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UNDERNUTRITION AND FOOD INSECURITY AS RISK FACTORS FOR LEPROSY IN NORTH GONDAR ZONE, ETHIOPIA

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Purdue University
2017

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ABSTRACT

UNDERNUTRITION AND FOOD INSECURITY AS RISK FACTORS FOR LEPROSY IN NORTH GONDAR ZONE, ETHIOPIA

By Puneet Vellareddy Anantharam

Ethiopia has nearly 4,000 new cases diagnosed every year. Prevention remains a challenge, as transmission pathways are poorly understood. Susceptibility and disease manifestations are highly dependent on the individual host-immune response. Nutritional deficiencies, such as protein-energy malnutrition, have been linked to reduced cell-mediated immunity and food insecurity has been associated with leprosy. The aim of this project was to identify nutritional risk factors for leprosy. Between June and August 2018, recently diagnosed patients were enrolled as leprosy cases and individuals without contact with known cases were enrolled as controls in North Gondar Zone. Participants answered survey questions on demographics, socioeconomic situation, and dietary habits and anthropometric data was collected. Urine was tested for *Schistosoma mansoni* infection by Schisto POC-CCA™ rapid diagnostic test. Descriptive statistics, univariate, and multivariate analyses were conducted to examine associations between undernutrition and leprosy. Eighty-one patients were enrolled (75% male) with an average age of 38.6 years (SD 18.3). The majority of cases had multibacillary leprosy (90%) and 21 participants (25.9%) had schistosomiasis. There was a high prevalence of undernutrition with 24 (29.6%) of participants underweight (BMI <18.5) and 17 (21%) with a low middle upper arm circumference (MUAC). On univariate analysis, both low BMI (OR = 7.20, 95% CI 2.34 22.11) and low MUAC were significantly associated with leprosy (OR = 6.82, 95% CI 1.78 26.13). On multivariate analysis, underweight was still significantly associated with leprosy (aOR = 6.67, 95% CI 1.43, 31.0) Cutting the size of meals/skipping meals (OR = 2.9, 95% CI 1.0, 8.32) or not having enough money to get more food (OR = 10.0, 95% CI 3.44 29.06) was more common in cases of leprosy than controls. These findings suggest a strong association between leprosy and undernutrition. Skipping meals and not having enough money to get more food support the framework that food insecurity could lead to undernutrition that then may increase susceptibility to leprosy. In conclusion, this study highlights the need to increase our understanding of the interplay between undernutrition, food insecurity, and the transmission of leprosy.

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Table of Contents

GLOSSARY OF TERMS

BDT	Bangladesh Taka
BMI	Body Mass Index
BB	Borderline Borderline
BL	Borderline Lepromatous
BT	Borderline Tuberculoid
ERS	Economic Research Service
GIS	Geographic Information Systems
HFIAS	Household Food Insecurity Access Scale
IRB	Institutional Review Board
MB	Multibacillary leprosy
MDT	Multidrug Therapy
MUAC	Middle Upper Arm Circumference
NTD	Neglected Tropical Diseases
PB	Paucibacillary leprosy
RDT	Rapid Diagnostic Test
SES	Socioeconomic Status
SNNP	Southern Nations Nationality and People
USD	United States Dollar
USDA	United States Department of Agriculture
WASH	Water, Sanitation, and Hygiene
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

BACKGROUND

Hansen's disease, commonly known as leprosy, is a crippling disease caused by infection with the bacterium *Mycobacterium leprae (M. leprae)* that can lead to permanent peripheral neuropathies and physical deformities (World Health Organization, 2015). Despite numerous developments improving the treatment of leprosy over the last half of the century, prevention remains a challenge, as transmission pathways are poorly understood (Bratschi, et al., 2015). *M. leprae* is transmitted through contact with the respiratory droplets or skin lesions of a person who has been infected. While those who may be exposed to the bacteria should practice contact precautions, the vast majority (95%) of the population has developed a natural immunity to the bacteria and thus will not develop disease even after exposure to *M. leprae* (Bratschi, et al., 2015).

With over 212,000 incident, or new, cases reported every year ("GHO | By category | Leprosy - Number of new leprosy cases - Data by country", 2019), leprosy remains the leading cause of disability from an infectious origin (Rodrigues, et al., 2011). Taking note of this global issue, health professionals have started looking toward other avenues to study transmission and disease presentation that have not previously been considered. One of these avenues, is the interface of nutrition and leprosy. Previous studies show that a large number of patients infected with leprosy also suffer from micronutrient deficiencies (Passos Vázquez et al., 2014). Due to likely reduced cell-mediated immunity (Ferguson, et al., 2000), nutritional deficiencies, such as protein energy malnutrition or lack of vitamins, make populations vulnerable and at higher-risk to develop active leprosy disease (Wagenaar, et al. 2015). Another risk factor is low socioeconomic status (SES) or income (Wagenaar, et al., 2015). Low SES and undernutrition are interconnected and can be linked to many infectious diseases; henceforth the phrase “diseases of poverty”.

HISTORY

Prior to the 1940s, the first breakthrough for the disease occurred through the discovery of a medication called dapsone. Compliance was difficult with this drug as the treatment regimen required many years and often a lifetime of taking dapsone (Leprosy, 2018). However, in the 1960s, when *M. leprae* started to develop resistance to dapsone, rifampicin and clofazimine were found to be effective against *M. leprae*. This combination of drugs formed the backbone of multidrug therapy (MDT) (Leprosy, 2018). MDT consists of 2 or 3 medicines depending on which type of leprosy the patient has. All treatment regimens required dapsone and rifampicin, with the addition of clofazimine for patients with multibacillary (MB) leprosy (Leprosy, 2018). Since 1995, World Health Organization (WHO) has provided MDT free of cost to all leprosy patients in the world through agreements with Novartis, who has extended its donation through 2020 (Leprosy, 2018).

In 2016, WHO launched its *“Global Leprosy Strategy 2016 – 2020: Accelerating towards a leprosy-free world”*. This strategy was primarily instituted to create a renewed movement for leprosy control and focus on reducing disabilities, especially among children (Leprosy, 2018). This Global Leprosy Strategy includes 3 core pillars; Pillar 1 is to strengthen government ownership, coordination, and partnership, Pillar 2 is to stop leprosy and its complication, and Pillar 3 is to stop discrimination and promote inclusion (Leprosy, 2018). Through these pillars, WHO hopes to reach the major targets of the Global Leprosy Strategy which are to have zero disabilities among new pediatric patients, a grade 2 disability rate of less than 1 case per 1 million people, and zero countries with legislation allowing discrimination on the basis of leprosy (Leprosy, 2018).

ETHIOPIA

Ethiopia is a country with a high burden of leprosy with nearly 4,000 new cases diagnosed every year, making it the fifth most burdened country globally (World Health Organization, 2013). According to Deribe, et al. (2012), in Ethiopia alone, over 30,000 people are living with permanent leprosy-related disability. Global statistics show that 94% of new leprosy cases were reported from 14 countries (Epidemiology, 2018), one of which is Ethiopia (Leprosy, 2018).

Since 1950, leprosy has been identified as a major health problem in Ethiopia. From then on, leprosy control efforts began with the establishment of a national leprosy office within the Ministry of Health in Ethiopia through the support of the German Leprosy Relief Association ("History of Leprosy in Ethiopia", 2019). There are currently three main regions in Ethiopia where leprosy is still endemic ("History of Leprosy in Ethiopia", 2019).

After introducing MDT along with a reduction in the duration of treatment, there was a steady decline in the prevalence of leprosy ("History of Leprosy in Ethiopia", 2019). Due to this reduction, leprosy programming was integrated into general health services. This integration has allowed programming with leprosy to cover a wider geographical area and extending to communities in need, while also reducing the stigma associated with the disease ("History of Leprosy in Ethiopia", 2019). Because of this ideology, leprosy patients are diagnosed and treated in all health facilities together with other patients. Currently, leprosy is not a major public health concern in Ethiopia as the prevalence rate has dropped to 0.8 per 10,000 cases, however there is a constant influx of new cases, which can be problematic and must be addressed ("History of

Leprosy in Ethiopia", 2019). A further concern is underreporting leading to a burden caused by missing cases. Among the fourteen regions within Ethiopia, three regions are major contributors for the national prevalence of leprosy; Oromia, Amhara, and the Southern Nations Nationality and People (SNNP) (Sori, 2019). Prevalence of the disease varies among regions, however the epidemiological factors contributing to the emerging new cases have yet to be studied in depth (Sori, 2019).

CHAPTER 2: LITERATURE REVIEW

NEGLECTED TROPICAL DISEASES AND LEPROSY

General NTDs

Neglected tropical diseases (NTD) are a group of infectious diseases and other related conditions that disproportionately affect the 2.7 billion people globally living on less than 2 USD per day (Deribe et al., 2012). According to a review by Deribe, et al., (2012), NTDs are important public health problems in Ethiopia. Ethiopia has the largest number of NTD cases only behind Nigeria and Democratic Republic of Congo in Africa. It has the highest burden for trachoma, podoconiosis and cutaneous leishmaniasis in sub-Saharan Africa (SSA) and second highest burden for ascariasis, leprosy, and visceral leishmaniasis (Deribe et al., 2012). Even with high burdens of infection, control programs for NTDs in Ethiopia are in the early stages. To better combat Ethiopia's burden of NTD, there must be an integrated control of NTD, integrated mapping, rapid scale of interventions and operational research (Deribe et al., 2012). Furthermore, an emphasis on improving surveillance systems, both passive and active, may reduce overall burden of NTDs in Ethiopia.

Leprosy

Although leprosy prevalence has declined tremendously worldwide over the past few decades, there are less-recognized regions throughout the world that have continued to report an increase in cases. In 2000, WHO released a statement announcing that leprosy had been "eliminated as a public health threat", defined as <1 case per 10,000 persons. This statement was misleading and does not truly reflect pockets of higher prevalence. The declaration led to a decline in leprosy control, which negatively impacted communities in need of support.

Aside from the declaration by WHO in 2000, there have been continuous barriers to leprosy control. Firstly, *M. leprae* bacteria cannot be grown in a petri dish. This makes diagnosis difficult by forcing clinicians to depend on skin smears and clinical symptoms for diagnosis. Not being able to grow *M. leprae* bacteria also makes it difficult to understand pathophysiology of leprosy and host response to infection (Rodrigues, et al., 2011). Stigma is another worldwide burden that leprosy patients have faced for decades and continue to face. Although stigma is declining, it is important to note the formation of leprosy colonies and isolation still exists today in many parts of the world, especially in regions where leprosy is highly endemic, despite laws against them (Rodrigues, et al., 2011; White & Franco-Paredes, 2015). Another barrier is underdiagnosing of leprosy as physicians are not learning enough about leprosy or recognizing it clinically (Gupta, Kar & Bharadwaj, 2012; Rodrigues, et al., 2011). This has a negative influence on the possibility for early diagnosis as well as the prevention of leprosy-associated disability. Finally, the lack of a good diagnostic tool for leprosy has long been a difficult aspect of control, again leading to underdiagnoses and missed cases (Rodrigues, et al., 2011; White & Franco-Paredes, 2015). Ultimately, complacency following the WHO declaration in 2000 after years of tremendous work in leprosy elimination has led to an unmet recognition of disease burden. It is essential that in order to control the burden of leprosy, the disease must be recognized as a public health concern and met with the resources to combat the disease.

