to market 2. Going to church 3. Attending a funeral 4. *Kebele* meeting 5. Attending a wedding 6. Ploughing 7. Planting 8. Harvesting 9. Work inside the house 10. Fetching water	
C07	For which of these activities you **do not** wear shoes? (**multiple answers possible**)	1. Walking to market 2. Going to church 3. Attending a funeral 4. *Kebele* meeting 5. Attending a wedding 6. Ploughing 7. Planting 8. Harvesting 9. Work inside the house 10. Fetching water	
C08	Do you own a pair of shoes right now?	1. Yes 2. No	If 'No' skip to **C12**
CO9	How many pairs of shoes do you have?	_______ Pairs	
C10	How many pairs of shoes do you need/year?	_______ Pairs	
C11	What type of shoes do you have? (**multiple answers possible**)	1. Sandals – plastic 2. Sandals – tyre/'*berbaso*'/ '*gilet'* 3. Closed shoes – plastic 4. Closed shoes – foam/EVA 5. Closed shoes – leather 6. Canvas/ '*shera'*	
C12	**OBSERVE**: What kind of shoe the interviewee is wearing at the time of interview?	1. Sandals – plastic 2. Sandals – tyre/'*berbaso*'/ '*gilet'* 3. Closed shoes – plastic 4. Closed shoes – foam/EVA 5. Closed shoes – leather 6. Canvas/ '*shera'* 7. Barefooted	

D. Washing Feet

No.	Question	Answer	Skip
D01	Can you get enough water to wash your feet?	1. Yes 2. No	If 'Yes' skip to **D03**
D02	What is the problem?	1. Seasonal shortage 2. Distance 3. Other (specify): ___________________	
D03	Did you wash your feet last night?	1. Yes 2. No	
D04	How many times/week do you wash your feet?	______times	
D05	Do you use soap for your feet?	1. Yes 2. No	If 'No' skip to **D07**
D06	How many times/week do you wash your feet with soap?	______times	
D07	**OBSERVE**: Are the interviewee's feet clean?	1. Clean and intact 2. Dirty 3. Cracked 4. Dirty and cracked	

E. Distances walked

No.	Question	Answer	Skip
E01	How many minutes' walk is your nearest field? (1 way)	___ minutes	
E02	How many times do you walk to your nearest field each month?	___ times	
E03	How many minutes' walk is your		

<table>
<tr><td></td><td>furthest field? (1 way)</td><td colspan="3">___ minutes</td><td></td></tr>
<tr><td>E04</td><td>How many times do you walk to your furthest field each month?</td><td colspan="3">___ times</td><td></td></tr>
<tr><td>E05</td><td>How many minutes' walk is your regular market? (1 way)</td><td colspan="3">___ minutes</td><td></td></tr>
<tr><td>E06</td><td>How many times do you walk to market each month?</td><td colspan="3">__________ times</td><td></td></tr>
<tr><td>E07</td><td>What is the source of your water?</td><td colspan="3">1. Pipe
2. Well
3. Stream/river
4. Spring
5. Other _____________</td><td></td></tr>
<tr><td>E08</td><td>How many minutes' walk is this water source? (1 way)</td><td colspan="3">________minutes</td><td></td></tr>
<tr><td>E09</td><td>How many times do you walk to this water source each month?</td><td colspan="3">_________ times</td><td></td></tr>
<tr><td>E10</td><td>Do you walk to other places for work purposes?</td><td colspan="3">1. Yes
2. No</td><td>If 'No' skip to E12</td></tr>
<tr><td>E11</td><td>Record activity, minutes walked and frequency per month</td><td>Activity</td><td>Minutes (1 way)</td><td>Frequency</td><td></td></tr>
<tr><td>E12</td><td>Do you walk to other places for social purposes?</td><td colspan="3">1. Yes
2. No</td><td>If 'No' skip to F 1</td></tr>
</table>

E13	Record activity, minutes walked and frequency per month	Activity	Minutes (1 way)	Frequency	
E14	Which road do you usually use when you go out of your house?	1. On the paved way 2. In between the ploughed field			
E15	Do you usually travel on foot or use animals?	1. On foot 2. Using animals (horse or donkey)			
E16	How much of your time do you spend on farming activities?	________months			
E17	How much of your time is spend on ploughing?	________months			
E18	How much of your time is spend on harvesting?	________months			
E19	How much of your time is spend on removing weeds?	________months			

F. Household Dietary Composition

	F01 Most frequently eaten type of food	F02 Frequency per week
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

G. Podoconiosis Patients Only.

No.	Question	Answer		Skip
G01	How old were you when you first noticed your legs were swollen?	___ Years		
G02	How old were you when you first tried to get treatment?	___ Years		
G03	How many years passed until your legs became as they are now?	___ Years		
G04	Does anyone else in your family have swollen legs?	1. Yes 2. No		If 'No', skip to **G05**
G05	Which family member(s) is/are affected?	**Family**	**Number**	
		Grandmother		
		Grandfather		
		Uncle		
		Aunt		
		Father		
		Mother		
		Brother		
		Sister		
		Cousin		
		Son		
		Daughter		
		Grandson		
		Granddaughter		
G06	Has your leg ever suddenly become hot, red and painful?	1. Yes 2. No		If 'No', skip to **G08**
G07	How often does your leg become hot, red and painful?	1. Every week 2. Every two weeks 3. Every month 4. Every 3 months 5. Every 6 months 6. Every year 7. Less often than every year		
G08	How long do you have to stop working when your leg is hot, red	___ days		

	and painful?			
G09	Under which weather conditions do you experience the most problems with your leg(s)	1. Hot and dry season 2. Hot and wet season 3. Cold and dry season 4. Cold and wet season 5. No difference by season		

H. Clinical Assessment

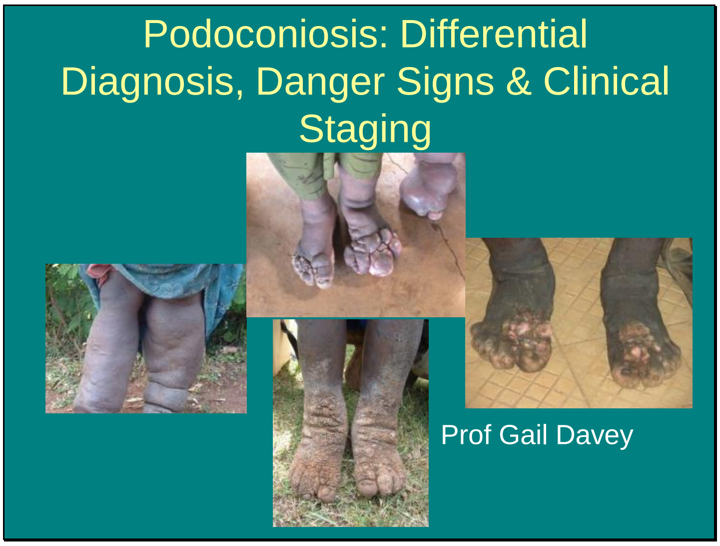
RIGHT LEG		**LEFT LEG**	
H01 Stage (1-5)	1 2 3 4 5	1 2 3 4 5	Stage (1-5)
H02 Moss	1. Yes 2. No	1. Yes 2. No	Moss
H03 Circumference (cm)			Circumference (cm)
H04 Wound	1. Yes 2. No	1. Yes 2. No	Wound
H05 Type	1. Water bag 2. Nodular 3. Mixed	1. Water bag 2. Nodular 3. Mixed	Type
H06 Inguinal nodes	1. Normal 2. Enlarged	1. Normal 2. Enlarged	Inguinal nodes
H07 Signs of ALA	1. Yes 2. No	1. Yes 2. No	Signs of ALA

We have finished the interview. Thank you for your time and participation!

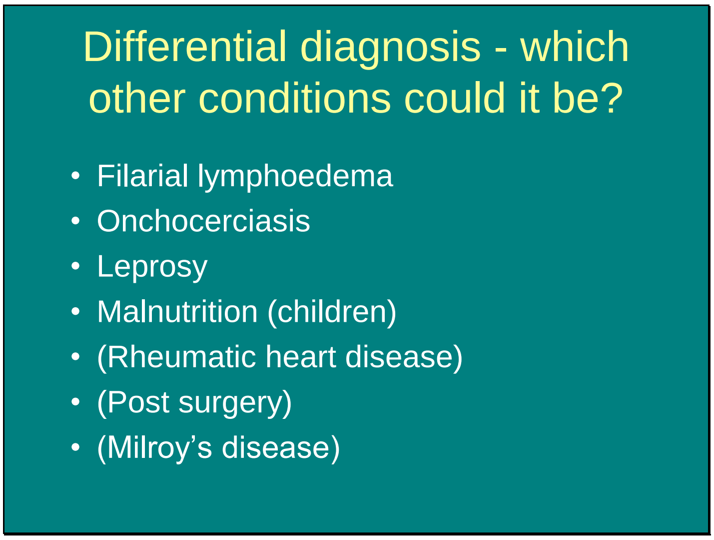
INTERVIEWER: PROVIDE HEALTH EDUCATION AND A BAR OF SOAP NOW

Appendix 6. *Standard training material used to train nurses and HEW*

Slide 1



Slide 2



Slide 3

Filarial lymphoedema

Very asymmetric disease – one leg looks normal

Slide 4

Filarial lymphoedema

Ask: Is patient from lowland area? Did the swelling start at the foot or higher up?

Look: Is leg swelling very asymmetrical (one leg ‘normal’)?

Examine: Check the groin for swollen lymph node

Do: Refer for tablet treatment at Health Centre, invite back for usual MFTPA leg care.

Slide 5

Onchocerciasis

Slide 6

Onchocerciasis

Ask: Does patient have itchy trunk or nodules?

Look: Look for onchodermatitis, pretibial depigmentation, onchocercomas, eye changes

Examine: Examine skin of whole body, check the groin for lymph nodes

Do: Refer for treatment of onchocerciasis, invite back for usual MFTPA leg care.

Slide 7

Leprosy

- Exaggerated eyebrow area
- Shiny skin on feet
- Toes may look short
- Foot ulcer may be present
- Patient cannot feel

Slide 8

Leprosy

Ask: Has the patient noticed any skin changes?

