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The relationship between reported food insecurity and anthropometric measures in TB affected households: a longitudinal analysis of anthropometric indices following a household TB diagnosis.

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Abstract

Background: There is a growing recognition that the impact of a TB diagnosis reaches far beyond the direct biomedical consequences of the disease. A TB diagnosis can cause catastrophic costs as a result of medical expenses and a loss of income, and may lead to household food insecurity. This study investigates the socioeconomic impact of a TB diagnosis by assessing weight loss in adolescent TB household contacts.

Methods: Longitudinal data from 619 adolescents aged 10-18 years were analysed from TB affected households in Zimbabwe, Mozambique and Tanzania. Linear mixed effect models were used to assess BMI z-score trajectories over 12 months (three visits). The impact of baseline food insecurity, socioeconomic status and household income loss (as measured by whether the person with TB was the main breadwinner) on baseline BMI z-scores and BMI z-score trajectories was assessed. To investigate whether changes in BMI were clinically significant, the number of adolescents moving into an underweight category was also assessed.

Results: Adolescents in Zimbabwe are losing weight following a TB diagnosis in the household by -0.07 change in BMI z-score per 6 months (95% CI -0.13 to -0.01, p=0.02). This appears to be clinically significant, translating to 10% of adolescents becoming underweight in the first six months. This is in comparison to Mozambique (0.08, 95% CI 0.02 to 0.14, p=0.01) and Tanzania (0.15, 95% CI 0.08 to 0.22, p<0.001), where adolescents are gaining weight overall. Lower SES status at baseline showed some association with lower BMI z-score and BMI trajectory.

Conclusions A TB diagnosis in the household can have wider socioeconomic consequences and can lead to weight loss in adolescents. Social protection interventions that intercept the TB-poverty cycle should be considered an area of interest for policy makers.

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Contents

Acronyms **v**

1 Introduction **1**
1.1 Background to tuberculosis . . . 1
1.1.1 The spectrum of disease . . . 2
1.1.2 TB risk factors . . . 3
1.2 A wider perspective of TB . . . 4
1.2.1 Food insecurity . . . 4
1.3 Study rationale and conceptual framework . . . 6
1.4 Aims and Objectives . . . 7
1.4.1 Overall aim . . . 7
1.4.2 Specific objectives of project . . . 7
1.4.3 Changes to CARE form . . . 7

2 Methods **8**
2.1 Data collection . . . 8
2.1.1 ERASE-TB . . . 8
2.1.2 Outcome measure . . . 9
2.1.3 Exposures . . . 9
2.2 Statistical analysis . . . 10
2.2.1 Descriptive analysis . . . 10
2.2.2 Assessment of covariates . . . 11
2.2.3 Bivariate analysis . . . 12
2.2.4 Baseline multivariable analysis . . . 12
2.2.5 Longitudinal BMI analysis . . . 12
2.2.6 Missing data . . . 13
2.2.7 Lost to follow-up analysis . . . 13
2.3 Ethics approval . . . 13
2.4 Reflexivity . . . 13

3 Results **15**
3.1 Sample characteristics . . . 15
3.2 Baseline multivariable analysis . . . 15
3.3 Longitudinal BMI analysis . . . 18
3.3.1 Modelling trajectory of BMI z-scores . . . 18
3.3.2 Change in BMI category . . . 19
3.4 Lost to follow up analysis . . . 19

4 Discussion **21**
4.1 Main findings . . . 21

4.2 Loss of income 22
4.3 Food insecurity 22
4.4 SES status 24
4.5 Strengths and limitations 24
4.5.1 Strengths 24
4.5.2 Limitations 25

5 Recommendations and conclusion **27**
5.1 Recommendations 27
5.2 Conclusion 28

Bibliography **29**

A Appendices **37**
A.1 Appendix 1 37

Acronyms

BMI body mass index
GDP gross domestic product
HIV human immunodeficiency virus
MUAC middle upper arm circumference
Mtb *mycobacterium tuberculosis*
SES socioeconomic status
TB tuberculosis
UHC universal health coverage
WHO World Health Organization

Chapter 1

Introduction

1.1 Background to tuberculosis

It's been nearly 140 years since Robert Koch first identified *mycobacterium tuberculosis* (Mtb) as the causative agent in tuberculosis (TB) and 20 years since the World Health Organization (WHO) declared TB as a global emergency[1]. However, TB continues to be a leading cause of morbidity and mortality, with 10.6 million cases and 1.6 million deaths in 2021 alone[2]. WHO's End TB strategy has a vision of a TB free world by 2035. It aims to reduce TB incidence by 90% and deaths by 95% by tackling the wider social determinants of the disease, as well as through achieving universal access to healthcare and pursuing innovative solutions to diagnosis and treatment[3].