Three different classification systems are used to diagnose leprosy patients. The earliest classification system being the Madrid classification system. Developed by the Madrid congress, the recommendation was that there were two polar types, tuberculoid and lepromatous, and two lesser groups, indeterminate and borderline (Davison, Kooij & Wainwright, 1960). The

Madrid classification was a great start in an effort to classify leprosy, however it did need improvement and simplification. The next classification developed was the Ridley-Jopling classification, which classifies leprosy into five categories and provides more of a pathological diagnosis. With this classification, tuberculoid and lepromatous were designated as the polar groups (similar to Madrid), however borderline tuberculoid (BT), borderline borderline (BB), and borderline lepromatous (BL) were defined as intermediate groups (Ridley & Jopling, 1966). Intermediate is defined by a leprosy patient who is unclassifiable in either of the polar groups because differentiating features have not yet developed (Ridley & Jopling, 1966). The most recent classification system is the WHO system, which classifies leprosy into two categories: paucibacillary (PB) and multibacillary (MB). MB, a type of leprosy, is important to differentiate from PB because it is linked to higher rates of transmission (Classification of Leprosy, 2018). PB is characterized by one or a few hypopigmented or hyperpigmented skin macules that exhibit loss of sensation due to the infection of peripheral nerves ("Clinical Disease | Hansen's Disease (Leprosy) | CDC", 2019). MB includes lepromatous, BL, BB, and some BT in Ridley-Jopling, and can be characterized by generalized or diffuse involvement of the skin in the lepromatous form, usually in the form of thickening peripheral nerves under microscopic examination with the potential to target other organs like the eyes, nose, testes, and bone ("Clinical Disease | Hansen's Disease (Leprosy) | CDC", 2019). Over the past few decades, there has been a shift in classification criteria changing from a bacterial index measurement to a skin lesion count approach for leprosy patients (Parkash, 2009). Although the system for leprosy classification is widely accepted, it is an imperfect system, especially in low-resource communities where the health system does not allow for the use of biopsy.

Clinical Signs & Symptoms

Grading the degree of disability at diagnosis of leprosy is an important part of evaluating patients in addition to surveillance programs. Grade 0 disability is classified by normal sensation along with no visible impairments. Common visible impairments include burns, ulcers, or absorption on the skin. A quick sensory test is needed to confirm for Grade 0 disability since a patient may have no visible impairments, but still have impaired sensation ("WHO disability grading: operational definitions", 2019). Grade 1 disability is classified as impaired sensation with no visible impairments. Sensory testing is typically done with a ballpoint pen and the inability to feel the ballpoint pen is used to determine this disability grade ("WHO disability grading: operational definitions", 2019). Grade 2 disability is classified as visible impairments and includes mild absorption of at minimum one finger or a severe crack because of dryness and contractures ("WHO disability grading: operational definitions", 2019). Grade 2 disabilities, having more physical deformities, lead to a significant impact on the ability of patients to carry on day to day activities. Grade 2 disability also often leads to stigma and isolation because of the visual characteristics of the disability. From a diagnosis perspective, Grade 2 disability is an indicator for late diagnosis.

Other complications stemming from the host immune response to leprosy, are two types of reactions classified as type 1 and type 2 reactions. Type 1 leprosy reactions are associated with delayed hypersensitivity reactions that can be present in both MB and PB forms of leprosy. In addition to nerve impairment from the direct effects of the bacteria, “leprosy reactions” are source of morbidity for patients and can occur in up to 30-50% of those diagnosed (Toh et al., 2018). With type 1 leprosy, there is a higher risk of permanent damage to the peripheral nerve trunks ("WHO Model Prescribing Information: Drugs Used in Leprosy: Treatment of lepra reactions", 2019). Type 2 reactions are more commonly associated with circulation and tissue deposition of immune complexes. This antibody response occurs only in MB leprosy ("WHO Model Prescribing Information: Drugs Used in Leprosy: Treatment of lepra reactions", 2019), and can cause severe systemic systems and painful skin nodules. Both reactions often require long courses of corticosteroid treatment or other immunosuppressive regimens that can lead to adverse effects like an increased susceptibility to serious infections or osteoporosis (White & Franco-Paredes, 2015).

MEASUREMENTS OF NUTRITION

Undernutrition

Body Mass Index (BMI) is a measure for indicating nutritional status in adults. It is defined as a person's weight in kilograms divided by the square of the person's height in meters (kg/m2) ("Body mass index - BMI", 2019). The classification system that is universally accepted is split into four categories; underweight, normal, overweight, and obese. Underweight is characterized as BMI less than 18.5. Normal is classified as greater than or equal to 18.5 and less than 25. Overweight is classified as greater than or equal to 25 and less than 30. Obese is characterized as BMI greater than 30. BMI is a simple measure to calculate and is therefore a commonly used indicator for nutritional status at a population level ("Body mass index - BMI", 2019). Like most measures, it is not the most accurate since it is dependent on height and weight, while disregarding age, physical activity levels, and sex ("Body mass index - BMI", 2019).

Another, less accepted, indicator for nutritional status in adults is Middle Upper Arm Circumference (MUAC). MUAC is less accepted due to the fact that there are no global standards using MUAC to classify acute malnutrition among adults. However, a study in South Africa found that MUAC is a feasible method to identify adult malnutrition and should be considered as a reliable tool for understanding malnutrition (Van Tonder et al., 2018). The universally accepted cutoffs for MUAC are shown in *Figure 1*. Adults with a MUAC below 18 cm are classified with malnutrition as “severe”. Adults with a MUAC between 18cm and 21cm are classified as “moderate”. Adults with MUAC greater than 21 cm are classified as “normal” without evidence of malnutrition.

MUAC Classification

MUAC	CLASSIFICATION
Children 6–11 months old: <11 cm Children 12–59 months old: <11 cm Children 5–9 years old: <13.5 cm Children 10–14 years old: <16 cm ***Adults: < 18.0 cm (Adults includes both non-pregnant, pregnant, and post-partum adults.)***	***SEVERE***
Infants 6–11 months old: 11–12 cm Children 12–59 months old: 11–13 cm Children 5–9 years old: 13.5–14.5 cm Children 10–14 years old: 16–18 cm Adults: 18–21 cm	***MODERATE***
Infants 6 – 11 month old : > 12 cm Children 12 -59 months old : > 13 cm Children 5 -9 years old : > 14.5 cm Children 10 – 14 years old > 18 cm Adults: > 21 cm	***NORMAL***

Figure 1. World Health Organization (WHO) MUAC Classification for adults and children (WHO, 2019)

Dietary Habits

Household Food Insecurity Access Scale (HFIAS) is an adaptation of the approach used to estimate the prevalence of food insecurity in the United States (US) annually. The methodology is based on the idea that the experience of food insecurity causes predictable reactions and responses that can be captured and quantified through a survey and summarized (FAO.org, 2019). Information collected by the HFIAS can be utilized to assess the prevalence of household food insecurity and detect changes in household food insecurity situations within a population over time (FAO.org, 2019). In a study looking at diet-related risk factors for leprosy, HFIAS was filled out for every participant. The aim was to monitor problems with food access, dietary modifications or concerns about food insecurity over the previous four weeks from when the questions were asked (Wagenaar, et al., 2015). Another study used HFIAS for the same purpose and found that HFIAS score was two times higher in cases compared to controls (Oktaria, et al., 2018).

The first general question in the HFIAS is, “In the past four weeks, did you worry that your household would not have enough food?”. One response to this is “Yes”, in which case the questioner would ask a sub-question, “How often does this happen?”. To this sub-question, respondents can respond with, “Rarely” (meaning once or twice in the past four weeks), “Sometimes” (meaning three to ten times in the past four weeks), or “Often” (meaning more than ten times in the past four weeks). Another response to the initial question is “No”, in which case the questioner would skip to Question 2. Other questions in the HFIAS include, “In the past four weeks, were you or any household member not able to eat the kinds of foods you preferred because of a lack of resources?” or “In the past four weeks, did you or any household member have to eat a smaller meal than you felt you needed because there was not enough food?” (FAO.org, 2019).

United States Department of Agriculture (USDA) food security survey questions provided through the Economic Research Service (ERS) is another accessible resource on how to measure household food security. It provides detailed guidance for researchers on how to use the survey module to measure food security and food insecurity ("USDA ERS - Survey Tools", 2019). One major limitation of this resource was a lack of determining food insecurity in children.

RELATIONSHIP BETWEEN NUTRITION AND LEPROSY

Food Shortage

Nutritional status is known to influence the development of other infectious diseases such as respiratory infections, infectious diarrhea, measles and malaria. These diseases are observed more commonly in malnourished children. Malnutrition affects the immune system negatively, causing infected individuals to be more vulnerable for developing a clinically apparent infection. In tuberculosis, which has similarities to leprosy since it is also caused by a mycobacterium, nutritional deficit has been identified as an important risk factor in the development of clinical symptoms of disease for tuberculosis (Cegielski et al., 2004). Since *M. leprae* also has a latent on incubation period, it follows that the immune system effects of undernutrition could predispose an individual latently infected with M. leprae to display signs of active leprosy, as with tuberculosis.

Food shortage, from a nutritional standpoint, was associated with increased incidence of leprosy in northwest Bangladesh in one study (Feenstra, et al., 2011). A recent period of food shortage, when controlled for poverty was identified as the only socio-economic risk factor significantly associated with clinical manifestation of leprosy in their study (Feenstra, et al., 2011). *Figure 2*, which includes data from Feenstra, et al. study in Bangladesh, emphasizes a relationship between a food shortage season and a spike in leprosy cases immediately following that continues for at least 5- 6 months following.

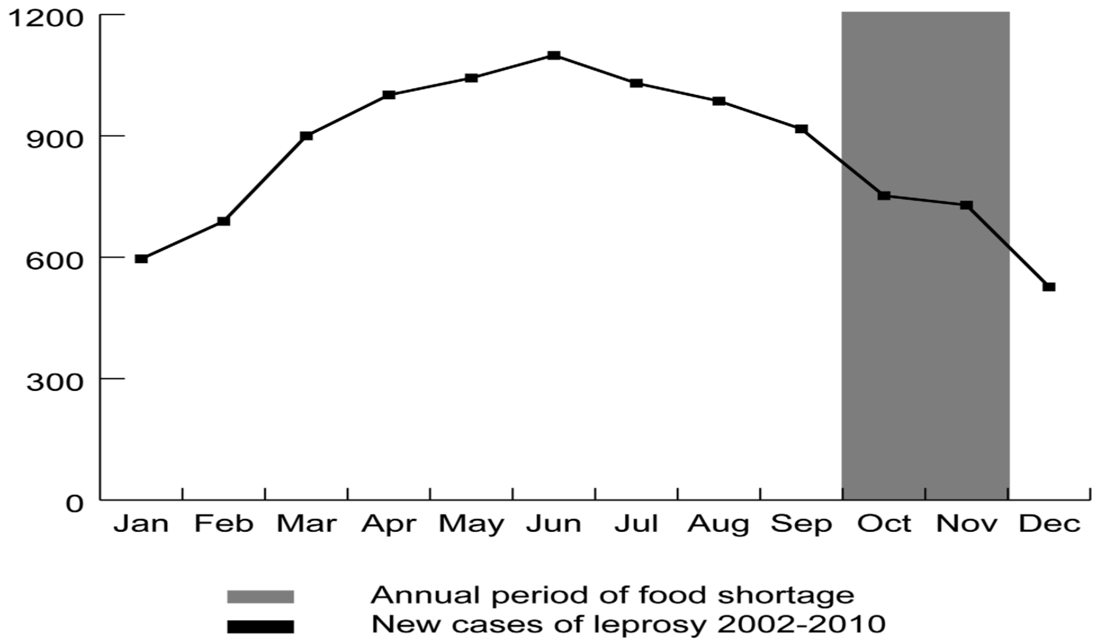

Figure 2. Seasonal pattern of leprosy cases in the study area (2002 – 2010) in relation to the annual period of food shortage (Feenstra, et al, 2011).