Look: Are there rough raised skin lesions?

Examine: For thickened nerves at the elbow or behind the ear; for foot ulcers; check if patient can feel you touch his feet?

Do: Refer for leprosy treatment. Invite back for follow up MFTPA foot care.

Slide 9

Malnutrition

Swollen feet and belly
Shiny skin
Thin, light coloured hair
Listless

Slide 10

Malnutrition

Ask: About food available to child

Look: Is child listless and lacking energy?

Examine: For swollen belly and light or reddish hair

Do: Refer to nearest health centre for assessment for therapeutic feeding.

Slide 11

Danger Signs

1. Painful, warm leg, recent increase in swelling ‘lymphangioadenitis’;
2. Ulcer not responding to wound care;
3. Deep fungal infection.

Slide 12

Hot, painful leg

Ask: Has the patient had fevers or ‘rigors’ (shivers)

Look: Is the patient clearly unwell?

Examine: Check temperature, examine legs and inguinal lymph nodes carefully.

Do: Prescribe antipyretic/analgesic; prescribe or refer for antibiotic treatment.

Slide 13

Ulcer not responding to basic care

Ulcer that has is still there despite good wound care.

Do: refer to surgeon for biopsy. This may be a form of cancer.

Slide 14

Deep fungal infection

Lump on one foot

May have small black dots on surface

Do: Refer to surgeon for biopsy, anti-fungal treatment/amputation.

Slide 15

Clinical Staging and Wound Care

Prof Gail Davey

Slide 16

Clinical Staging

Why is staging important?

- So program planners can assess burden of disease in given area;
- So patients can see effect of self-treatment;
- So health professionals can document effectiveness of medical and surgical treatment;
- So researchers can document effects of public health interventions.

Slide 17

Staging System Basics

Each leg examined and given score separately;
‘Swelling’ = general increase in size of foot or leg.
‘Knob or bump’ = discrete hard lump seen or felt to protrude.
‘Ankle’ = level of 2 ankle bones, patient standing
‘Knee’ = level of top of knee cap, patient standing.
‘Moss’ = tiny, rough lesions like moss.
‘Circumference’ = greatest below knee measurement (cm).

Slide 18

Staging with Patients

Slide 19

Stages 0-2

Stage 0. No disease present.
Stage 1. Swelling reversible overnight.

Stage 2.
Persistent below-knee swelling; if present, knobs or bumps are below the ankle ONLY.

Slide 20

Stage 3

Stage 3.
Persistent below-knee swelling; knobs or bumps present above the ankle.

Slide 21

Stage 4

Stage 4.

Persistent above-knee swelling; knobs or bumps present at any location.

Slide 22

Stage 5

Stage 5.

Joint fixation; swelling at any place in the foot or leg.

(X-rays may show tuft erosion and loss of bone density)

Appendix 7. Variable Assessment and Selection

Note:

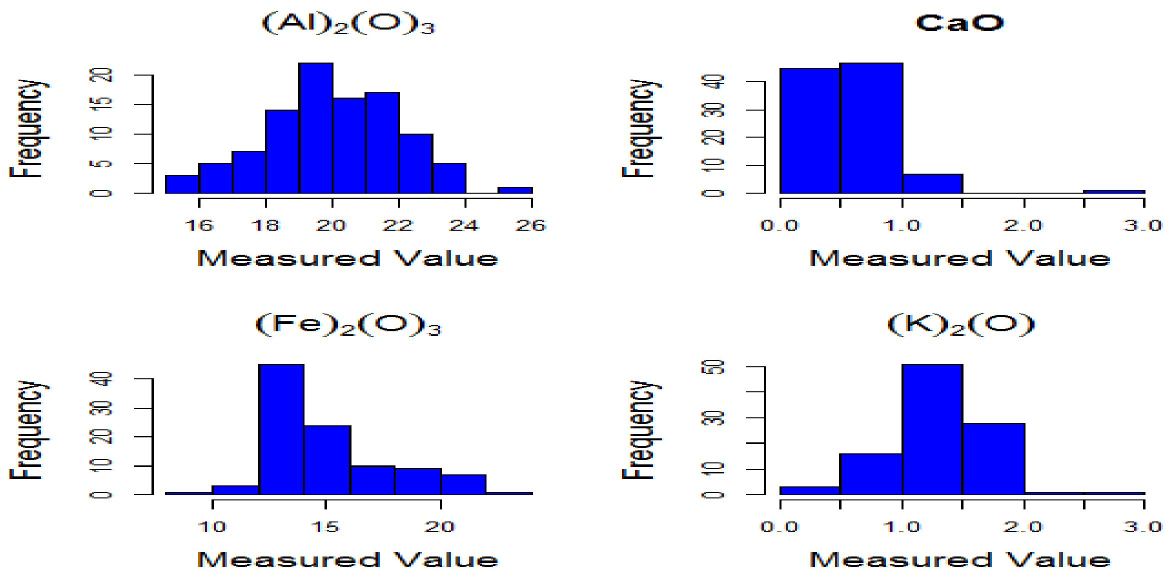
1. The soil data set used here were collected in the field from 100 sample sites
2. The metrology data were extracted per village from the WordClim website (http://www.worldclim.org) where 147 villages with podoconiosis prevalence data were included.
3. The distribution of each measurement was assessed using: mean, median, standard deviation (sd), range, skewness, kurtosis and standard error (se)
4. Both Pearson and Spearman correlation has been done for comparison (*two-tailed and 95% Confidence Interval (CI)*). Since most of the variables were not normally distributed, variable selection depended on Spearman's correlation

CHEMICAL SYMBOLS USED

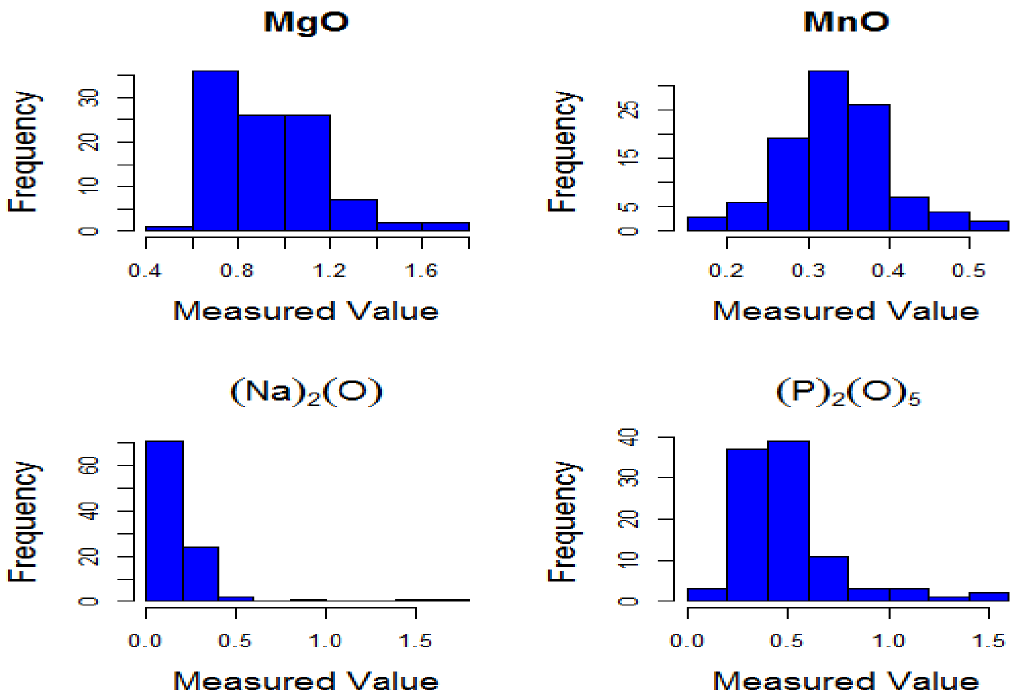
Al_2O_3	Aluminum oxide	**Fe_2O_3**	Iron oxide	**Sb**	Antimony/ Stibium
As	Arsenic	**K_2O**	Potassium oxide	**Sc**	Scandium
Ba	Barium	**MgO**	Magnesium oxide	**SiO_2**	Silicon dioxide
CaO	Calcium oxide	**MnO**	Manganese oxide	**Sr**	Strontium
Cd	Cadmium	**Na_2O**	Sodium oxide	**TiO_2**	Titanium dioxide
Co	Cobalt	**Ni**	Nickel	**V**	Vanadium
Cr	Chromium	**P_2O_5**	Phosphorus pentoxide	**Y**	Yttrium
Cu	Copper	**Pb**	Lead	**Zr**	Zirconium

A - Examples: Assessing distribution distribution using histograms and summary statistics for covariate