TB is highly concentrated in the poorest countries (Figure 1.1) and within poor countries it disproportionately affects those living under the most socioeconomically challenging circumstances[4]. Two thirds of all TB cases arise in eight countries alone and almost 90% are accounted for by the 30 countries with the highest TB burden[2]. The most recent report from the World Health Organization[2] demonstrated the strong association between TB incidence and

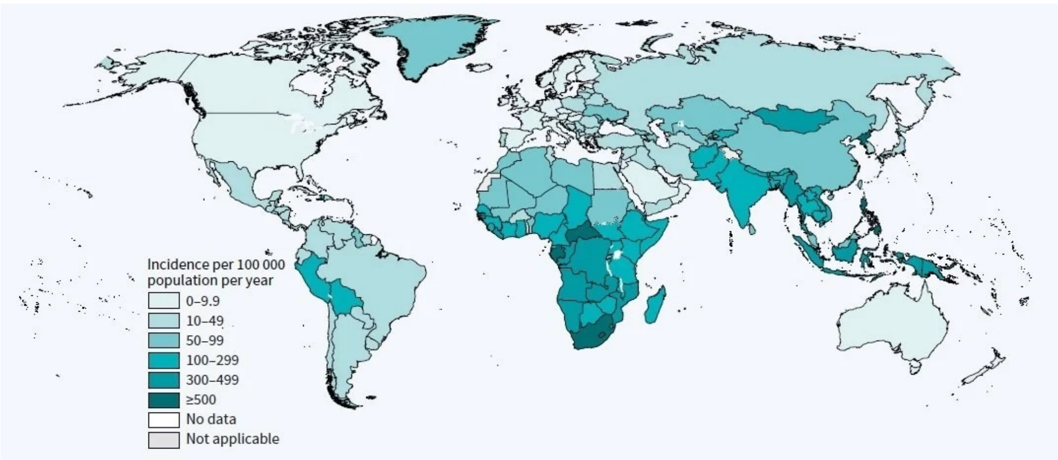

Figure 1.1: The uneven global distribution of TB incidence rates. Figure taken from World Health Organization[2].

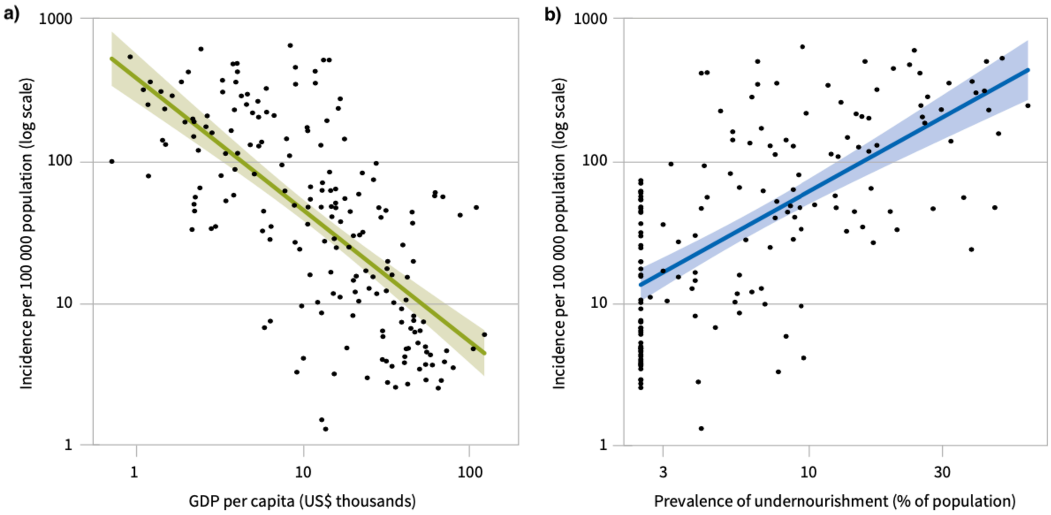

Figure 1.2: The relationship between TB incidence and a) GDP per capita and b) undernourishment. Figure taken from World Health Organization[2].

both gross domestic product (GDP) and undernourishment (Figure 1.2).