In Bangladesh, seasonal income changes were closely related to daily expenditure on food and thus influences the nutritional status of the people in this area (Feenstra, et al., 2011). The hypothesis that seasonal food deficiencies might be associated with leprosy is strengthened by the seasonal pattern in number of new leprosy cases registered per month over a nine-year period (2002–2010) in the districts where the study was carried out (Feenstra, et al., 2011). The number of newly registered cases rises from February, four months following the seasonal low-income period, and reaches a maximum in June at the beginning of the monsoon period in Bangladesh which is also six months following the end of the low-income period (Feenstra, et al., 2011). The difference in social norms regarding nutritional requirements and case definitions between countries, in this case of Bangladesh and Indonesia, could possibly be an explanation for a difference in time of the year when newly registered cases tend to rise (Feenstra, et al., 2011).

Feenstra, et al., (2011), suggests that targeted nutritional support to high risk groups should therefore be included in leprosy control programs in endemic areas to reduce risk of disease. It would also be useful to give contacts of leprosy patients, who are at high risk of developing leprosy themselves, dietary advice to prevent malnutrition. Because food shortage is seasonal and poverty related in northwest Bangladesh, extra attention and support should be given to the poorest families with leprosy patients. It is important to prevent malnutrition in these families to prevent clinical leprosy among contacts of patients (Feenstra, et al., 2011).

The following limitations were all reflective of the Feenstra, et al., study. The first limitation is the use of self-reported data on income, educational level, and food shortage as measured by a questionnaire, which by definition are all subjective. However, the effect of this bias on the study was reduced by asking cases and controls the exact same questions (Feenstra, et al., 2011). Another limitation is that the yearly period of food shortage mentioned previously roughly coincides with the start of symptoms of leprosy (Feenstra, et al., 2011). This limitation is focusing more on the idea that it would take time following the food shortage for there to be physical manifestations of disease. The final limitation to be considered is that in poor rural communities of Bangladesh, seasonal income changes are common. In the Feenstra, et al., (2011), study, the reported income changed from a monthly average of 3000 Bangladesh Taka (BDT), or 43 United States Dollar (USD), to 9000 BDT (130 USD) per household. Seasonal income changes are closely tied to daily expenditure on food and influences the nutritional status of the people in rural Bangladesh.

Another study in Indonesia enrolled 300 subjects, 100 leprosy cases and 200 controls. According to this study by Oktaria, et al., (2018), in univariate analysis, around 53% of cases also experienced food shortage at some time in their lives (with a mean length of 42.84±70.49 weeks) that was significantly associated with leprosy in Indonesia. High scores on the HFIAS index and experiencing food shortage at any time in life increased the risk of having leprosy (Oktaria, et al., 2018). Kerr-Pontes, et al., (2006), also found positive associations between food shortage or food insecurity and leprosy. One plausible explanation is that an impaired host immune response against the causative bacteria from insufficient nutritional intake leads to active leprosy.

Dietary Diversity and Poverty

Due to the fact that poverty is such a broad and complex topic to characterize, a causal relationship between poverty and leprosy is difficult to demonstrate, and uncertainty exists about how leprosy and poverty are associated (Kerr-Pontes et al., 2006). Findings suggest that food poverty is an important risk factor for leprosy susceptibility, yet the mechanisms underlying this association other than nutrient deficiencies still need to be identified (Oktaria, et al., 2018). Most individuals affected by leprosy are born and raised in poor environments and continue being pushed into poverty due to the stigma and disabilities associated with the disease (Lockwood, 2004). To go beyond that, most of the leprosy affected countries are underdeveloped (Lockwood, 2004). Another important aspect to understand is that in order for patients to be diagnosed with leprosy they need to be present at a health center or hospital. Thus, there may be a hidden bias that underestimates the association between poverty and leprosy found in Feenstra, et al., (2011), because only registered cases were included in the study. Registered cases receive leprosy treatment and have access to health services, therefore, the association between leprosy and poverty may be underestimated.

Another study suggests that people with leprosy have less favorable socioeconomic and demographic conditions, as well as dietary consumption. Low education levels, unstable incomes, and no land ownership are some aspects of poverty that were associated with the risk of having leprosy (Oktaria, et al., 2018). With regards to education level, it had a protective association against leprosy. Thus, the more educated someone is, the lower chance they will contract leprosy (Oktaria, et al., 2018). Other important factors associated with leprosy were unstable income and land ownership, which are related to income inequality. Based on the study analysis, people with unstable incomes were five times more likely to develop leprosy, while owning private land decreased the risk of getting leprosy by 60% (Oktaria, et al., 2018). Similar associations with SES were also found in Brazil (Pescarini, et al., 2018; Kerr-Pontes et al., 2006; Matos et al., 2018)

With a relatively stable incidence rate of leprosy despite the implementation of chemoprophylaxis and MDT, improving dietary diversity through food-based approaches should be initiated and directed toward high-prevalence villages. The possible underlying factors that link poverty to leprosy other than nutrient deficiencies also need to be identified (Oktaria, et al., 2018). Poverty means more than just a lack of income; it also encompasses the multiplicity of non-monetary aspects that often combine and intensify the negative effects of being poor, including lack of proper food and nutrient intakes (United Nations Sustainable Development, 2019). Correspondingly, food shortage, food insecurity, and lower dietary diversity are several aspects of poverty that are more commonly found in those struggling with leprosy (Abdullah, et al., 1985).

Although the aforementioned articles describe poverty and dietary diversity as associated risk factors with the study, there are some limitations to be brought to the limelight from the Oktaria, et al., study. Because leprosy is a slowly developing infectious disease with a very long incubation period, it is difficult to determine a causal relationship using short-term longitudinal studies as done in Indonesia (Oktaria, et al., 2018). Another limitation was that the data were collected following the diagnosis of leprosy and due to strong stigma in the areas where the study was conducted, researchers were not allowed to specifically ask for changes in the subjects' income and diet following diagnosis, thus leading to more of a cross-sectional study design (Oktaria, et al., 2018). This also plays a role in making it difficult to determine a causal relationship, since it is not completely clear if the food shortage was a cause or a result of leprosy. Further studies to assess dietary intake more objectively should utilize biomarkers to analyze for micro- and macronutrients in blood (Oktaria, et al., 2018).

Diet-related Risk Factors

Diet-related risk factors are possible mechanisms for *M. leprae* infection. According to Wagenaar, et al., (2015), low income families have only little money to spend on food and consequently have a low intake of highly nutritious non-rice foods such as meat, fish, milk, eggs, fruits and vegetables. As shown in *Figure 3,* there is a difference in how cases versus controls reported their food insecurity.

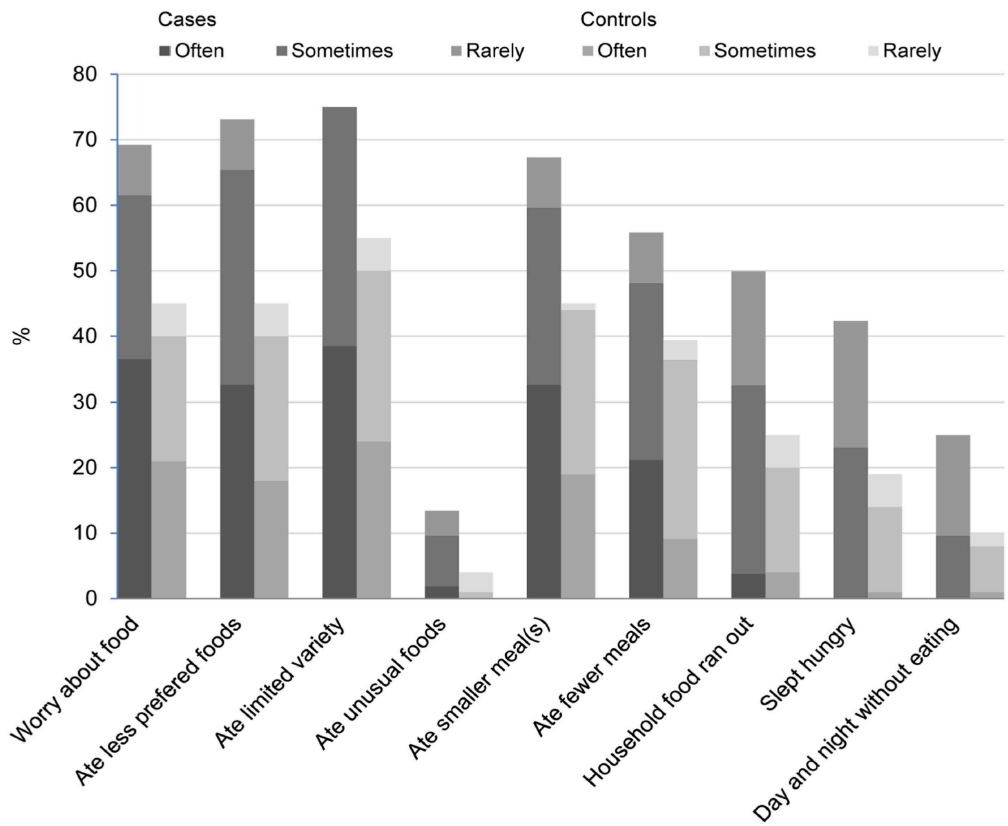

Figure 3. Frequency of occurrence for each Household Food Insecurity Access Scale item for leprosy patients and controls (Wagenaar, et al., 2015).

Development of clinical leprosy could be explained by deficiencies of the nutrients that these foods normally provide. In the study conducted by Wagenaar, et al., (2015), food insecurity was significantly higher among the people suffering from food shortage: their HFIAS score was on average 10.8, versus 0.6 for people not experiencing food shortage ($p<0.001$). Although food shortage is a standalone risk factor, it is also strongly influential of diet-related risk factors, which can in turn affect *M. leprae* infection. That being said, the risk of contracting subclinical *M. leprae* infection is not necessarily increased by food shortage, but it could facilitate the progression from infection to the clinical presentation of leprosy (Wagenaar, et al., 2015). Note that during times of food shortage, control subjects reduced their intake of foods, while cases were forced into eliminating foods from their diet altogether (Wagenaar, et al., 2015). One indicator for measuring nutritional risk factors is BMI. In the same study by Wagenaar, et al., (2015), BMI was the only significant factor in the uni- and multivariate analysis ($p<0.05$); a lower BMI increased the risk of leprosy. Food shortage experienced in the year prior was significantly associated with leprosy in univariate analysis, but not significant in multivariate analysis.

While it makes sense that some diet related factors may be associated with *M. leprae* infection, the data suggesting these trends are limited to very few small studies. Therefore, it is important to consider limitations. One limitation was the cross-sectional design that was employed because the study aimed to collect data during a food shortage period. An assumption was made that the persons experiencing food shortage this year have also experienced this in the previous years and that their overall diets did not change over time (Wagenaar, et al., 2015). A final limitation of the Wagenaar study is that most of the data were self-reported through questionnaires, introducing recall and response biases. Especially for very poor people with an unstable income their average income is difficult to estimate. This was addressed by asking the same questions to cases and controls to limit the effect on the results (Wagenaar, et al., 2015).