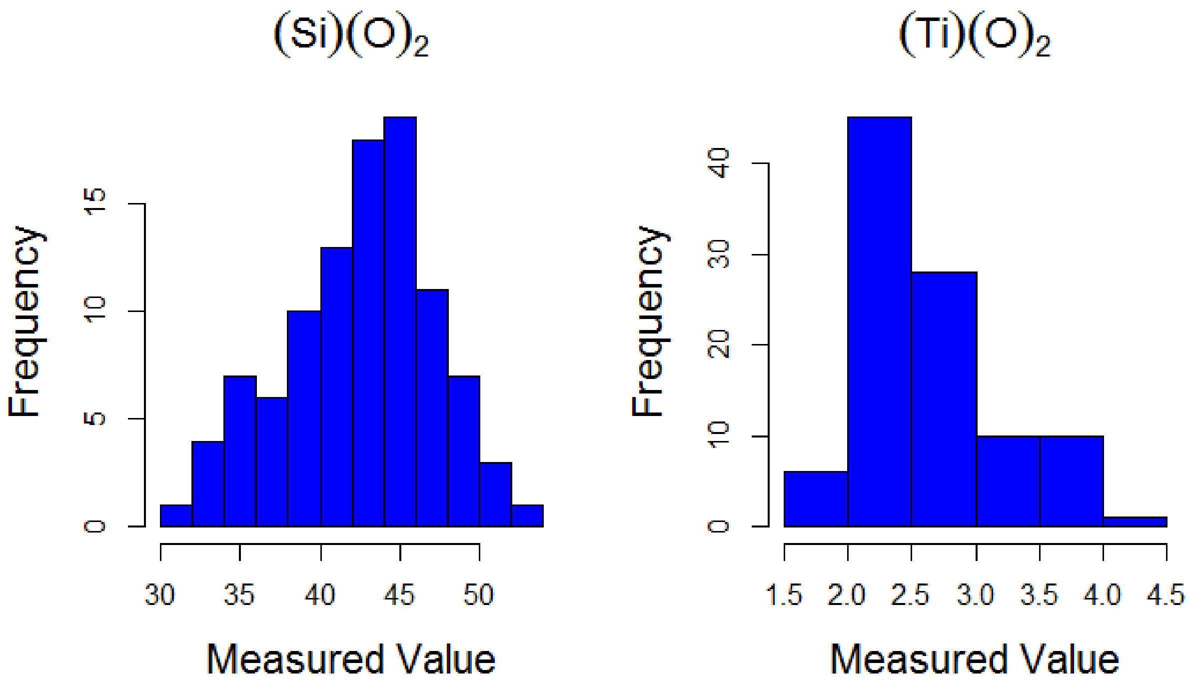
1. Soil chemical oxides - *weight percent (wt%)*



	n	*mean*	*sd*	*median*	*trimmed*	*mad*	*min*	*max*	*range*	*skew*	*kurtosis*	*se*
Al_2O_3	100	20	1.98	19.96	20.03	1.87	15.17	25.12	9.95	-0.08	-0.24	0.2
CaO	100	0.57	0.32	0.55	0.53	0.26	0.16	2.65	2.49	2.95	15.6	0.03
Fe_2O_3	100	15.04	2.75	14.05	14.7	1.79	9.68	22.96	13.28	0.99	0.26	0.27
K_2O	100	1.29	0.38	1.35	1.32	0.28	0.34	2.9	2.56	0.06	2.63	0.04

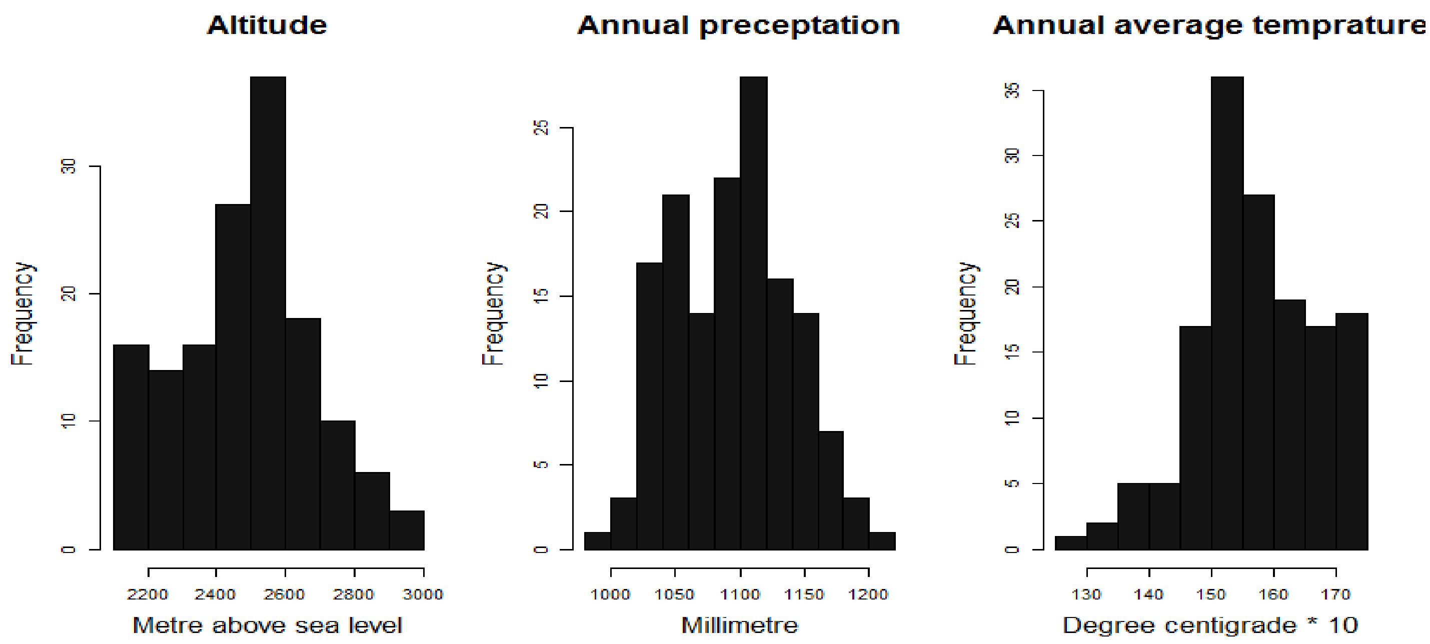


	n	mean	sd	median	trimmed	mad	min	max	range	skew	kurtosis	se
MgO	100	0.95	0.23	0.88	0.92	0.2	0.57	1.74	1.17	1.08	1.26	0.02
MnO	100	0.33	0.07	0.33	0.33	0.05	0.19	0.55	0.36	0.5	0.85	0.01
Na_2O	100	0.21	0.22	0.16	0.17	0.06	0.06	1.69	1.63	5.03	28.08	0.02
P_2O_5	99	0.5	0.26	0.46	0.45	0.2	0.12	1.5	1.38	1.72	3.4	0.03



	n	*mean*	*sd*	*median*	*trimmed*	*mad*	*min*	*max*	*range*	*skew*	*kurtosis*	*se*
SiO_2	100	42.45	4.75	43.2	42.67	4.68	30.89	52.26	21.37	-0.38	-0.5	0.47
TiO_2	100	2.64	0.55	2.49	2.59	0.31	1.51	4.09	2.58	0.79	0.23	0.05

2. Meteorology- mean annual precipitation (millimetre), annual average temperature (°C * 10) and altitude/elevation (metre above sea level)



	n	*mean*	*sd*	*median*	*trimmed*	*mad*	*min*	*max*	*range*	*skew*	*kurtosis*	*se*
Altitude	147	2486.97	190.5	2512	2483.23	177.91	2151	2994	843	0.12	-0.43	1.3
Precipitation	147	1094.07	44.95	1096	1093.26	48.93	997	1202	205	0.08	-0.71	0.31
Temperature	147	157.18	9.76	157	157.49	8.78	129.42	174.08	44.66	-0.24	-0.21	0.07

B - Scatter plots matrix and correlation for soil covariates

1. **Soil chemical oxides**

Pearson's correlation

	Al_2O_3	CaO	Fe_2O_3	K_2O	MgO	MnO	Na_2O	P_2O_5	SiO_2	TiO_2
Al_2O_3	1.00	-0.42	0.35	-0.43	-0.58	-0.08	-0.57	-0.44	-0.17	0.14
CaO	-0.42	1.00	-0.15	0.29	0.42	0.00	0.61	0.51	-0.20	-0.13
Fe_2O_3	0.35	-0.15	1.00	-0.83	-0.01	0.50	-0.31	0.00	-0.79	0.89
K_2O	-0.43	0.29	-0.83	1.00	0.21	-0.31	0.47	0.17	0.67	-0.75
MgO	-0.58	0.42	-0.01	0.21	1.00	0.14	0.50	0.48	-0.10	-0.03
MnO	-0.08	0.00	0.50	-0.31	0.14	1.00	0.02	0.41	-0.44	0.47
Na_2O	-0.57	0.61	-0.31	0.47	0.50	0.02	1.00	0.36	0.06	-0.31
P_2O_5	-0.44	0.51	0.00	0.17	0.48	0.41	0.36	1.00	-0.31	0.02
SiO_2	-0.17	-0.20	-0.79	0.67	-0.10	-0.44	0.06	-0.31	1.00	-0.70
TiO_2	0.14	-0.13	0.89	-0.75	-0.03	0.47	-0.31	0.02	-0.70	1.00

Spearman's Correlation

	Al_2O_3	CaO	Fe_2O_3	K_2O	MgO	MnO	Na_2O	P_2O_5	SiO_2	TiO_2
Al_2O_3	1.00	-0.349	0.404	-0.356	-0.466	-0.098	-0.824	-0.378	-0.127	0.140
CaO	-0.349	1.00	-0.032	-0.010	0.298	0.150	0.421	0.458	-0.321	0.057
Fe_2O_3	0.404	-0.032	1.00	-0.824	0.138	0.364	-0.343	0.106	-0.706	0.769
K_2O	-0.356	-0.010	-0.824	1.00	0.052	-0.226	0.328	0.076	0.707	-0.658
MgO	-0.466	0.298	0.138	0.052	1.00	0.171	0.527	0.381	-0.197	0.015
MnO	-0.098	0.150	0.364	-0.226	0.171	1.00	0.148	0.425	-0.397	0.407
Na_2O	-0.824	0.421	-0.343	0.328	0.527	0.148	1.00	0.299	0.194	-0.149
P_2O_5	-0.378	0.458	0.106	0.076	0.381	0.425	0.299	1.00	-0.433	0.281
SiO_2	-0.127	-0.321	-0.706	0.707	-0.197	-0.397	0.194	-0.433	1.00	-0.617
TiO_2	0.140	0.057	0.769	-0.658	0.015	0.407	-0.149	0.281	-0.617	1.00

2. Soil minerals

Pearson's Correlation

	Iron oxide	Quartz	Volcanic glass	Feldspars	Kaolinite	Smectite	Mica	Chlorite
Iron oxide	1.00	-0.54	0.41	-0.19	0.37	0.03	-0.26	-0.13
Quartz	-0.54	1.00	-0.45	0.03	-0.12	-0.19	-0.28	0.04
Volcanic glass	0.41	-0.45	1.00	-0.09	-0.24	-0.13	0.21	-0.03
Feldspars	-0.19	0.03	-0.09	1.00	-0.35	0.04	-0.26	0.16
Kaolinite	0.37	-0.12	-0.24	-0.35	1.00	0.09	-0.62	-0.24
Smectite	0.03	-0.19	-0.13	0.04	0.09	1.00	-0.20	-0.17
Mica	-0.26	-0.28	0.21	-0.26	-0.62	-0.20	1.00	-0.03
Chlorite	-0.13	0.04	-0.03	0.16	-0.24	-0.17	-0.03	1.00