A quarter of global incident TB occurs in Africa[2]. Zimbabwe, Tanzania and Mozambique are southern African countries with estimated TB incidence in 2021 of 190, 208 and 361 per 100,000, respectively[2]. Although Zimbabwe has recently been transferred from WHO's 30 high burden countries to a watch list due to declining incidence, Tanzania and Mozambique remain.

1.1.1 The spectrum of disease

Although classically considered as having two forms, latent infection and active disease, TB is increasingly recognised as a spectrum of pathology (Figure 1.3). Exposure to *Mtb* can result in either elimination or persistence of the pathogen. It is estimated that 25% of the world's population are infected with *Mtb*[5]. Studies from household contacts of people with TB suggest that only about 50% of those exposed get infected[6].

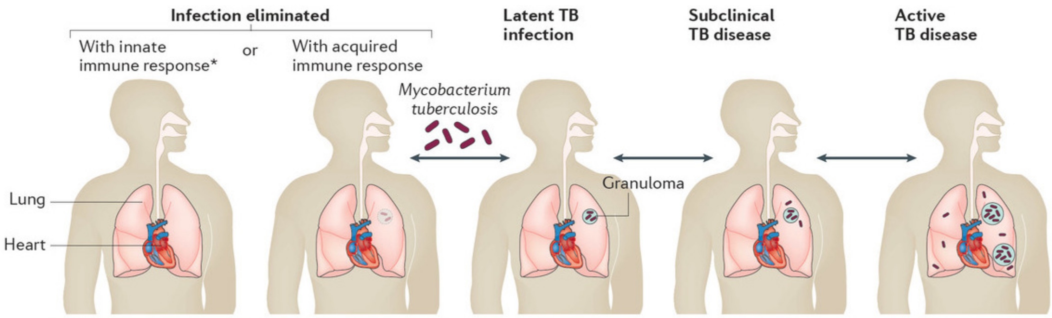

Figure 1.3: The spectrum of TB. Figure taken from Pai et al.[7].

Only 5-15% of those with *Mtb* infection will progress to active TB[8]: the symptomatic and transmissible form of the disease which is diagnosed using culture-based or molecular diagnostics. The timescale for progression to active TB is variable and can occur within weeks or after many years[7]. Some people progress rapidly to TB within the first two years of infection, known as pri-