CONCLUSION

Although the literature speaks to an interplay between leprosy and nutrition, there are still further investigations that need to take place to solidify this understanding. Food insecurity, dietary diversity, poverty, and food shortages are gaps within the literature that can be further studied to provide more comprehensive knowledge on the interaction between nutrition and leprosy. Although the evidence may suggest that nutritional habits can lead to leprosy infection, it is important to remember that many of the conclusions made in the articles presented are associations and do not reflect causation between undernutrition and leprosy. Therefore, further investigation may be necessary to understand if leprosy infection leads to undernutrition or a change in dietary habits. This will allow the literature to speak more effectively to the relationship between nutrition and leprosy. Another important understanding is that Wagenaar argues that food shortage does not impact susceptibility to leprosy infection, but rather the progression from infection to clinical manifestation. This is not completely in line with Feenstra who argues that seasonal food shortage increases susceptibility to disease, not progression of disease.

Another major finding connecting leprosy to undernutrition was a study that found BMI to be a single significant factor in uni- and multivariate analysis ($p<0.05$) that was associated with an increased risk of leprosy infection (Wagenaar, et al., 2015). With BMI representing a more well accepted indicator for nutritional status in adults, this conclusion was very promising in understanding a possible risk factor for leprosy infection. Micronutrients are important to the integrity and functions of the immune system, specifically with regards to cellular response and antibody production (Passos Vázquez et al., 2019). Nutritional balance may have the ability to reduce risk of acquiring disease (Passos Vázquez et al., 2019).

Importantly, progress in the eradication of leprosy can only come from a close collaboration between physicians, biologists, epidemiologists, and geneticists. Leprosy, so long a cause of social isolation and stigmatization of those who suffer the disease, will only be eradicated by a joint effort of all components within the scientific community. Although findings were similar among the handful of studies described, it is important to note that none of the studies are in the context of Africa or Ethiopia to be specific. Beyond that, our study supports the body of knowledge that exists outside of the context, while still being able to integrate a variety of tools; BMI, MUAC, food insecurity questions, and SES-related questions. The complexities of poverty, SES, undernutrition (as indicated by BMI and MUAC in adults), dietary diversity or habits, and food shortage make the interpretation of data much more difficult and much less conclusive, however it is vital to the progression of fully understanding and eradicating leprosy that these gaps in the literature must be pursued and brought into the limelight.

CHAPTER 3: MANUSCRIPT

ABSTRACT

UNDERNUTRITION AND FOOD INSECURITY AS RISK FACTORS FOR LEPROSY IN NORTH GONDAR ZONE, ETHIOPIA

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Introduction/Objectives

Ethiopia has nearly 4,000 new cases diagnosed every year. Prevention remains a challenge, as transmission pathways are poorly understood and susceptibility and disease manifestations are highly dependent on the individual host immune response. An immune response that predisposes an individual to active leprosy, in particular MB infection, could be a driver of more infectious cases in the community. Nutritional deficiencies, such as protein-energy malnutrition, have been linked to reduced cell-mediated immunity and food insecurity has been associated with leprosy. The aim of this project was to identify nutritional risk factors for leprosy.

Methods

Between June and August 2018, recently diagnosed patients were enrolled as leprosy cases and individuals without contact with known cases were enrolled as controls in Gondar and surrounding health centers. Participants answered survey questions on biometric data, demographics, socioeconomic situation, and dietary habits. Anthropometric data was collected and tabulated. Descriptive statistics, univariate and multivariate analyses were conducted to examine associations between undernutrition, specifically BMI, MUAC, and leprosy.

Results

Eighty-one patients were enrolled (75% male) with an average age of 38.6 years (SD 18.3). The majority of cases were MB (90%) and 21 participants (25.9%) had schistosomiasis. There was a high prevalence of undernutrition with 24 (29.6%) of participants underweight (Body mass index (BMI) <18.5) and 17 (21%) with a low Middle Upper Arm Circumference (MUAC). On univariate analysis, both low BMI (OR = 7.20, 95% CI 2.34 22.11) and low MUAC were significantly associated with leprosy (OR = 6.82, 95% CI 1.78 26.13). On multivariate analysis, underweight was still significantly associated with leprosy (aOR = 6.67, 95% CI 1.43, 31.0). Cutting the size of meals/skipping meals (OR = 2.9, 95% CI 1.0, 8.32) or not having enough money to get more food (OR = 10, 95% CI 3.44 29.06) was more common in cases of leprosy than controls.

Conclusion

These findings suggest a strong association between leprosy and undernutrition. Skipping meals and not having enough money to get more food support the framework that food insecurity could lead to undernutrition that then may increase susceptibility to leprosy. In conclusion, this study highlights the need to further study the interplay of undernutrition, food insecurity, and the transmission of leprosy and incorporate nutritional programs into leprosy prevention strategies.

INTRODUCTION

Ethiopia is endemic for leprosy (*M. leprae* infection), with nearly 4,000 new cases diagnosed every year, making it the fifth most burdened country globally (World Health Organization, 2013). Prevention remains a challenge, as transmission pathways are poorly understood and susceptibility and disease manifestations are highly dependent on the individual host immune response (Bratschi, et al., 2015). An immune response that predisposes an individual to active leprosy, in particular multibacillary (MB) infection, could be a driver of more infectious cases in the community. Nutritional deficiencies, such as protein-energy malnutrition, have been linked to reduced cell-mediated immunity and susceptibility to infection (Ferguson, et al., 2000; Lima, et al., 2007; Mandal et al., 2015; Lu'o'ng & Nguyên, 2012) and food insecurity has been associated with leprosy (Wagenaar, et al., 2015; Pescarini, et al., 2018; Feenstra, et al., 2011; Oktaria, et al., 2018).

Body mass index (BMI) is a measure of nutritional status in adults. The classification system that is universally accepted is split into four categories; underweight, normal, overweight, and obese. Another, less accepted, indicator for nutritional status in adults is Middle Upper Arm Circumference (MUAC). However, a study in South Africa found that MUAC is a feasible method to identify adult malnutrition (Van Tonder et al., 2018). Nutrition has long been known to influence the development of infectious diseases such as respiratory infections, infectious diarrhea, measles, and malaria (Schaible et al., 2007). Looking at this closely, these diseases are observed more commonly in malnourished children. Malnutrition affects the immune system negatively, causing infected individuals to be more vulnerable for developing a clinically apparent infection. In tuberculosis, which has many similarities to leprosy, nutritional deficit has been identified as an important risk factor for the development of clinical symptoms of disease (Cegielski et al., 2004).

Due to the fact that poverty is such a broad and complex topic to characterize, a causal relationship between poverty and leprosy is difficult to demonstrate. In addition, uncertainty exists about how leprosy and poverty are associated (Pescarini, et al., 2018). Most individuals affected by leprosy are born and raised in poor environments and continue being pushed into greater depths of poverty due to the stigma and disabilities associated with the disease (Feenstra, et al., 2011). Low income families have only little money to spend on food and consequently have a low intake of highly nutritious non-rice foods such as meat, fish, milk, eggs, fruits and vegetables. There are few studies investigating leprosy and nutrition, however they all suggest that nutrition plays a role in the disease (Feenstra et al., 2011; Wagenaar et al., 2015; Oktaria et al., 2018). We seek to increase the body of knowledge on the associations of leprosy and nutrition in the context of Ethiopia, which has not been studied thus far. More specifically, we hypothesize that undernutrition may be a risk factor for leprosy while controlling for other factors such as *S. mansoni* co-infection and socioeconomic status (SES).

METHODS

Study Design & Overview

Between June and August 2018, participants were recruited in North Gondar Zone, Ethiopia. North Gondar Zone part of the Amhara Region within Ethiopia and had a census population of 3,225,022 as of July 1, 2017 ("North Gondar Zone", 2019). With an urban population of 509,228 (15.79%), a vast majority of the population in North Gondar Zone live in rural or agricultural areas ("North Gondar Zone", 2019). The total land area of North Gondar Zone is 45,945 square kilometers ("GeoHive - Ethiopia Population Statistics", 2019). Participants were enrolled at the University of Gondar referral hospital and health centers in and around the North Gondar Zone. The study design utilized is a case-control study. The aim of the study design was to assess possible differences in undernutrition and dietary intake between diagnosed leprosy patients and control subjects. The rationale for this approach was to identify relationships between undernutrition, food shortage, or diet-related factors that could exacerbate the clinical development or manifestations of leprosy.

Study Population

Cases were enrolled as persons with active leprosy disease diagnosed by a practicing dermatologist within the previous 12 months. Both MB and PB cases were included. Other case inclusion criteria were being 18 years of age or older or residing in North Gondar Zone of Ethiopia. Controls were adults without contact of known cases of leprosy and resided in the same communities as the cases. Individuals with suspicious skin or nerve symptoms were excluded as controls. Pregnant women and children were excluded from the study.

Data Collection

Data collected from participants included anthropometric data (height, weight, etc.), demographic information (age, sex, etc), and survey questions inquiring about food insecurity, dietary habits, and socioeconomic status (SES). Food security survey questions were derived from the United States Department of Agriculture (USDA) through the Economic Research Service (ERS) and is an accessible resource on how to measure household food security. It provides detailed guidance for researchers on how to use the survey module to measure food insecurity ("USDA ERS - Survey Tools", 2019). The classification system that is universally accepted for BMI is split into four categories; underweight, normal, overweight, and obese. Underweight is characterized as BMI less than 18.5. Normal is classified as greater than or equal to 18.5 and less than 25. Overweight is classified as greater than or equal to 25 and less than 30. Obese is characterized as BMI greater than 30. To calculate BMI by value, patient anthropometric data was collected. BMI for patients were calculated by weight (kg)/ height^2 (m). For MUAC, circumference was measured by finding the midpoint between the participants' elbow and shoulder. From there, the measuring tape was wrapped around the participants' arm at the midpoint to determine MUAC in centimeters. Adults with a MUAC below 18 cm are classified as "severe" or "low". Adults with a MUAC between 18cm and 21cm are classified as "moderate" or "low". Adults with MUAC greater than 21 cm are classified as "normal". Urine was tested for *S. mansoni* infection by Schisto POC-CCA^{TM} rapid diagnostic test (RDT). Surveys were translated to Amharic and conducted in Amharic local health center workers or University of Gondar collaborators on the study.

Data Management & Analysis

Statistical Analysis: There are no published data on undernutrition or dietary habits, as they relate to leprosy, in North Gondar Zone, Ethiopia, therefore, a sample size could not be calculated based on anthropometric data. Instead, the sample size was determined using schistosomiasis as a risk factor for leprosy. Based on an estimated helminth burden of 20-25% prevalence in North Gondar Zone, sample size was calculated using an alpha of 0.05 and power of 0.8, resulting in a goal of 40 cases and 40 controls. Data from the questionnaires were entered into an Excel database. After data cleaning, analysis was performed using SAS Version 9.4 (SAS Institute, Cary NC). Descriptive statistics were performed on the main study variables and p-values describing differences between participants that were cases or controls were calculated for each variable using the appropriate test (chi-square, Fisher's Exact test, or t-test). In univariate analyses, calculation of odds ratios provided insight into an association between exposures of interest, such as BMI, MUAC, and dietary habits, and the outcome of interest, a clinical diagnosis of leprosy. A p-value of < 0.05 was considered significant. Figures for visual analysis and representation were developed using Microsoft Excel (2017) and R (Version 1.1.456 – © 2009-2018 RStudio, Inc).