Spearman's correlation

	Fe oxide	Quartz	Volcanic glass	Feldspars	Kaolinite	Smectite	Mica	Chlorite
Fe oxide	1.00	-0.490	0.420	-0.223	0.329	0.396	-0.231	-0.159
Quartz	-0.490	1.00	-0.540	0.035	-0.028	-0.392	-0.276	0.035
Volcanic glass	0.420	-0.540	1.00	-0.106	-0.249	0.163	0.260	-0.016
Feldspars	-0.223	0.035	-0.106	1.00	-0.363	-0.269	-0.231	0.147
Kaolinite	0.329	-0.028	-0.249	-0.363	1.00	0.391	-0.605	-0.318
Smectite	0.396	-0.392	0.163	-0.269	0.391	1.00	-0.135	-0.320
Mica	-0.231	-0.276	0.260	-0.231	-0.605	-0.135	1.00	-0.008
Chlorite	-0.159	0.035	-0.016	0.147	-0.318	-0.320	-0.008	1.00

3. **Soil particle size-** analysis done with water

Pearson's correlation

	W particle < 1	W particle < 2	W particle < 5	W particle < 10	W particle < 20	W particle < 100
W particle < 1	1.00	0.95	0.58	0.45	0.95	0.00
W particle < 2	0.95	1.00	0.81	0.68	0.94	0.19
W particle < 5	0.58	0.81	1.00	0.96	0.67	0.49
W particle < 10	0.45	0.68	0.96	1.00	0.58	0.56
W particle < 20	0.95	0.94	0.67	0.58	1.00	0.15
W particle < 100	0.00	0.19	0.49	0.56	0.15	1.00

Spearman's Correlation

	W particle < 1	W particle < 2	W particle < 5	W particle < 10	W particle < 20	W particle < 100
W particle < 1	1.00	0.995	0.756	0.619	0.942	0.184
W particle < 2	0.995	1.00	0.779	0.645	0.946	0.191
W particle < 5	00.756	0.779	1.00	0.956	0.714	0.495
W particle < 10	0.619	0.645	0.956	1.00	0.624	0.554
W particle < 20	0.942	0.946	0.714	0.624	1.00	0.235
W particle < 100	0.184	0.191	0.495	0.554	0.235	1.00

4. **Soil particle size-** analysis done with dispersant Na pyrophosphate

Pearson's Correlation

	D particle < 1	D particle < 2	D particle < 5	D particle < 10	D particle < 20	D particle < 100
D particle < 1	1.00	0.96	0.64	0.66	0.54	0.25
D particle < 2	0.96	1.00	0.69	0.79	0.67	0.34
D particle < 5	0.64	0.69	1.00	0.71	0.62	0.33
D particle < 10	0.66	0.79	0.71	1.00	0.97	0.68
D particle < 20	0.54	0.67	0.62	0.97	1.00	0.80
D particle < 100	0.25	0.34	0.33	0.68	0.80	1.00

Spearman's Correlation

	D particle < 1	D particle < 2	D particle < 5	D particle < 10	D particle < 20	D particle < 100
D particle < 1	1.00	0.900	0.268	0.595	0.485	0.282
D particle < 2	0.900	1.00	0.434	0.808	0.698	0.487
D particle < 5	0.268	0.434	1.00	0.554	0.513	0.373
D particle < 10	0.595	0.808	0.554	1.00	0.975	0.807
D particle < 20	0.485	0.698	0.513	0.975	1.00	0.885
D particle < 100	0.282	0.487	0.373	0.807	0.885	1.00

5. Soil content of carbon, hydrogen and nitrogen

Pearson's Correlation

	Organic carbon	**Inorganic carbon**	**Nitrogen**	**Hydrogen**
Organic carbon	1.00	0.07	0.20	0.18
Inorganic carbon	0.07	1.00	0.16	0.32
Nitrogen	0.20	0.16	1.00	0.15
Hydrogen	0.18	0.32	0.15	1.00

Spearman's Correlation

	Organic carbon	**Inorganic carbon**	**Nitrogen**	**Hydrogen**
Organic carbon	1.00	0.120	0.399	0.285
Inorganic carbon	0.120	1.00	0.242	0.453
Nitrogen	0.399	0.242	1.00	0.181
Hydrogen	0.285	0.453	0.181	1.00

6. Soil trace elements

Pearson's correlation

	As	Ba	Cd	Co	Cr	Cu	Ni	Pb	Sb	Sc	Sr	Y	V	Zr
As	1.00	0.01	-0.11	-0.01	-0.12	-0.08	-0.17	0.03	0.24	0.09	-0.02	-0.09	0.19	-0.13
Ba	0.01	1.00	-0.44	-0.14	-0.27	-0.21	-0.22	0.01	0.15	0.38	0.60	-0.23	0.09	-0.31
Cd	-0.11	-0.44	1.00	0.03	0.50	0.33	0.23	0.03	-0.09	-0.29	-0.27	0.05	-0.34	0.15
Co	-0.01	-0.14	0.03	1.00	-0.03	0.03	-0.07	0.08	0.15	0.21	-0.12	0.14	-0.06	0.14
Cr	-0.12	-0.27	0.50	-0.03	1.00	0.61	0.56	-0.01	-0.13	-0.43	0.07	0.09	-0.13	0.05
Cu	-0.08	-0.21	0.33	0.03	0.61	1.00	0.31	0.17	0.02	-0.21	0.05	0.23	0.08	0.11
Ni	-0.17	-0.22	0.23	-0.07	0.56	0.31	1.00	-0.12	-0.18	-0.36	-0.23	0.22	0.06	0.20
Pb	0.03	0.01	0.03	0.08	-0.01	0.17	-0.12	1.00	-0.04	0.05	-0.09	0.00	0.04	-0.06
Sb	0.24	0.15	-0.09	0.15	-0.13	0.02	-0.18	-0.04	1.00	0.36	0.15	0.02	0.12	-0.06
Sc	0.09	0.38	-0.29	0.21	-0.43	-0.21	-0.36	0.05	0.36	1.00	0.10	-0.16	0.04	-0.10
Sr	-0.02	0.60	-0.27	-0.12	0.07	0.05	-0.23	-0.09	0.15	0.10	1.00	-0.11	-0.08	-0.15
Y	-0.09	-0.23	0.05	0.14	0.09	0.23	0.22	0.00	0.02	-0.16	-0.11	1.00	0.21	0.78
V	0.19	0.09	-0.34	-0.06	-0.13	0.08	0.06	0.04	0.12	0.04	-0.08	0.21	1.00	0.08
Zr	-0.13	-0.31	0.15	0.14	0.05	0.11	0.20	-0.06	-0.06	-0.10	-0.15	0.78	0.08	1.00

Spearman's correlation

	As	Ba	Cd	Co	Cr	Cu	Ni	Pb	Sb	Sc	Sr	Y	V	Zr
As	1.00	0.06	-0.10	-0.02	-0.19	-0.13	-0.20	0.08	0.15	-0.07	-0.03	-0.04	0.13	-0.13
Ba	0.06	1.00	-0.46	-0.10	-0.25	-0.17	-0.29	0.09	0.02	0.23	0.64	-0.40	-0.01	-0.61
Cd	-0.10	-0.46	1.00	0.03	0.47	0.34	0.15	0.01	-0.02	-0.34	-0.29	0.20	-0.26	0.35
Co	-0.02	-0.10	0.03	1.00	-0.03	0.02	-0.02	0.04	0.24	0.10	-0.10	0.11	-0.07	0.10
Cr	-0.19	-0.25	0.47	-0.03	1.00	0.58	0.60	-0.07	-0.03	-0.33	0.08	0.11	-0.01	0.10
Cu	-0.13	-0.17	0.34	0.02	0.58	1.00	0.31	0.13	0.02	-0.13	0.09	0.19	0.12	0.13
Ni	-0.20	-0.29	0.15	-0.02	0.60	0.31	1.00	-0.15	-0.15	-0.06	-0.23	0.19	0.12	0.29
Pb	0.08	0.09	0.01	0.04	-0.07	0.13	-0.15	1.00	0.02	0.02	-0.04	-0.03	-0.02	-0.04
Sb	0.15	0.02	-0.02	0.24	-0.03	0.02	-0.15	0.02	1.00	0.05	0.22	0.12	0.05	0.01
Sc	-0.07	0.23	-0.34	0.10	-0.33	-0.13	-0.06	0.02	0.05	1.00	0.09	-0.24	0.01	-0.19
Sr	-0.03	0.64	-0.29	-0.10	0.08	0.09	-0.23	-0.04	0.22	0.09	1.00	-0.16	-0.08	-0.38
Y	-0.04	-0.40	0.20	0.11	0.11	0.19	0.19	-0.03	0.12	-0.24	-0.16	1.00	0.19	0.68
V	0.13	-0.01	-0.26	-0.07	-0.01	0.12	0.12	-0.02	0.05	0.01	-0.08	0.19	1.00	0.04
Zr	-0.13	-0.61	0.35	0.10	0.10	0.13	0.29	-0.04	0.01	-0.19	-0.38	0.68	0.04	1.00