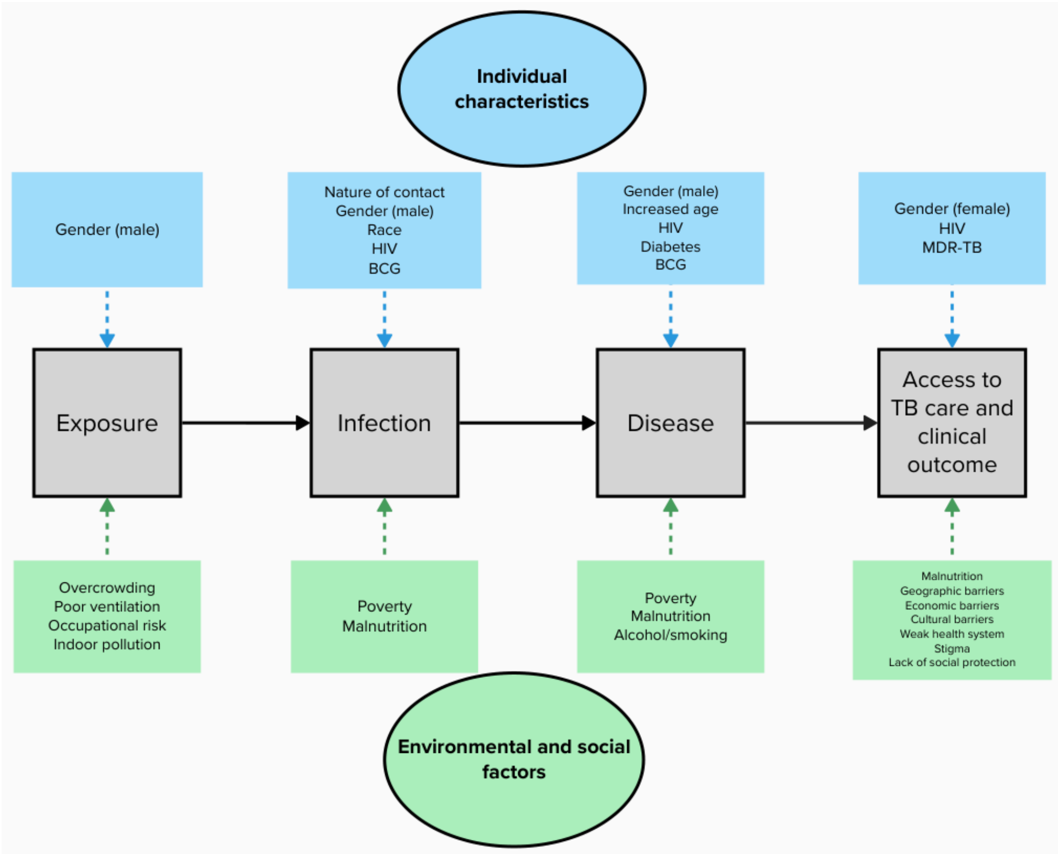

Figure 1.4: TB risk factors. Figure adapted from Hargreaves et al.[4] Narasimhan et al.[9]

mary progressive TB, whereas others experience the onset of active disease after many years of latent infection, known as TB reactivation. Active TB causes symptoms such as a cough, fever and weight loss and results in death in approximately 50% of individuals[7]. Some individuals diagnosed with active TB do not develop symptoms and can be characterised as having a subclinical form (Figure 1.3).

1.1.2 TB risk factors

Although TB can affect anyone, there are certain risk factors that increase the likelihood of disease. The different "stages" from exposure, infection, disease, diagnosis and outcome, are all associated with different risk factors, which can be on an individual, household or a wider environmental/social level (Figure 1.4). Exposure to *Mtb* is largely influenced by environmental factors, such as living and working conditions that are poorly ventilated, overcrowded and with high levels air pollution[4;9]. The risk of *Mtb* infection and progression to TB disease are associated with individual level factors, of which one of the most important is human immunodeficiency virus (HIV) infection. This is especially true in southern Africa where the proportion of people with TB who were co infected with HIV exceeded 50%[2]. Other conditions such as diabetes increase the risk of developing TB[10], as does alcohol and smoking[11]. Malnutrition is a hugely important risk factor at many stages of disease and will be discussed in more detail in Section 1.2.1. Access to TB treatment is significantly influenced by environmental and social factors, such as economic barriers like out-of-pocket healthcare costs, or cultural barriers like stigmatisation. These wider determinants of TB will be discussed in detail in the following section.

1.2 A wider perspective of TB

TB has long been recognised as a disease of poverty. In Europe and the United States, the dramatic fall in TB deaths in the 20th Century can be attributed to widespread improvements in socioeconomic conditions, as opposed to medical advances[12]. To achieve progress on the same scale in current high burden settings, there is a growing recognition of the need for a paradigm shift away from a purely biomedical approach to one that addresses the social determinants of TB[7].