Multivariate Analysis: The goal of the analysis was to determine the adjusted odds ratio of undernutrition (exposure) in those with and without leprosy (outcome). Initially, univariate analysis was carried out and the variables significantly associated with *M. leprae* infection were included in a multivariate backward stepwise logistic regression. Multivariate logistic regression was used to assess the association between undernutrition and leprosy infection while controlling for potential confounding factors such as age, sex, or education. The variables that remained statistically significant in these multivariate analyses were considered as the main result. A p-value of < 0.05 was determined to be significant. All multivariate analyses were done using SAS 9.4 (SAS Institute, Cary NC).

Human Subject & Ethical Approval Considerations

This study was approved by the Emory Institutional Review Board (IRB) and the ethical review board of the University of Gondar. Given the low-risk nature of the study, informed consent was sought through a verbal consent process, asserting patients' understanding of the risks associated with the study. Participant privacy was assured by the use of de-identified study identification numbers and all private data was locked in a password-safe computer and protected by in-country collaborators.

Deliverables

Emory University and University of Gondar mutually owned data collected from this study for the purposes of continued collaboration and research. The findings from the study will empower the advancement of this research that may lead to prevention strategies focused on malnutrition and limit the risk of reduced-immunity from nutrient deficiencies in the region. In addition, interventions to support socioeconomic situations may be a useful outcome of this research. Major deliverables from this study will include primary pilot data for the prevalence of undernutrition and dietary habits in patients with leprosy. Additional deliverables include the development of a survey tool and a database for data collection.

RESULTS

Eighty-one participants, 40 patients (cases) and 41 controls, were enrolled (75% male) with an average age of 38.6 years (SD 18.3). 52 participants (64.2%) had less than eight years of formal education. The majority of cases were MB (90%) and 21 participants (25.9%) had *S. mansoni* infection. All demographic and clinical data are presented in *Table 1*.

Cases were also stratified by age group in *Table 2*, to better describe the patient population. Among the 40 cases, 19 (47.5%) were between 18 and 38 years of age. 11 cases (27.5%) were between the age of 39 and 59. The remaining 10 cases (25%) were greater than 60 years of age. 8 (20%) patients were diagnosed with Grade II disability, according to WHO classification. Disability Grade II was highest among patients between the age of 39-59 accounting for 36% of cases within that group.

Table 1. Demographic and clinical data of study population

Variable	Cases (n = 40)	Controls (n = 41)	Total (n = 81)
Age (years), mean (SD)	42.9 (19.1)	34.4 (16.5)	38.6 (18.3)
Sex, n (%)			
Male	31 (77.5)	30 (73.2)	61 (75.3)
Female	9 (22.5)	11 (26.8)	20 (24.7)
WHO Classification, n (%)			
Paucibacillary (PB)	4 (10.0)	N/A	N/A
Multibacillary (MB)	36 (90.0)		
Grade of Disability, n (%)			
Grade 1	12 (30.0)	N/A	N/A
Grade 2	8 (20.0)		
Education Level , n (%)			
Less than Grade 8	27 (67.5)	25 (61.0)	52 (64.2)
Grade 8 and above	4 (10.0)	15 (36.6)	19 (23.5)
Missing	9 (22.5)	1 (2.4)	10 (12.3)
Body Mass Index (BMI), n (%)			
Underweight (<18.5)	20 (50.0)	5 (12.2)	25 (30.9)
Normal - Obese (≥ 18.5)	20 (50.0)	36 (87.8)	56 (69.1)
Middle Upper Arm Circumference (MUAC), n (%)			
Low (18 – 21 cm)	14 (35.0)	3 (7.3)	17 (21.0)
Normal (>21 cm)	26 (65.0)	38 (92.7)	64 (79.0)
S. mansoni infection, n (%)	8 (20.0)	13 (31.7)	21 (25.9)

Table 2. General Characteristics of leprosy cases among study population

Age Group (in years)	Case N (%)	MB (% of cases)	Disability Grade II (% of cases)
18 – 38	19 (47.5)	17 (89.4)	2 (10.5)
39 – 59	11 (27.5)	10 (90.9)	4 (36.4)
≥60	10 (25.0)	9 (90.0)	2 (20.0)
Total	40 (100.0)	36 (90.0)	8 (20.0)

There was a high prevalence of undernutrition with 24 (29.6%) of participants underweight (BMI <18.5) and 17 (21%) with “low” MUAC. *Figure 4* depicts a case-control comparison of BMI. 5 (12.2%) controls were characterized as underweight, while 20 (50%) cases were classified as underweight by BMI. Figure 4 shows the difference in the proportion of patients and controls that were underweight.

Figure 4. Case-control comparison of BMI by classification

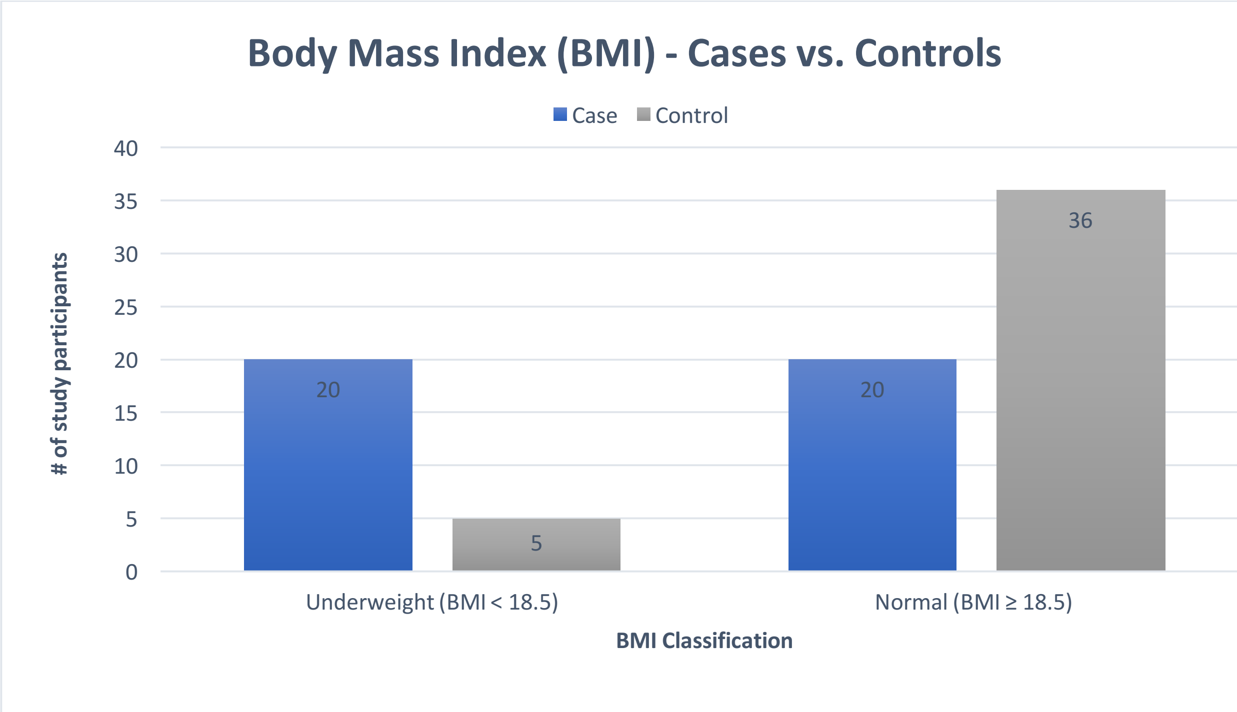


Figure 5 depicts a case-control comparison of BMI by value showing that the cases' mean BMI is lower than that of controls' mean BMI and is statistically significant. *Figure 6* depicts a case-control comparison of MUAC by value. To calculate MUAC by value, patient anthropometric data was collected. In the *Figure 6* boxplot, cases' mean MUAC value is lower than that of controls' mean MUAC value. With a p-value < 0.05, MUAC by value is also significantly associated with leprosy. Both of these figures show a clear distinction in BMI and MUAC values when comparing cases and controls.

Figure 5. Case-control boxplot comparison of BMI by value

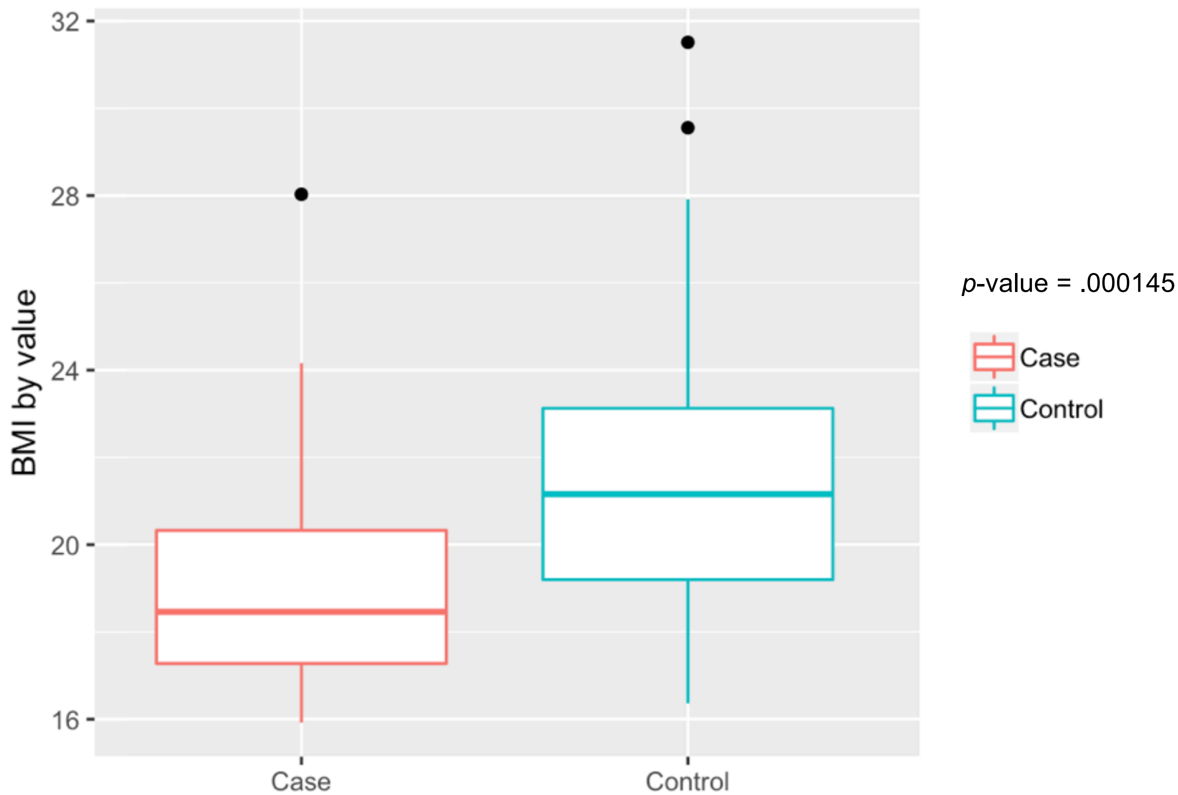
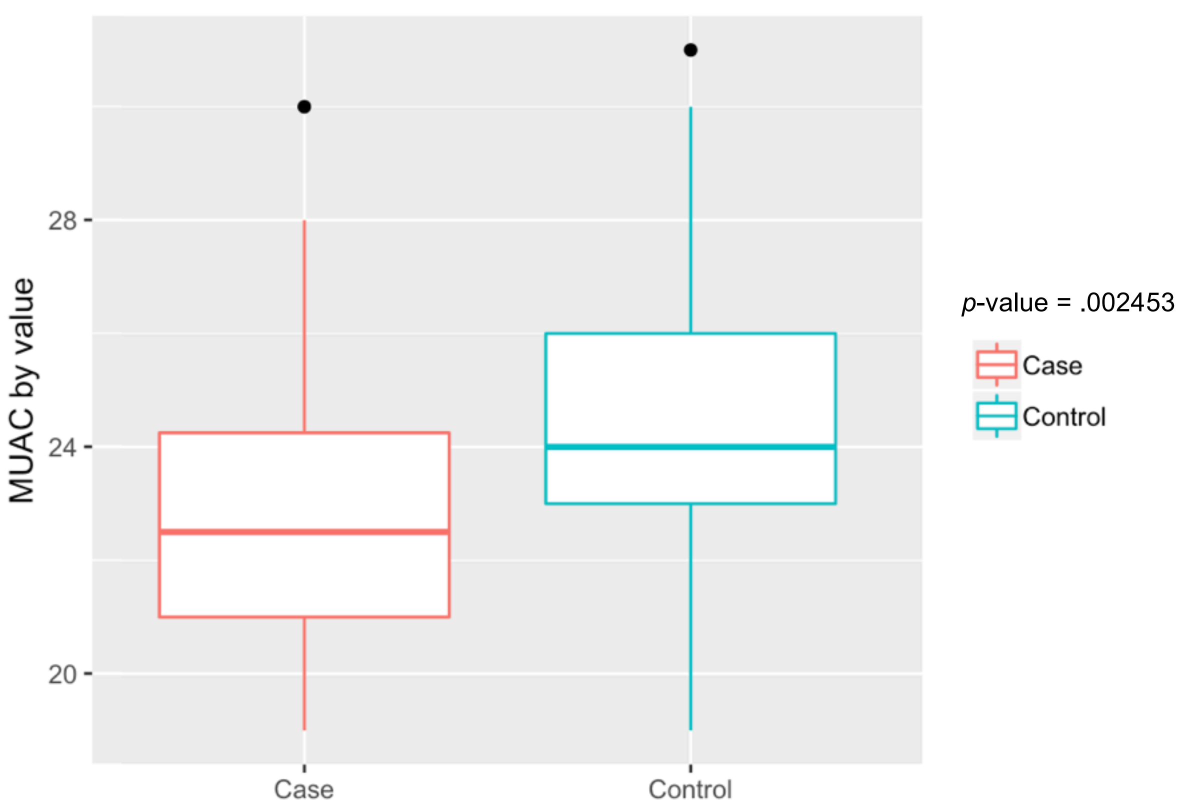