7. **Meteorology-** Precipitation, temperature and altitude

Pearson's correlation

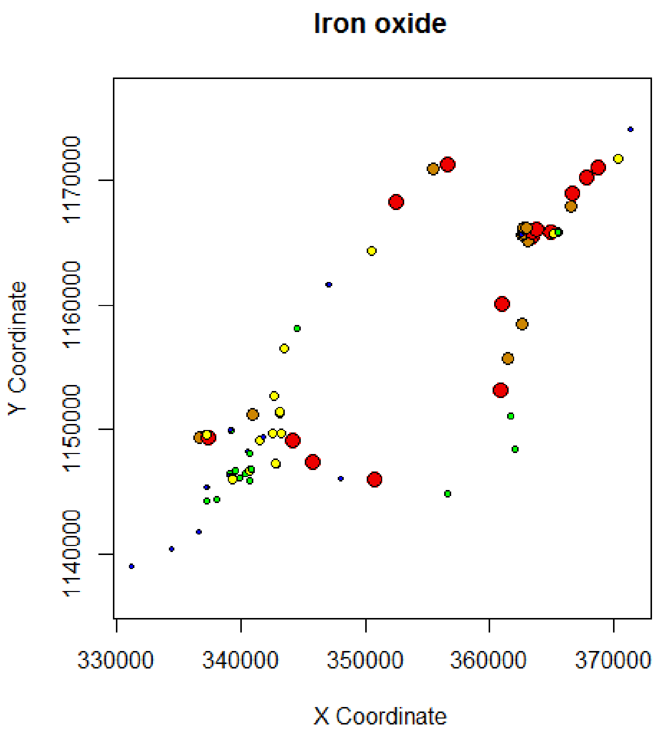
	Precipitation - annual average	Altitude	Temperature - average	Temperature - minimum	Temperature - maximum
Precipitation - annual average	1.00	0.854	-0.870	-0.892	-0.846
Altitude	0.854	1.00	-0.998	-0.990	-0.998
Temperature - average	-0.870	-0.998	1.00	0.995	0.996
Temperature - minimum	-0.892	-0.990	0.995	1.00	0.983
Temperature - maximum	-0.846	-0.998	0.996	0.983	1.00

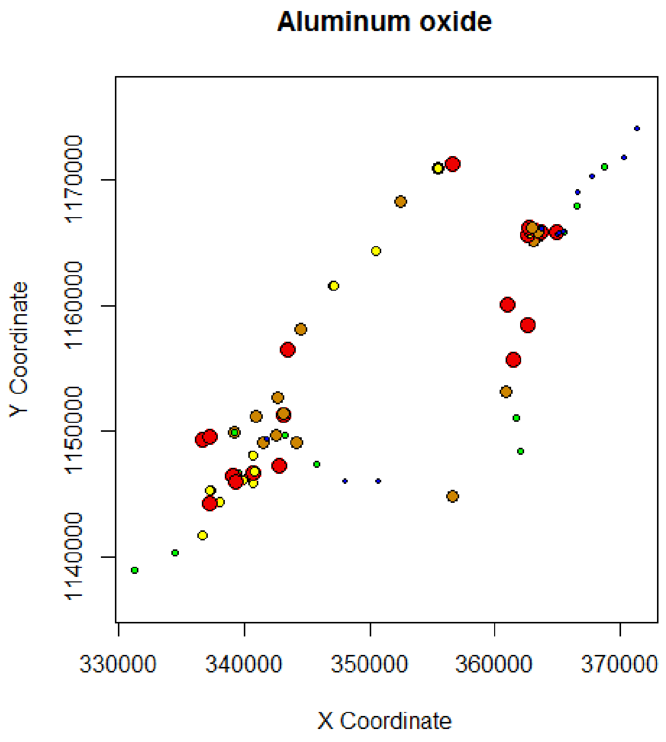
Spearman's correlation

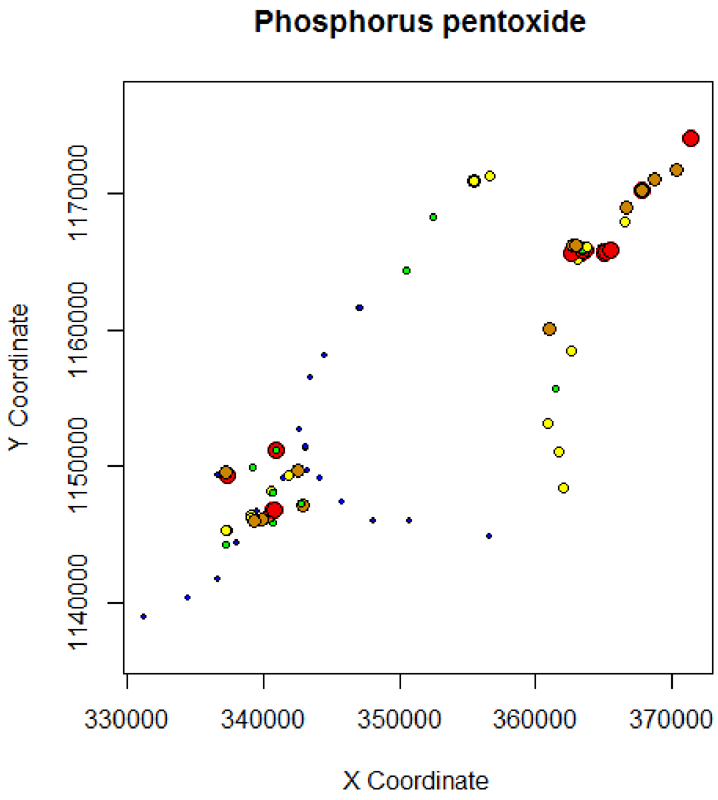
	Precipitation - annual average	Altitude	Temperature - average	Temperature - minimum	Temperature - maximum
Precipitation - annual average	1.000	0.820	-0.839	-0.873	-0.809
Altitude	0.820	1.000	-0.998	-0.993	-0.998
Temperature - average	-0.839	-0.998	1.000	0.996	0.997
Temperature - minimum	-0.873	-0.993	0.996	1.000	0.989
Temperature - maximum	-0.809	-0.998	0.997	0.989	1.000

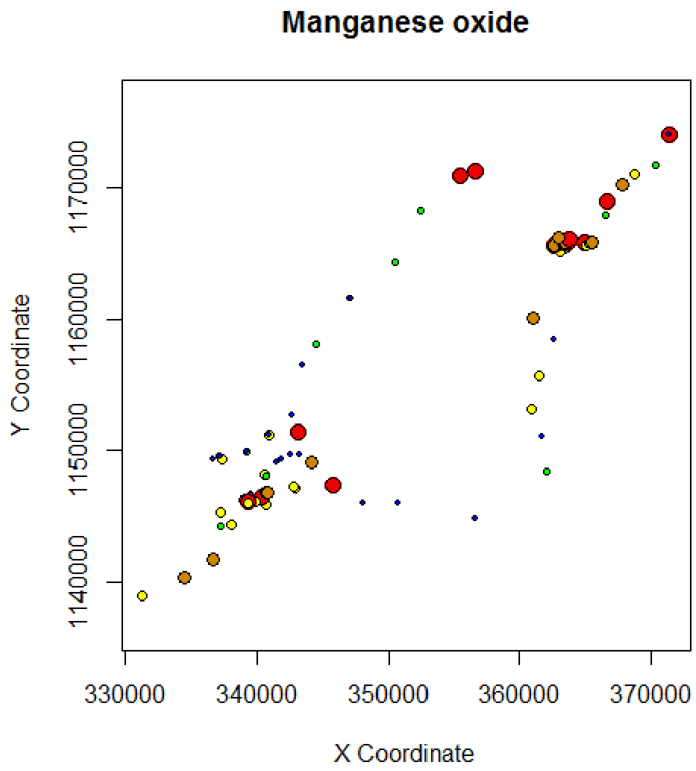
C - Spatial distribution of soil characteristics measurements

1. Soil chemical oxides






Phosphorus pentoxide
Y Coordinate
1140000
1150000
1160000
1170000
330000
340000
350000
360000
370000
X Coordinate


Manganese oxide
Y Coordinate
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1160000
1170000
330000
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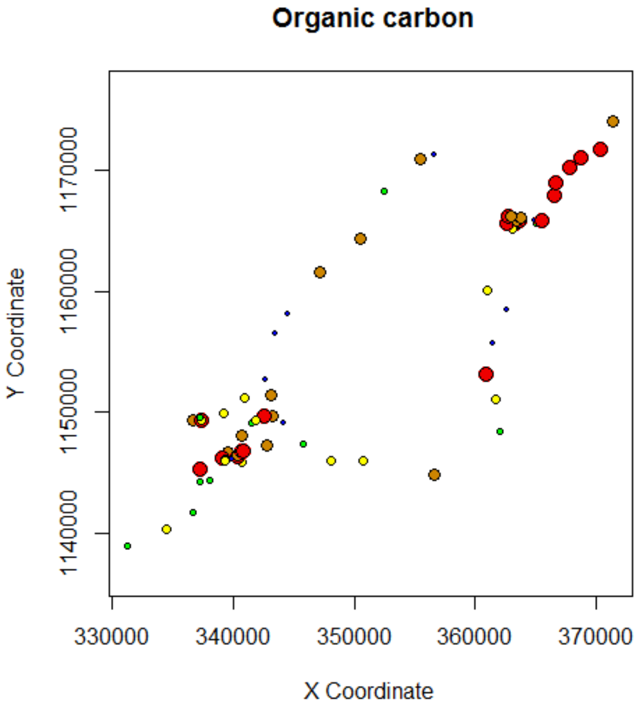
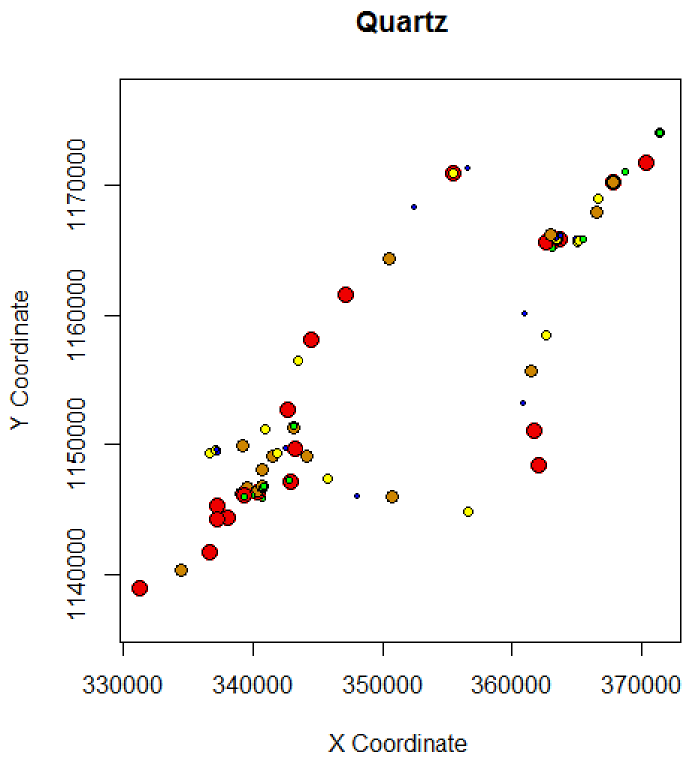
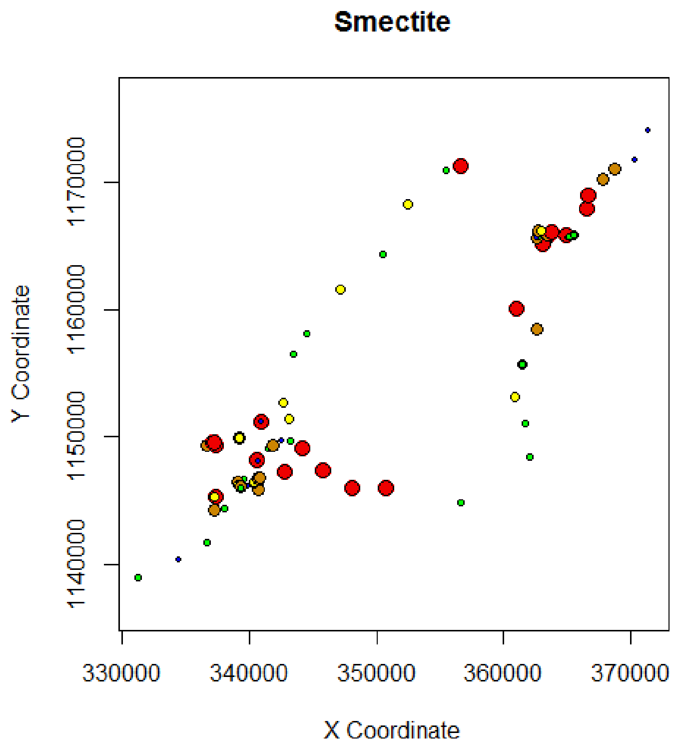
350000
360000
370000
X Coordinate