As demonstrated in Figure 1.4, within any society, TB is most commonly found in the most vulnerable populations, associating with poverty, poor living conditions, malnutrition, HIV, tobacco and alcohol use[13;4;14]. As well as these social determinants of TB, a TB diagnosis itself can have wide ranging socioeconomic impacts. A TB diagnosis often results in high medical costs and when combined with income loss and existing poverty, can lead to families experiencing extraordinary financial hardship. In Zimbabwe, whilst TB diagnosis and treatment is free of charge, substantial out-of-pocket costs still occur due to hospitalisations and radiology services[15]. Sustainable development goal SDG3.8 aims to ensure that all people across the globe have access to quality healthcare without financial hardship by 2030, known as universal health coverage (UHC)). Currently, there are only 46% of people in sub-Saharan Africa with timely access to the full range of quality health services they need, with UHC ranging between 55% in Zimbabwe, to 42-43% in Tanzania and Mozambique. Whilst direct medical costs are high, it is often non-medical costs such as accommodation and transport, and indirect costs such as income loss[16] that account for the biggest financial burden.

An important milestone set out by WHO's END TB strategy was that no household should experience TB related "catastrophic costs", defined as a costs above 20% of the annual household income. A recent systematic review of 29 national patient cost surveys found that on average 43% of TB affected households faced catastrophic costs[17]. Zimbabwe's patient cost survey showed that 80% of TB affected households experienced catastrophic costs, rising to 90% in households affected by MDR-TB[15]. In Tanzania, an estimated 40% of TB affected households (80% with MDR-TB) experienced catastrophic costs[18]. Mozambique is yet to carry out such a survey.

1.2.1 Food insecurity

In the face of catastrophic costs, many household adopt coping strategies to deal with the increased costs and loss of income. These include selling assets, relocating closer to caregivers or pulling their children out of school[16;19;20]. One area that is particularly vulnerable to the impacts of catastrophic expenditure is food security[21;20;22;19].

Food insecurity is defined as not having "physical, social and economic access to sufficient,

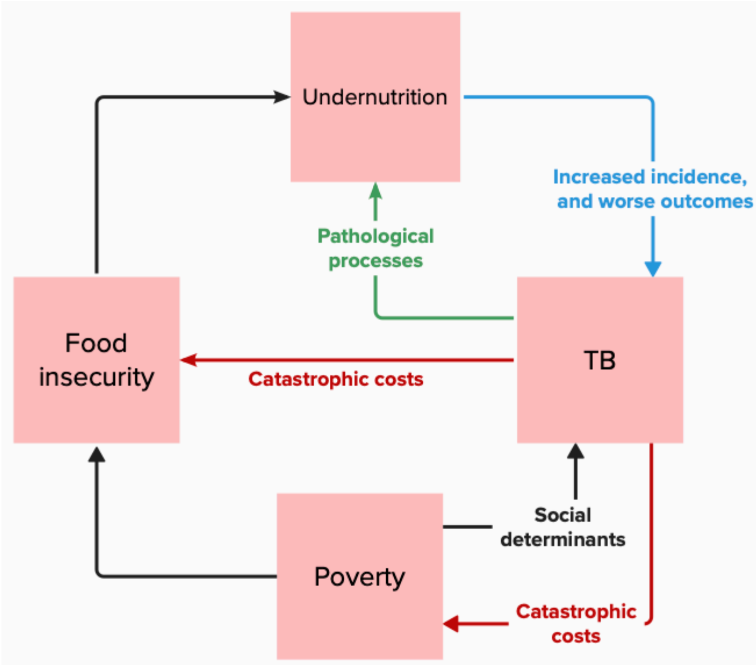

Figure 1.5: The complex relationship between TB, food insecurity and undernutrition

safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life"[23]. An estimated 45.6 million people are in a food security crisis in central and southern Africa, according to the UN World Food Programme's latest global report on food crises[24]. This is estimated to be 35% of the population in Zimbabwe, 16% in Mozambique and 13% in Tanzania.

The relationship between TB, food insecurity and undernutrition is complex and multifaceted (Figure 1.5). A bidirectional relationship is well characterised; weight loss is a cardinal symptom of TB[25], whilst food insecurity and undernutrition significantly increase TB risk. The African Food Security Network 2008-2009 survey found that only 10% of individuals with both TB and HIV lived in food secure households[26]. More recently, WHO found in its 2020 report that undernutrition is one of the most significant drivers of TB, accounting for 15% of incident cases[27]. Evidence suggests that food insecurity increases the severity of disease, increases the risk of progression from latent to active TB and affects treatment adherence[28;29]. The most prominent mechanistic theory is that undernutrition inhibits the innate and adaptive immune response to *Mtb* infection[30].