Figure 6. Case-control boxplot comparison of MUAC by value



On univariate analysis (*Table 3)*, both low BMI (OR = 7.20, 95% CI 2.34 22.11) and low MUAC were significantly associated with leprosy (OR = 6.82, 95% CI 1.78 26.13). Low education level, defined as less than Grade 8, was significantly associated with leprosy (OR = 4.05, 95% CI 1.18 13.85). Cutting the size of meals/skipping meals (OR = 2.9, 95% CI 1.0 8.32) or not having enough money to get more food (OR = 10, 95% CI 3.44 29.06) was more common in cases of leprosy than controls. Additional outcomes looking at dietary habits and SES as they relate to leprosy can be seen in *Table 3*. On multivariate analysis (*Table 4*), underweight was still significantly associated with leprosy (aOR = 6.67, 95% CI 1.43 31.0) after controlling for age, sex, and education.

Table 3. Univariate analysis of study outcome, M. leprae infection, and study variables BMI, MUAC, Sex, education, *S. mansoni infection, and dietary habits.* ***(Bolded results are significant with a p-value <0.05.)***

Variable	Odds Ratio (95% CI)	P-Value (α = 0.05)
Underweight – BMI (<18.5)	**7.20 (2.34, 22.11)**	**0.0003**
Low – MUAC (≤ 21 cm)	**6.82 (1.78, 26.13)**	**0.0025**
Sex Male (ref = Female)	1.26 (0.46, 3.48)	0.6629
Education level (Less than Grade 8)	**4.05 (1.18, 13.85)**	**0.0222**
S. mansoni infection	0.54 (0.19, 1.49)	0.1219
Reducing or skipping meals	**2.87 (1.00, 8.32)**	**0.0477**
Insufficient funds for meals	**10.0 (3.44, 29.06)**	**0.0000**
Length of time between each market visit? Less than once a week (ref = at least once a week)	1.83 (0.71, 4.71)	0.2175
Did not eat for a day due to lack of food	1.86 (0.50, 6.82)	0.3734
Ate less than participant felt they should have	1.27 (0.42, 3.84)	0.6824
Not taking dietary supplements	8.29 (1.21, 197)	0.0523
Recently modified dietary intake	**9.39 (1.96, 45.0)**	**0.0015**
No utilization of institutional banking	**2.89 (1.17, 7.14)**	**0.0212**

Table 4. Multivariate analysis (logistic regression) analysis of study outcome, M. leprae infection, and study variables Age, Sex, BMI, MUAC, and Education. ***(Bolded results are significant with a p-value <0.05.)***

Variable	Adjusted Odds Ratio (95% CI)
Age	1.02 (0.98, 1.05)
Sex Male (ref = Female)	1.89 (0.45, 7.90)
Underweight – BMI (<18.5)	**6.67 (1.43, 31.00)**
Low– MUAC (≤ 21 cm)	1.96 (0.32, 11.87)
Education (Less than Grade 8)	1.87 (0.41, 8.52)

DISCUSSION

In this study, we wish to identify whether or not undernutrition and dietary habits could be considered as risk factors for leprosy or the progression of leprosy. Specifically, we hypothesize that there would be differences in BMI, MUAC, SES, dietary habits and food insecurity between leprosy patients and controls. With eighty-one participants, 40 patients (cases) and 41 controls, enrolled in the study, undernutrition, or low BMI, was identified as the only significantly associated risk factor with clinical manifestation of leprosy disease in this study, under multivariate analysis.

This was consistent with the findings of Wagenaar, et al., (2015) in Bangladesh, who found BMI to be a single significant factor in uni- and multivariate analysis (p<0.05) that was associated with an increased risk of leprosy infection. More specifically, Wagenaar, et al. found 25% of cases to be underweight, while only 14% of controls were found to be underweight. According to Oktaria, et al., a paired t-test showed a significant difference in BMI between cases and controls (p <0.05). Although both studies' findings were consistent with our findings overall, their calculations used mean BMI as a continuous variable to compare between cases and controls. Both studies also provided percentage distribution across categorical BMI variables. In our study, we went a step further and compared Underweight (BMI < 18.5) to Normal – Obese

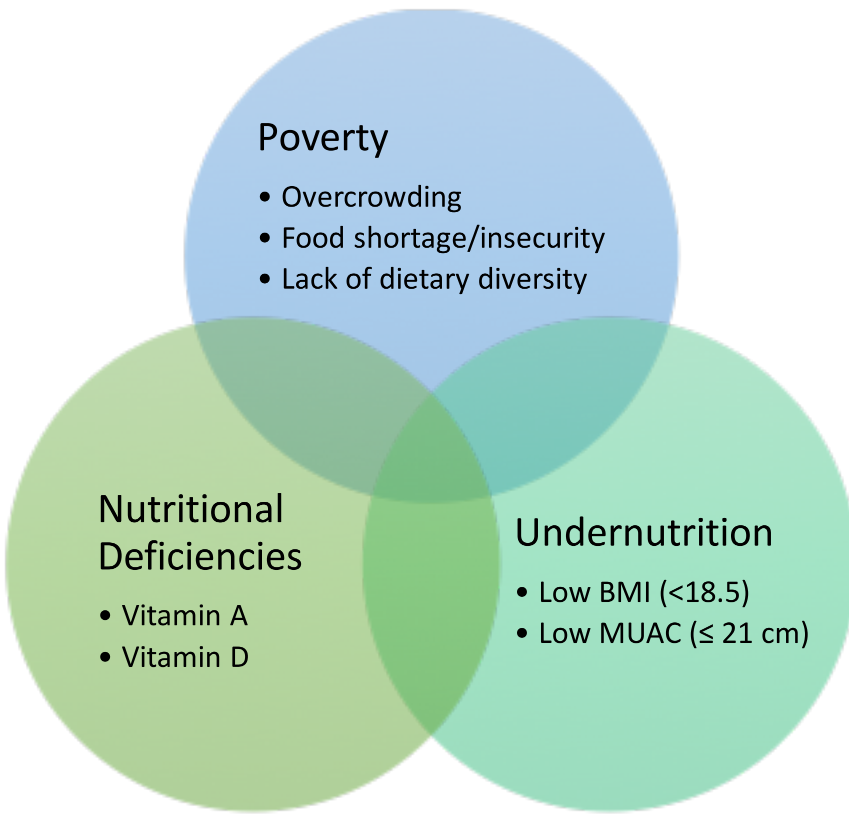
(BMI ≥ 18.5) as point estimate (odds ratio) to better assess the relationship between undernutrition and leprosy. Therefore, this study provides a more comprehensive look at undernutrition and the implications it has on leprosy in this region. According to Rao, et al., (2012), findings in India showed that undernutrition (BMI < 18.5) was more common in people affected by leprosy than in those without leprosy. A commonality among all the studies is a high burden of undernutrition, as defined by low BMI, that was present within "case" study populations. The other aspect of undernutrition is the influence that undernutrition may have on cell-mediated immunity. As Wagenaar et al., suggests, undernutrition may have a greater influence on the conversion of latent leprosy to active leprosy, rather than the increase for initial *M. leprae* infection rates.

Another important outcome of this study is that food insecurity, measured by having insufficient funds for meals, also associated with leprosy, supports the framework that poor dietary habits may increase susceptibility to *M. leprae* infection (as opposed to the opposite). This was consistent with Wagenaar, et al., (2015), who found that low income families have only little money to spend on food and consequently have a low intake of highly nutritious non-rice foods such as meat, fish, milk, eggs, fruits and vegetables. In addition, a recently modified dietary intake, as noted by participants, was associated with leprosy. With regard to SES, education and lack of bank utilization was significantly associated with leprosy. Similar indicators were also found to be significant in other studies looking at SES and leprosy (Pescarini, et al., 2018).

The majority of cases being MB (90%) within the study population may highlight comorbid conditions such as undernutrition that may play a role in the shift from PB to MB among patients, since MB is associated with a lack of a sufficient cell-mediated (Th1) response as opposed to a robust cell-mediated response in PB cases (Misch, et al., 2010). Although this link was not studied directly, further investigation could support undernutrition as a risk factor for leprosy or even leprosy progression. Consistent with our study, Oktaria et al., enrolled 100 patients (cases) and identified 89 (89%) of them to have MB disease. Wagenaar, et al., enrolled 52 cases in their study, however only 18 (34.6%) had MB disease. As more studies suggesting an increase in MB proportion among cases of leprosy appear, it is important to remember that much higher rates of transmission occur from MB patients than PB (Classification of Leprosy, 2018). In addition to the MB proportion of patients, about 21 participants (25.9%) in this study presented with *S. mansoni* infection. Although our study did not find an association with *S. mansoni* infection and leprosy, further investigations into co-infections and the influence on immune response mechanisms is needed to better understand this interaction with leprosy.