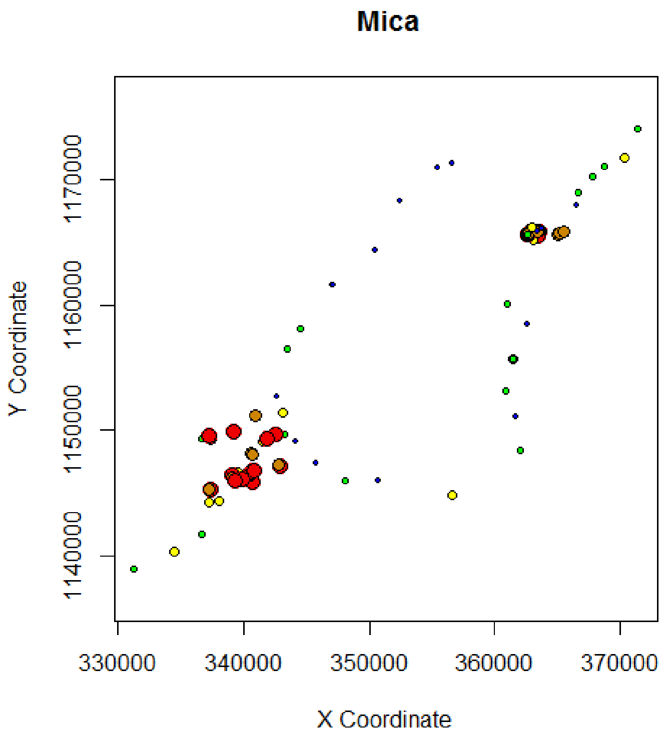
2. Organic carbon



3. Soil minerals







Mica
Y Coordinate
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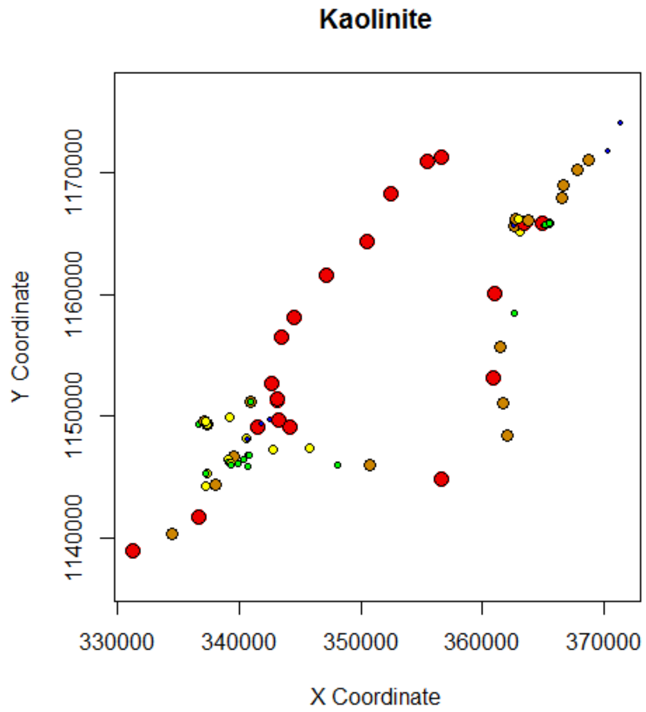
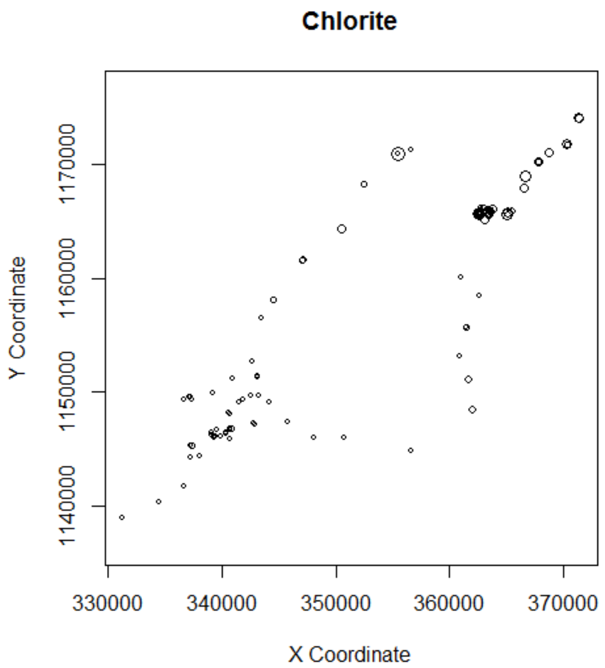
1150000
1160000
1170000
330000
340000
350000
360000
370000
X Coordinate



Kaolinite
Y Coordinate
1140000
1150000
1160000
1170000
330000
340000
350000
360000
370000
X Coordinate



Chlorite
Y Coordinate
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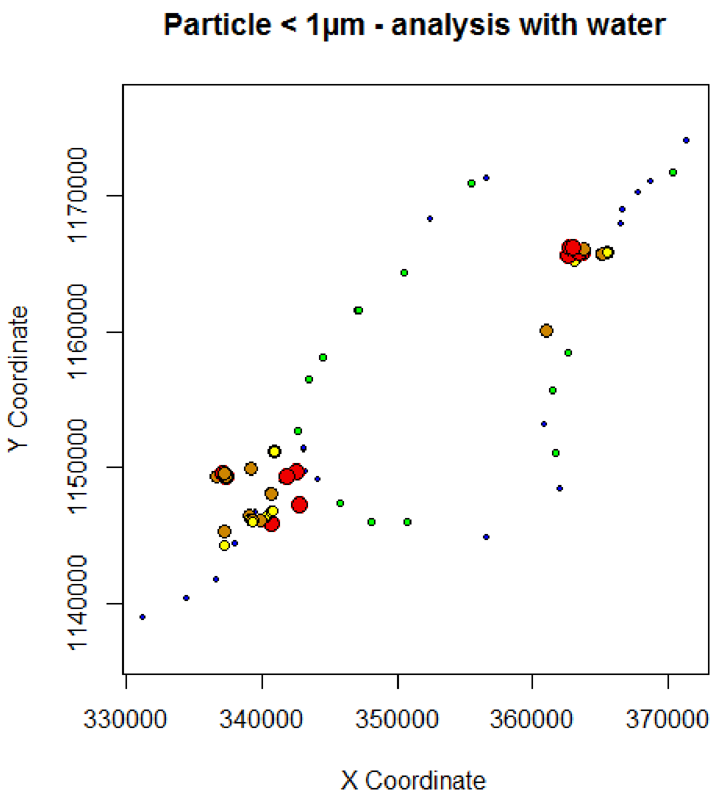
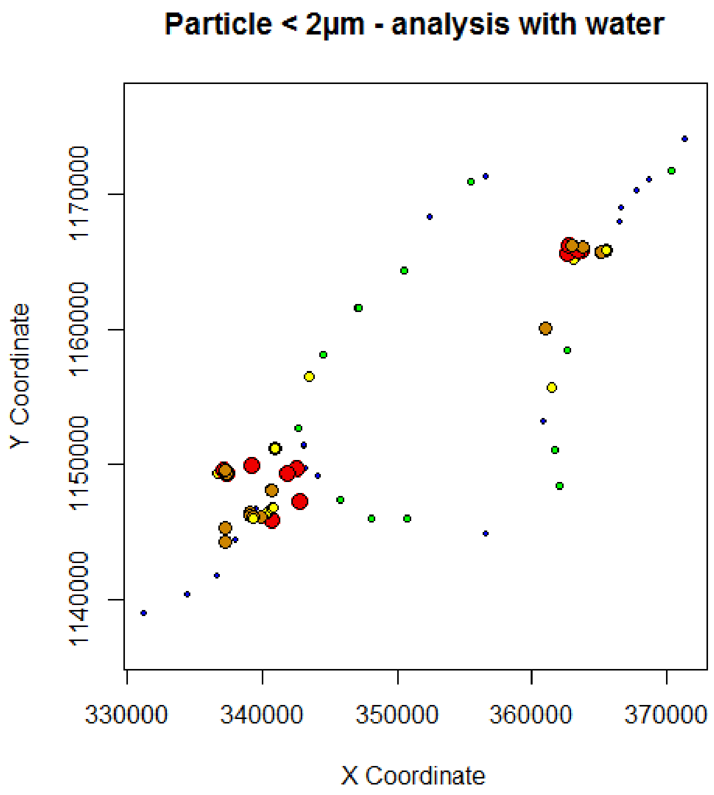
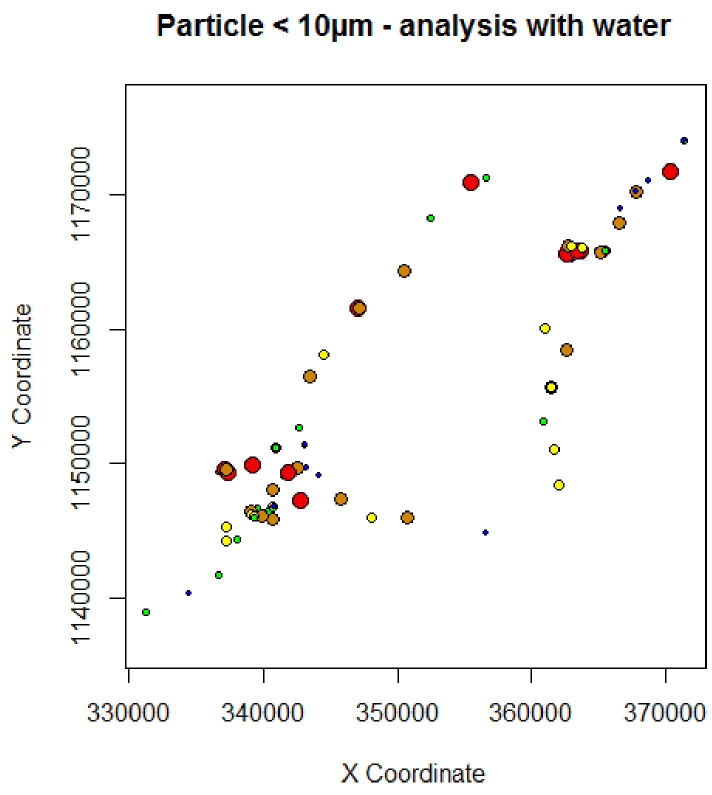
1150000
1160000
1170000
330000
340000
350000
360000
370000
X Coordinate