Despite a number of high quality reviews and commentaries on food insecurity, undernutrition and TB[26;21;29;31], very few have yet investigated the effect of TB-associated socioeconomic decline on nutritional status of the household. Qualitative and quantitative studies from South Africa, Zimbabwe, Vietnam and India showed that TB affected households were more likely to be food insecure and report struggling to cater for the nutritional requirements of their households members as a result of TB[20;32;33].

There have been very few studies that have attempted to quantify the nutritional impact of food insecurity in a household affected by TB. Goyal-Honavar et al.[22] assessed a small sample of

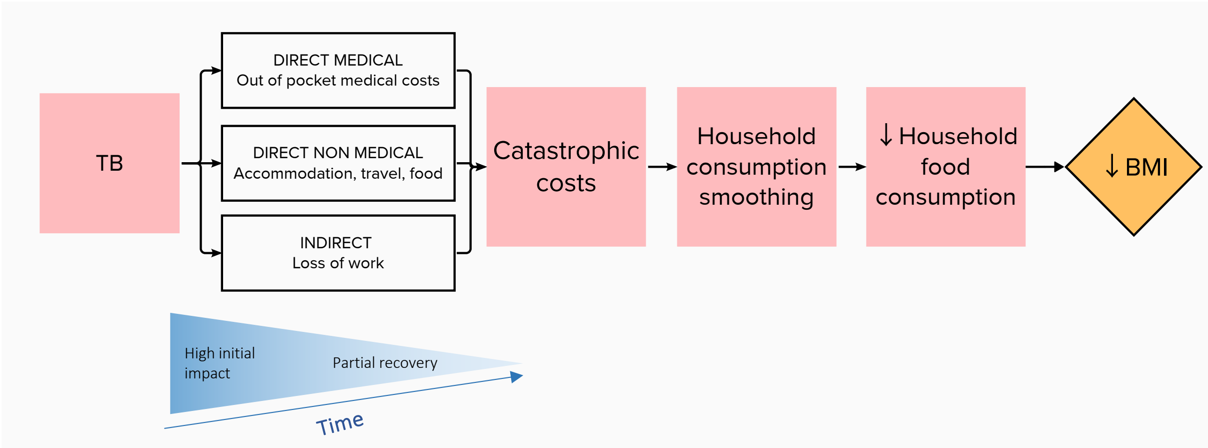

Figure 1.6: The conceptual framework

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children's body mass index (BMI) from households with a recent TB diagnosis, finding that only 29% were of a normal weight compared to 77% in households without TB. In a small study from Peru, 14% of household contacts had a low BMI[34]. Both studies were cross-sectional and did not examine the longer lasting effects of a TB diagnosis in the household.

1.3 Study rationale and conceptual framework

The overarching rationale for this study is that the impact of a TB diagnosis reaches far beyond the direct biomedical consequences, especially when households already live under extremely challenging socioeconomic circumstances. Food insecurity can also be used as an indicator for these wider socioeconomic effects that TB has on households. Households identified as food insecure should be targeted for social protection, which has the potential to enhance well-being, increase educational attainment of children and adolescents, improve productivity among adults and protect the households against future TB episodes[19;21;35;36].

The impact of food insecurity on health outcomes has been found to be most severe in children and young people, affecting overall health, growth and performance at school[37;38]. Studies have shown that younger children are often protected from the impacts of food insecurity by their parents, compared to adolescents[39]. Adolescents are an understudied group in terms of food insecurity despite their vulnerability.

The conceptual framework for this study is laid out in Figure 1.6. The main hypothesis is that costs incurred due to TB can impact upon food insecurity, as people adopt coping strategies such as consumption smoothing. A further hypothesis is that the greatest socioeconomic impact of TB to a household will occur close to the time of diagnosis, due to diagnostic costs causing an initial financial shock[16]. This means that BMI of household contacts measured close to the time of TB diagnosis (i.e. at baseline) is already likely to be impacted. Currently there is very little research on the trajectory of BMI among household contacts following a TB diagnosis and so this work is novel.