Findings from this study, support the limited data that exists in the literature and presents the first study to look at nutrition and leprosy in the Ethiopian context, a country that has dealt with a lot of food insecurity for its citizens in recent decades. A major strength of this study is the survey combining the collection of anthropometric data and nutritional questions relating to dietary habits and food insecurity. One limitation of the study is the smaller study size. However, with regard to BMI, sample size was sufficient to validate our findings with 80% power at a 0.05 alpha level. Challenges with sample size stemmed from a limited number of reported cases, accessibility to health centers, and willingness of patients to enroll in the study. Additionally, this study did not measure micronutrient deficiencies in participants. Doing so may have provided a more comprehensive study that would add to the literature. Although *S. mansoni* co-infection data was collected, other co-infections were not studied that could potentially affect immune responses, and thus the risk of active leprosy. Although this study found an association with BMI and leprosy, further knowledge and understanding is needed to corroborate the idea that there is a causal pathway between undernutrition and leprosy. Another important understanding is that Wagenaar argues that food shortage does not impact susceptibility to leprosy infection, but rather the progression from latent infection to clinical manifestation.

Figure 7. Venn-Diagram showing possible relationship between poverty, nutritional deficiencies, undernutrition.



This study is the first of its kind to look at nutrition, dietary habits, food insecurity, and SES in the context of North Gondar Zone, Ethiopia. Addressing the interplay between poverty, undernutrition, and nutritional deficiencies (as shown in *Figure 7)* may have the potential for impact on leprosy burden in this region and similar endemic areas. As we begin looking forward toward the elimination of leprosy, there are two major components that must be addressed; the reservoir and the host. This study has focused primarily on the host, in terms of undernutrition and dietary habits' influence on leprosy susceptibility, infection, and/or development of leprosy in a specific population. It is a worthwhile endeavor to pursue a greater understanding of the interconnectedness of nutrition and leprosy to further improve leprosy control, prevention, and intervention.

CHAPTER 4: PUBLIC HEALTH IMPLICATIONS

SUMMARY

Although leprosy prevalence has reduced dramatically worldwide over the past few decades, there are less-recognized regions throughout the world that have continued to report a steady number of yearly cases. In 2000, WHO released a statement announcing that leprosy had been "eliminated as a public health threat", defined as <1 case per 10,000 persons. This statement was misleading and does not truly reflect pockets of higher prevalence. The declaration led to a decline in leprosy control as it negatively impacted communities in need of support. WHO, government agencies, Ministries of Health, and other programming agencies removed resources from leprosy control programs. Starting in 2016, WHO introduced what is called the "Global Leprosy Strategy 2016 – 2020". The document (see APPENDIX *Figure 2*) sets a four-year plan including a vision, goals, and targets for eliminating leprosy worldwide.

Throughout history, there have been continuous barriers to leprosy control. Not being able to grow *M. leprae* bacteria in a petri dish makes it difficult to understand pathophysiology of leprosy and host response to infection. Stigma, another worldwide burden, has reduced over time, yet the formation of leprosy colonies and isolation, stemming from stigma, continues to persist in highly endemic areas of the world. Another barrier is the lack of clinical recognition to diagnose leprosy appropriately; this leads to an underdiagnoses of patients and reduces the possibility of early diagnosis that can lead to the prevention of leprosy-associated disability. Additionally, underreporting is a barrier that stems from underdiagnosing, stigma, and accessibility to care. Ultimately, following decades of tremendous work in leprosy elimination, the WHO declaration in 2000 has led to an unmet recognition of true disease burden. It is essential that in order to control the burden of leprosy, specifically in pockets of higher prevalence, the disease must be recognized as a public health concern and met with the resources to combat the disease.

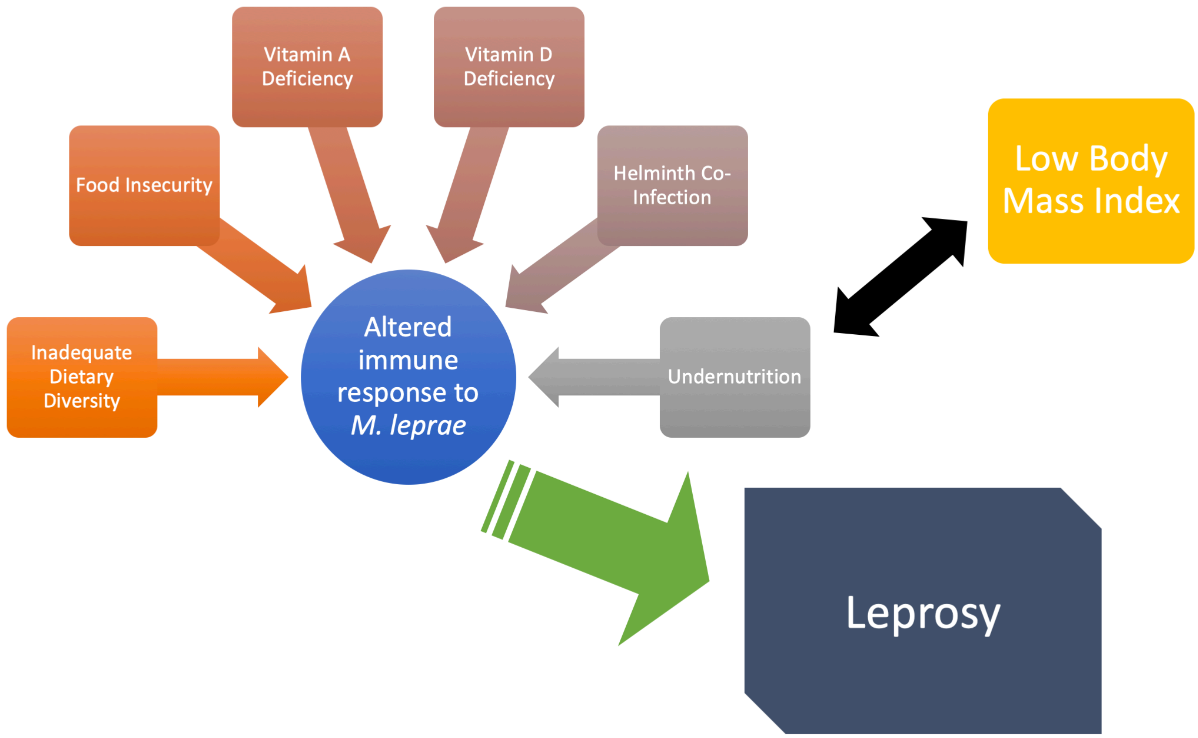
The literature suggests a clear association between leprosy and poverty. For instance, leprosy is a disease that disproportionately affects low and middle-income areas. Geographic Information Systems (GIS) and spatial systems analyses also support the association between low SES and leprosy. Beyond that, there is a well-known and accepted association between crowding and leprosy primarily because of leprosy's primary transmission route being from person to person. Although literature on leprosy exists, associations between nutrition and leprosy is limited to only a few studies, and this needs to change given the consistent associations found.

Undernutrition or low BMI in this study was identified as the only significantly associated risk factor with clinical manifestation of leprosy disease in North Gondar Zone, Ethiopia. This was consistent with the findings of Wagenaar, et al., (2015) in Bangladesh, who found BMI to be a single significant factor in uni- and multivariate analysis ($p<0.05$) that was associated with an increased risk of leprosy infection. Additionally, Rao, et al., (2012), found that in India, undernutrition ($BMI < 18.5$) was more common among people affected by leprosy than in those without leprosy, while controlling for age and sex. A high burden of undernutrition, as defined by BMI and MUAC, was present with the "case" study population. The consensus on undernutrition and BMI in the literature are indicative of nutrition playing a major role in the susceptibility and/or development of leprosy in various populations.

FUTURE DIRECTIONS

As we begin looking forward toward the elimination of leprosy, there are two major components that must be addressed; the reservoir and the host. Programming around contact tracing (including post-exposure prophylaxis), improving case treatment protocols, and strengthening surveillance systems are vital to success in combatting leprosy control by addressing the reservoir. More recent research is showing the environment (such as soil, water, etc.) as being a reservoir for *M. leprae*. Therefore, further studies and understanding of environmental health and water, sanitation, and hygiene (WASH) on leprosy will be of significance. Diniz, et al. (2010), shows that leprosy, specifically MB disease, was more common among helminth-leprosy co-infected patients as compared to leprosy-only infected patients. Another study suggest that soil-transmitted helminth infections may have a role in the progression to MB leprosy, as well as the occurrence of Type 2 reaction (Oktaria et al., 2016). The other component in eliminating leprosy is by addressing the host. Pursuing a greater knowledge on what increases susceptibility to *M. leprae* infection through immunological research will assist in prevention mechanisms that ultimately reduce transmission. Disease manifestations are highly dependent on individual host immune responses. Wagenaar, et al. (2015), suggests that nutritional deficiencies are linked to a reduced cell-mediated immunity putting individuals at higher risk to contract leprosy. Kerr-Pontes, et al. (2006) states that impaired host-immune response against causative bacteria, as a result of insufficient nutritional intake, is a possible cause of disease conditions. One specific methodology is to conduct a longitudinal study of high risk individuals for leprosy, collecting detailed data on diet and health, and taking blood samples for micronutrients and immunologic parameters to compare long-term data of the persons who developed leprosy with data of persons who did not.

Figure 8. Proposed mechanisms for the effect of altered immune response to M. leprae infection



Due to the limited research on nutrition and leprosy together, a more comprehensive approach to understanding the complexities of nutrition, host-immune interactions, the environment, and leprosy (as seen in *Figure 8*) must be pursued in order to support these major findings as they relate to undernutrition and leprosy. Analyzing the data between dietary diversity, undernutrition, food shortage, and poverty will support surveillance efforts, fund programming initiatives, and implement novel applications to controlling and eliminating leprosy worldwide.

REFERENCES

Abdullah, M., Wheeler, E.F. Seasonal variations, and the intra-household distribution of food in a Bangladeshi village. Am J Clin Nutr. 1985; 41:1305–13. PMID: 4003335

A guide to leprosy control, 2nd ed. Geneva, World Health Organization, 1988, and WHO Technical Report Series, No. 768, 1988 (*WHO Expert Committee on Leprosy,* sixth report).

Barreto, J.G., De Souza Guimarães, L., Leão, M.R.N., Ferreira, D.B.G., Lima, R.A., Salgado, C.G. 2011. Anti-PGL-I seroepidemiology in leprosy cases: household contacts and school children from a hyperendemic municipality of the Brazilian Amazon. Leprosy Review. 82(4): 358-70.

Body mass index - BMI. (2019). Retrieved from http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

Bratschi, M. W., Steinmann, P., Wickenden, A., Gillis, T. P. (2015). Current knowledge on Mycobacterium leprae transmission: a systematic literature review. Leprosy Review.

Britton, W., & Lockwood, D. (2004). Leprosy. The Lancet, 363(9416), 1209-1219. doi: 10.1016/s0140-6736(04)15952-7

Cegielski JP, McMurray DN (2004) The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. International Journal Tuberculosis Lung Disease 8: 286–298.

Classification of leprosy. (2018). World Health Organization. Retrieved 21 February 2018, from http://www.who.int/lep/classification/en/

Clinical Disease | Hansen's Disease (Leprosy) | CDC. (2019). Retrieved from https://www.cdc.gov/leprosy/health-care-workers/clinical-diseases.html

Davison, A., Kooij, R., & Wainwright, J. (1960). Classification of Leprosy. Application of the Madrid Classification of Various Forms of Leprosy. International Journal of Leprosy, 28(2), 113-125.