4. Particle size

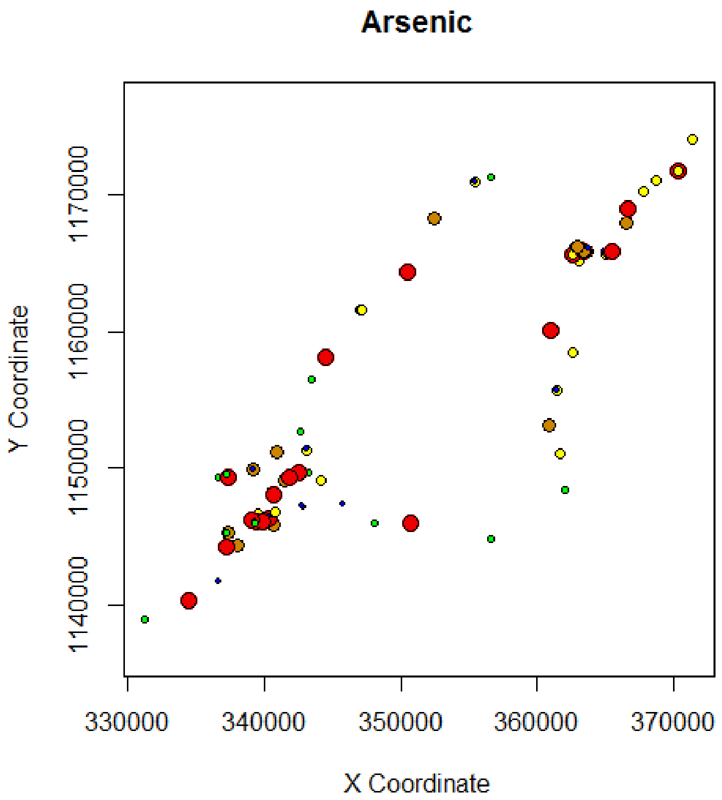


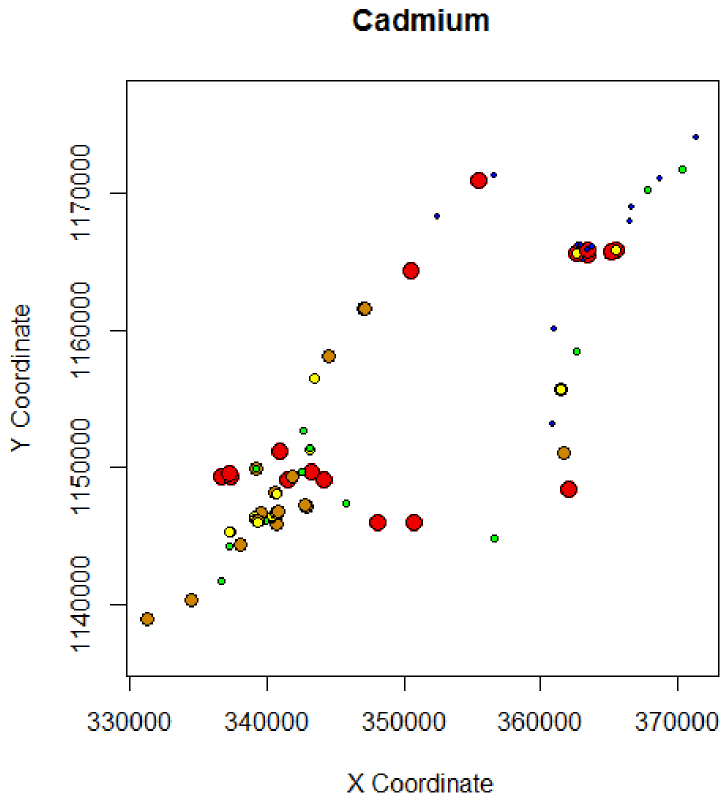


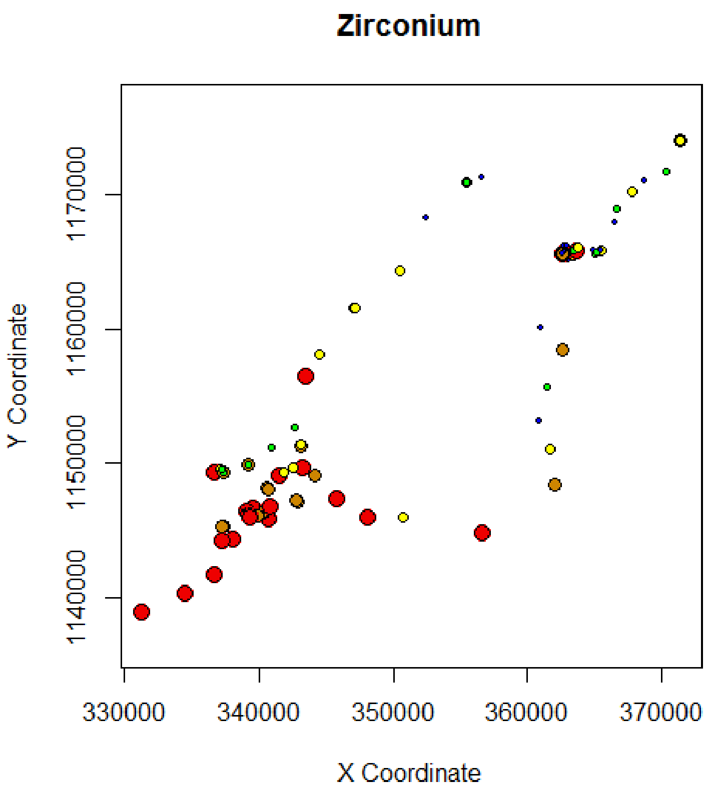


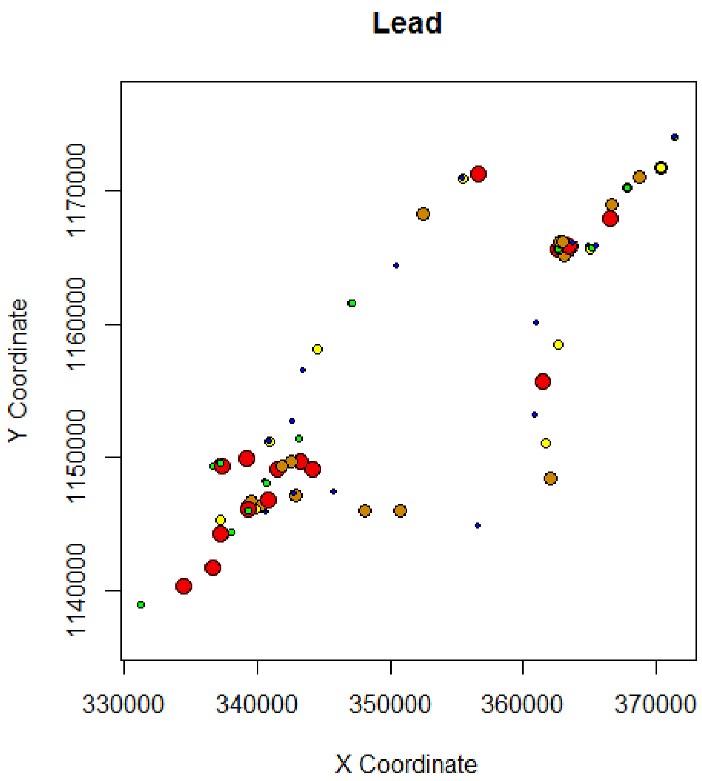
Particle < 10µm - analysis with water
Y Coordinate
1140000
1150000
1160000
1170000
330000
340000
350000
360000
370000
X Coordinate