1.4 Aims and Objectives

1.4.1 Overall aim

The overall aim of this project is to investigate whether adolescents lose weight following a TB diagnosis in the household, and to assess any impact of baseline food insecurity, loss of income and socioeconomic status (SES).

1.4.2 Specific objectives of project

1. To investigate whether baseline BMI is associated with SES, food insecurity status or loss of income among adolescent TB household contacts.
2. To investigate the trajectory of BMI among adolescent TB household contacts over 12 months following a TB diagnosis in the household.
3. To investigate whether any change in BMI is associated with SES, food insecurity status or loss of income.
4. To investigate the number of adolescents that move into an underweight BMI category following a TB diagnosis in the household.

1.4.3 Changes to CARE form

After extensive discussions with my supervisors, it was decided to focus in on an adolescent study population, as opposed to one that also includes adults. The rationale for this change, as discussed in Section 1.3, is due to adolescents being a vulnerable yet understudied group in terms of food insecurity. Additionally, the decision was also made to focus on BMI as the sole outcome measure, as opposed to BMI and middle upper arm circumference (MUAC). This was due to the lack of an internationally accepted reference for MUAC scores in 5 to 18-year-olds and it was felt that creating one suitable for this population was beyond the scope of this project.

Chapter 2

Methods

2.1 Data collection

2.1.1 ERASE-TB

Data was obtained for this project from ERASE-TB, a multi-country cohort study located across three African countries (Mozambique, Tanzania and Zimbabwe). ERASE-TB aims to evaluate novel diagnostics for early TB diagnosis and prediction of disease progression among 2100 household contacts (adolescents and adults) of confirmed pulmonary TB cases[40]. Consenting household contacts were enrolled into the study at the time a household member with pulmonary TB was diagnosed. At baseline, a household questionnaire asking about the number of people living in the household, household income and assets was administered to the head of the household. In addition, a physical examination of each household contact was performed, including weight, height and MUAC, along with a questionnaire to determine food security status. Recruitment was completed in March 2023 and follow-up is ongoing. Household contacts are followed up every six months for 18-24 months. At each visit height, weight and MUAC is performed.

The inclusion criteria for ERASE-TB are as follows:

- Aged ≥10 years
- Substantial and recent exposure to an infectious TB case in the household (sleeping ≥3 nights in the same household over the past 4 weeks)
- Voluntary written informed consent for study participation (or parent/guardian consent and assent in the case of minors)

The exclusion criteria for ERASE-TB are as follows:

- If there is doubt on free, uncoerced informed consent
- Prisoners
- Recent treatment for active TB (completed in the last 30 days) or on current TB treatment

(if HIV negative)

Zimbabwe has a population of roughly 15 million people, with approximately 2 million living in the capital city Harare. Recruitment took place in the high-density communities in southern Harare and was therefore from urban and peri-urban areas. Mozambique has a population of 32 million, with 1.1 million living in in the capital city Maputo. Recruitment took place in rural, urban and peri-urban areas. Tanzania has a population of 64 million, with 2.7 million living in Mbeya, a southern highland area. Recruitment took place in urban and peri-urban areas.

For this project, this analysis was limited to a subset of the ERASE-TB data, as only adolescent household contacts were included (10 to 18 years old at baseline).

2.1.2 Outcome measure

BMI-for-age and sex z-scores were calculated using WHO references[41]. The following BMI-for-age and sex z-score cut-points were used to define undernutrition:

- Underweight: Less than -2SD
- Mildly underweight: -2SD to -1 SD
- Normal: -1SD to +1SD
- Overweight: Greater than +1SD

2.1.3 Exposures

For the longitudinal analysis, the primary exposure is time, as measured by visit number (visit 1 at baseline, visit 2 at 6 months and visit 3 at 12 months).

The primary exposures in the baseline analysis are 1) SES, 2) income loss, and 3) food insecurity.

2.1.3.1 SES

Asset-based SES was selected as the primary socioeconomic exposure due to it being well validated[42] and its correlation with measures such as household crowding and income[43;44]. Additionally, asset-based SES may more accurately reflect “longer-term” SES and is less impacted by acute changes in income.