Deribe, K., Meribo, K., Gebre, T., Hailu, A., Ali, A., Aseffa, A., & Davey, G. (2012). The burden of neglected tropical diseases in Ethiopia, and opportunities for integrated control and elimination. Parasites & Vectors, 5(1), 240. http://dx.doi.org/10.1186/1756-3305-5-240

Diniz, L.M., Magalhaes, E.F., Pereira, F.E., Dietze, R., Ribeiro-Rodrigues, R. 2010. Presence of intestinal helminthes decreases T helper type 1 responses in tuberculoid leprosy patients and may increase the risk for multi-bacillary leprosy. Clinical & Experimental Immunology. 161(1): 142-150.

Epidemiology. (2018). World Health Organization. Retrieved 16 February 2018, from http://www.who.int/lep/epidemiology/en/

FAO.org, (2019). Retrieved from http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf

Feenstra, S.G., Nahar, Q., Pahan, D., Oskam, L., Richardus, J.H. Recent food shortage is associated with leprosy disease in Bangladesh: a case-control study. PLoS Negl Trop Dis 2011;5:e1029.

Ferguson A, Griffin GE (2000) Nutrition and the immune system In: Garrow JS, James WPT, Ralph A, editors. Human Nutrition and Dietetics. London: Elsevier Science Ltd; pp. 747–764.

GeoHive - Ethiopia Population Statistics. (2019). Retrieved from https://web.archive.org/web/20120805184429/http://www.geohive.com/cntry/ethiopia.aspx

GHO | By category | Leprosy - Number of new leprosy cases - Data by country. (2019). Retrieved from http://apps.who.int/gho/data/node.main.A1639?lang=en

Global Leprosy Strategy. (2019). Retrieved from https://apps.who.int/iris/bitstream/handle/10665/208824/9789290225096_en.pdf?sequence=14&isAllowed=y

Goal 1: End poverty in all its forms everywhere - United Nations Sustainable Development. (2019). Retrieved from http://www.un.org/sustainabledevelopment/poverty

Gupta, R., Kar, H., & Bharadwaj, M. (2012). Revalidation of various clinical criteria for the classification of leprosy--a clinic-pathological study. *Leprosy Review*, *83*(4), 354-362.

History of Leprosy in Ethiopia. (2019). Retrieved from http://english.aifo.it/leprosy/documents/Ethiopia%20leprosy%20&%20ALERT.pdf

Kerr-Pontes, L., Barreto, M., Evangelista, C., Rodrigues, L., Heukelbach, J., & Feldmeier, H. (2006). Socioeconomic, environmental, and behavioural risk factors for leprosy in North-east Brazil: results of a case–control study. International Journal of Epidemiology, 35(4), 994-1000. doi: 10.1093/ije/dyl072

Leprosy. 2018. (Accessed February 25, 2018, at http://www.who.int/mediacentre/factsheets/fs101/en.)

Lima, E.S.; Roland, I.A.; Maroja, M.F., Marcon, J.L. (2007). Vitamin A and lipid peroxidation in patients with different forms of leprosy. Rev. Inst. Med. Trop. S. Paulo, 49(4):211-214.

Lockwood, D. (2004). Commentary: Leprosy and poverty. International Journal Of Epidemiology, 33(2), 269-270. doi: 10.1093/ije/dyh115

Lu'o'ng, K., & Nguyên, L. (2012). Role of the Vitamin D in Leprosy. *American Journal Of Medical Sciences*, *343*(6), 471-482.

Mandal, D., Reja, A., Biswas, N., Bhattacharyya, P., Patra, P., & Bhattacharya, B. (2015). Vitamin D receptor expression levels determine the severity and complexity of disease progression among leprosy reaction patients. *New Microbes And New Infections*, *6*, 35-39. doi: 10.1016/j.nmni.2015.04.001

Matos, A., Coelho, A., Araújo, L., Alves, M., Baquero, O., Duthie, M., & Teixeira, H. (2018). Assessing epidemiology of leprosy and socio-economic distribution of cases. Epidemiology and Infection, 146(14), 1750-1755. doi:10.1017/S0950268818001814

Misch, E., Berrington, W., Vary, Jr, J., & Hawn, T. (2010). Leprosy and the Human Genome. Microbiology and Molecular Biology Reviews, 74(4), 589–620.

North Gondar Zone. (2019). Retrieved from http://www.csa.gov.et/

Oktaria, S., Effendi, E., Indriatmi, W., van Hees, C., Thio, H., & Sjamsoe-Daili, E. (2016). Soil-transmitted helminth infections and leprosy: a cross-sectional study of the association between two major neglected tropical diseases in Indonesia. BMC Infectious Diseases, 16(1). doi: 10.1186/s12879-016-1593-0

Oktaria, S., Hurif, N.S., Naim, W., Thio, H.B., Nijsten, T.E.C., Richardus, J.H. (2018). Dietary diversity and poverty as risk factors for leprosy in Indonesia: A case-control study. PLoS Neglected Tropical Diseases 12(3): e0006317. https://doi.org/10.1371/journal.pntd.0006317

Parkash, O. (2009). Classification of leprosy into multibacillary and paucibacillary groups: an analysis. FEMS Immunology & Medical Microbiology, 55(1), 1-5. doi: 10.1111/j.1574-695x.2008.00491.x

Passos Vázquez, C., Mendes Netto, R., Ferreira Barbosa, K., Rodrigues de Moura, T., Pacheco de Almeida, R., Duthie, M., & Ribeiro de Jesus, A. (2019). Micronutrients influencing the immune response in lepro. Nutrición Hospitalia, 29(1), 26-36. doi: 10.3305/nh.2014.29.1.6988.

Pescarini JM, Strina A, Nery JS, Skalinski LM, Andrade KVFd, Penna MLF, et al. (2018) Socioeconomic risk markers of leprosy in high-burden countries: A systematic review and meta-analysis. PLoS Negl Trop Dis 12(7): e0006622. https://doi.org/10.1371/journal.pntd.0006622

Rao, P.S., John, A.S., (2012). Nutritional status of leprosy patients in India. Indian Journal for leprosy.

R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

Ridley, D., & Jopling, W. (1962). A classification of leprosy for research purposes. Leprosy Review, 33(2). Doi: 10.5935/0305-7518.19620014

Ridley, D., & Jopling, W. (1966). Classification of Leprosy According to Immunity A Five-group System. International Journal Of Leprosy, 34(3), 255-273.

Rodrigues, L.C., Lockwood, D.N. 2011. Leprosy now: epidemiology, progress, challenges, and research gaps. The Lancet Infectious Disease. 11: 464-470.

Schaible UE, Kaufmann SHE (2007) Malnutrition and infection: complex mechanisms and global impacts. PLoS med 4: e115.

SAS Institute Inc., SAS 9.4, Cary, NC: SAS Institute Inc., 2002-2019.

Sori, Ermias. (2019). Review on the Burden of Leprosy in Ethiopia.

Toh, H., Maharjan, J., Thapa, R., Neupane, K., Shah, M., & Baral, S. et al. (2018). Diagnosis and impact of neuropathic pain in leprosy patients in Nepal after completion of multidrug therapy. PLOS Neglected Tropical Diseases, 12(7), e0006610. doi: 10.1371/journal.pntd.0006610

USDA ERS - Survey Tools. (2019). Retrieved from https://www.ers.usda.gov/topics/food-nutrition-assistance/food-security-in-the-us/survey-tools.aspx#guide

Van Tonder, E., Mace, L., Steenkamp, L., Tydeman-Edwards, R., Gerber, K., & Friskin, D. (2018). Mid-upper arm circumference (MUAC) as a feasible tool in detecting adult malnutrition. South African Journal of Clinical Nutrition, 1-6. doi: 10.1080/16070658.2018.1484622

Wagenaar, I., van Muiden, L., Alam, K., Bowers, R., Hossain, M., Kispotta, K., & Richardus, J. (2015). Diet-Related Risk Factors for Leprosy: A Case-Control Study. PLOS Neglected Tropical Diseases, 9(5), e0003766. http://dx.doi.org/10.1371/journal.pntd.0003766

White, C., & Franco-Paredes, C. (2015). Leprosy in the 21st Century. Clinical Microbiology Reviews, 28(1), 80-94. doi: 10.1128/cmr.00079-13

World Health Organization (WHO). 2015. Leprosy. World Health Organization. Retrieved from: http://www.who.int/mediacentre/factsheets/fs101/en/

World Health Organization (WHO). 2013. Global leprosy: update on the 2012 situation. World Health Organization. 88: 365-380. Retrieved from: http://www.who.int/wer/2013/wer8835.pdf?ua=1

WHO disability grading: operational definitions. (2019). Retrieved from https://www.lepra.org.uk/platforms/lepra/files/lr/Dec03/10-366.pdf

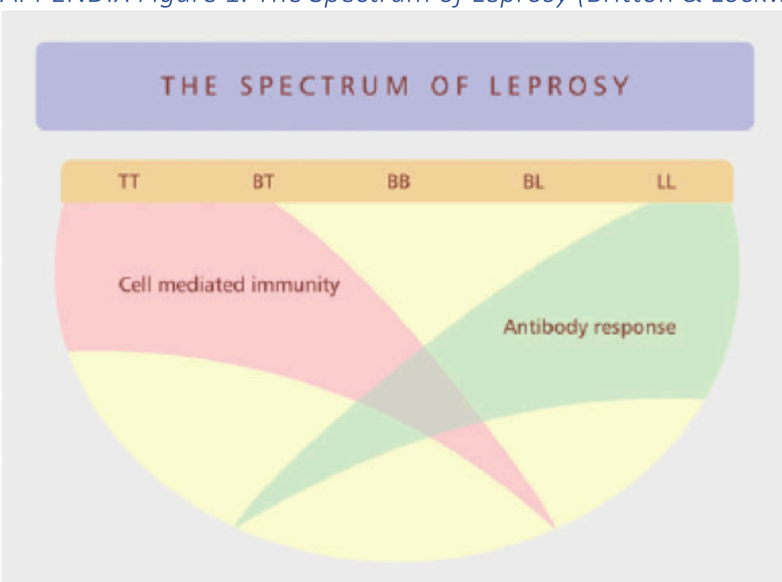
WHO Model Prescribing Information: Drugs Used in Leprosy: Treatment of lepra reactions. (2019). Retrieved from http://apps.who.int/medicinedocs/en/d/Jh2988e/6.html

APPENDIX

APPENDIX Table 1 Ridley-Jopling classification (left) and WHO classification (right) of M. leprae (Ridley & Jopling, 1962; WHO, 2015)

Ridley-Jopling Classification			WHO Classification
Tuberculoid (TT)	Single or few lesions, negative or rare bacilli on histology	Very good cell – mediated immunity	Paucibacillary
Borderline Tuberculoid (BT)	Single or few lesions, rare bacilli on histology	Good cell – mediated immunity	Paucibacillary if ≤ 5 lesions Multibacillary if > 5 lesions
Borderline Borderline (BB)	Several lesions, more bacilli on histology	Fair cell – mediated immunity	Multibacillary
Borderline lepromatous (BL)	Many lesions, many bacilli on histology	Fair – poor cell-mediated immunity	Multibacillary
Lepromatous (LL)	Diffuse lesions, heavy bacilli load	Poor cell – mediated immunity	Multibacillary

APPENDIX Figure 1. The Spectrum of Leprosy (Britton & Lockwood, 2004)



APPENDIX Figure 2. WHO Global Leprosy Strategy 2016 – 2020 ("Global Leprosy Strategy", 2019)