5. Soil elements

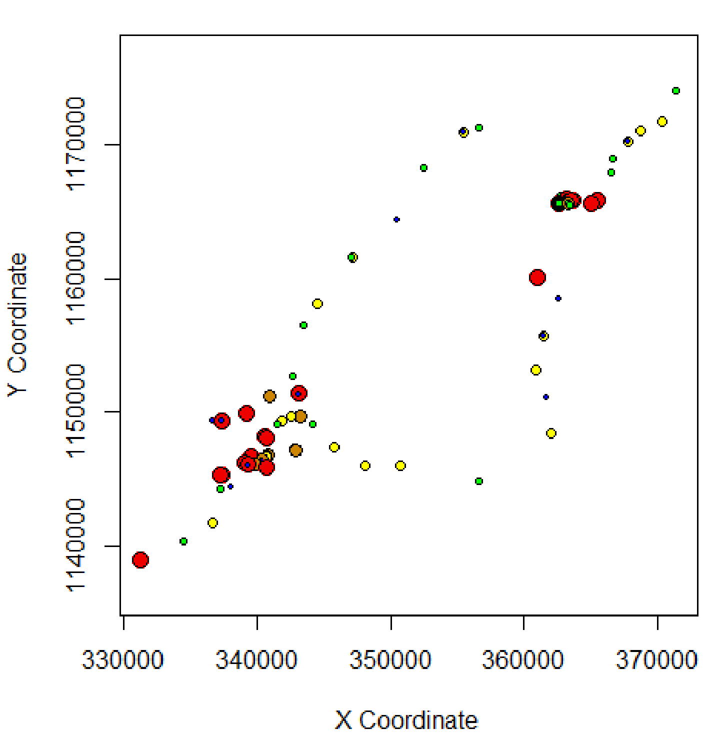




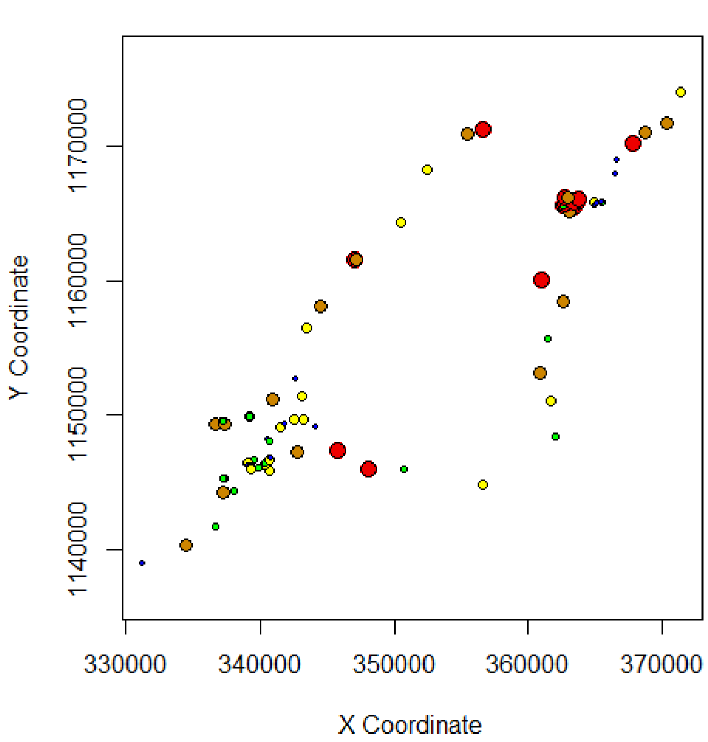

Zirconium
Y Coordinate
1140000
1150000
1160000
1170000
330000
340000
350000
360000
370000
X Coordinate

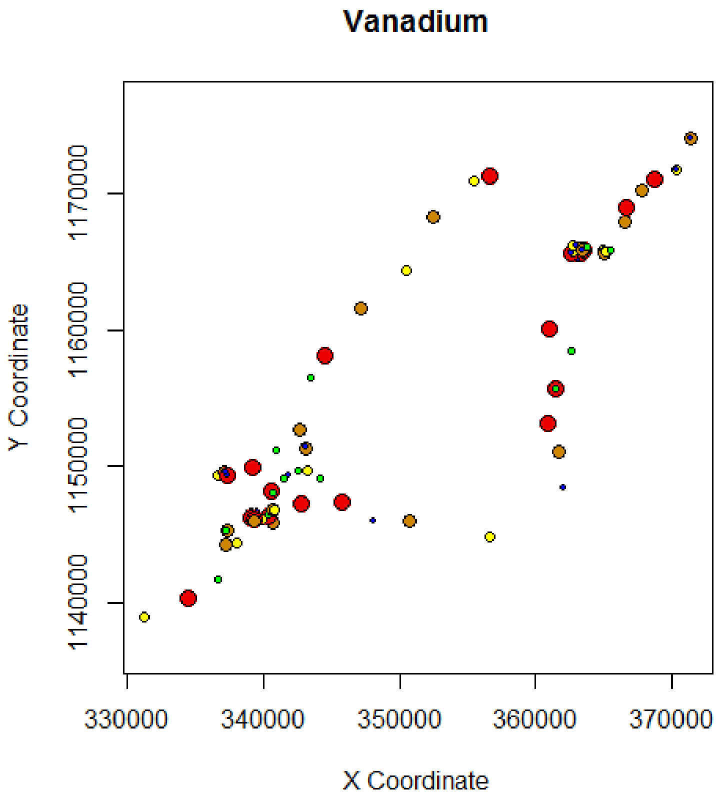

Lead
Y Coordinate
1140000
1150000
1160000
1170000
330000
340000
350000
360000
370000
X Coordinate

Antimony/ Stibium



Scandium




Vanadium
Y Coordinate
1140000
1150000
1160000
1170000
330000
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X Coordinate

Appendix 8. *Ethical clearance Addis Ababa University*

Addis Ababa University
Office of the Vice President
for Research and Dean of the School of
Graduate Studies

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Ref. No.: RDP/LT-061/2011

Date: 04 April 2011

TO WHOM IT MAY CONCERN

This refers to Dr. Gail Davey, MD, faculty member of the Brighton and Sussex Medical School, University of Sussex, UK, is currently a collaborating researcher with faculty members of Addis Ababa University in a project entitled: "***Comparative study to identify the environmental trigger of podoconiosis in Ethiopia***".

This project is implemented and closely monitored by the Department of Earth Sciences of the College of Natural Sciences of Addis Ababa University (AAU) with collaborating scientists, namely, Mrs. Yordanos Belayneh and Dr. Dagnachew Legesse of the same department.

As the project involves human subjects it obviously calls for securing ethical clearance procedures. In this regard, the project has already obtained international ethical clearance as indicated in the letter dated 07/12/2010 of the Research and Development Directorate of the Royal Sussex County Hospital of Brighton, UK.

The Office of the Chief Academic Officer for Research of AAU has also assessed the same project in perspective of its newly approved research policy and the ethical clearance regulations promulgated therein. The Office also holds that the testimony given by the Research and Development Directorates of UK prevails in the Ethiopian context.

This is therefore to confirm to all concerned that the research conducted by Dr. Gail Davey of UK in collaboration with the faculty members of the Department of Earth Sciences of AAU has obtained the necessary ethical clearance from the AAU side.

Sincerely,

Brook Lemma

Brook Lemma (Dr.)
Chief Academic Officer for Research, CAOR

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የጥናትና ምርምር ም/ፕሬዚዳንትና
የድህረ ምረቃ ት/ቤት ዲን
Vice President for Research and Dean of the School of Graduate Studies
ADDIS ABABA UNIVERSITY

Tel.: (251 1) 239769 or 239749 Email: vpr_dgs@aau.edu.et P.O. Box 1176, Addis Ababa, Ethiopia.

Appendix 9. *Ethical clearance Brighton and Sussex Medical School*

R&D OFFICE

Research Director Prof Kevin Davies
R&D Manager: Scott Harfield
Research Administrator: Caroline Brooks

E-mail: caroline.brooks@bsuh.nhs.uk

Tel: 01273 696955 ext 3905

brighton and sussex
medical school

Research & Development Directorate
Royal Sussex County Hospital
Clinical Investigation & Research Unit
Eastern Road
Brighton
BN2 5BE

07/12/2010

Dr Gail Davey
Brighton and Sussex Medical School
Community Health
Addis Ababa University
Addis Ababa
26905/10
Ethiopia

Dear Dr Davey

Full Study Title: **Comparative study to identify the environmental trigger of podoconiosis in Ethiopia**

R&D Ref No. : **10/159/DAV**

I am writing to inform you that the BSMS Research Governance and Ethics Committee which met on Monday 29th November have assessed your application and have granted you full Research Governance approval to proceed with the above named project. This letter acknowledges that you have all the necessary internal and external regulatory approvals to proceed.

The Committee were impressed with the quality of this well written application which they were happy to approve. A number of minor issues were also raised, of which the Committee would like you to be aware:

Appendix 10. Published article 1:

Molla, Y.B., S. Tomczyk, et al. (2012). "Podoconiosis in East and West Gojam zones, northern Ethiopia " PLoS Negl Trop Dis 6(7): e1744.

Appendix 11. Published article 2:

Molla, Y.B., S. Tomczyk, et al. (2012). "Patients' perceptions of podoconiosis causes, prevention and consequences in East and West Gojam, Northern Ethiopia." BMC Public Health 12(1): 828.

Appendix 12. Published article 3:

Molla, Y.B., J. Le Blond, et al. (2013). "Individual correlates of podoconiosis in areas of varying endemicity: a case-control study." PLoS Negl Trop Dis 7(12): e2554.

Appendix 13. Published article 4:

Molla, Y., N. Wardrop, et al. (2014). "Modelling environmental factors correlated with podoconiosis: a geospatial study of non-filarial elephantiasis." International Journal of Health Geographics 13(1): 24.

Pictures from field data collection










20/09/2011 06:51