2.1.3.2 Income loss

We hypothesised that households where the person with TB had been the main breadwinner prior to the disease would experience more significant income loss due to TB disease than those households where this was not the case. Hence households where the main breadwinner was affected by TB may have experienced more significant financial hardship (and acute food insecurity as a result) at baseline.

Table 2.1: Exposures of interest

Exposure	Level	Collection/calculation method
Age	Individual	Collected via questionnaire.
Sex	Individual	Collected via questionnaire.
HIV status	Individual	Collected via questionnaire.
Insufficient food status	Individual	Collected via questionnaire - ”Have there been days with insufficient food in the last 6 months? Yes, No, Refuse to Answer”
TB affected household breadwinner	Household	Collected via questionnaire
Socioeconomic status	Household	Derived from principal component analysis based on self-reported possession of a standardised, country-specific list of assets (including type and material of residency, type of windows, household possessions). Socioeconomic tertiles were calculated for each country separately.
Income per day	Household	Calculated from total household income divided by the number of people in the household.
Poverty line	Household	A dichotomised variable derived from income per day, using the the international poverty line (US$ 1.90 per person per day (World Bank)).
Household crowding	Household	Calculated using the UN crowding index and derived from data on the total number of people in the household.

2.1.3.3 Food insecurity

Food insecurity status was measured by self-reported insufficient food. Prior to the project, some validation of this measure had been carried out by assessing its association with SES. Food insufficiency in the last 6 months was found to be well correlated with SES, whereas measures of meals per day were not. The decision was therefore made to use insufficient food as the measure of food insecurity in this study.

2.2 Statistical analysis

Stata version 17 (Stata Corporation, College Station, TX, USA) was used for the majority of the statistical analysis in this thesis. The graphs and tables were produced using R version 4.2.2.

The analysis for this project is divided into baseline analysis (Objective 1) and longitudinal analysis (Objectives 2-4). The main exposures and covariates in each type of analysis differ and will be discussed in the following sections.

2.2.1 Descriptive analysis

The data was investigated for errors by checking variable ranges for implausible values. Distributions of variables were explored for the full cohort, and then stratified by country. Means and standard deviations, along with histograms to assess normality were used for continuous variables. Data tabulations were used for categorical variables.

2.2.2 Assessment of covariates

An initial assessment of the plausibility of covariates to be a confounder or an effect modifier (in both baseline and longitudinal analyses) based on prior knowledge and literature was carried out and is discussed below. A confounder is defined as being associated with both the outcome of interest and the primary exposure, and not being on the causal pathway between exposure and outcome.

2.2.2.1 Household

Adolescents part of the same household are more likely to be similar to each other, resulting in clustering at the household level. Households are likely to be affected in similar ways in terms of food insecurity and so household was accounted for in all models.

2.2.2.2 Country

All baseline and longitudinal analyses were stratified by country because of the very different living circumstances (rural, urban, peri-urban) and economic situations in each of the countries. For example in Zimbabwe and Mozambique the study was conducted in the capital city and enrolled households in urban and peri-urban areas. In Tanzania, household contacts were enrolled from villages around Mbeya town where households live from subsistence farming. Additionally, there are likely to be differences in the socioeconomic situation and health system that could affect the socioeconomic impact of a TB diagnosis. The baseline and longitudinal analyses were therefore carried out in each country separately.

2.2.2.3 Age and gender

The use of z-scores ensures that BMI is normalised by age and gender. Despite this, an association between BMI z-score and both age and gender was observed, indicating that the WHO reference population is not ideal for this context. In terms of associations with the exposures in the baseline analysis, age and gender could plausibly be associated with SES, food insecurity and income loss. Older, male adolescents might be more likely to be working and therefore contributing to a higher SES or income to buy food[45]. These factors combined with the fact that they are not on causal pathway, means that age and gender were considered as a priori covariates in the baseline BMI models. In the longitudinal analysis looking at BMI trajectories over time, age was associated with the exposure (time) and is not on the causal pathway and was therefore included as a confounder. Although gender is not associated with the exposure (time), it was still included in the model as a correction to the z-scores.

2.2.2.4 HIV

HIV and TB tend to cluster among vulnerable populations, especially in southern Africa[2]. HIV has also been shown to cause weight loss among adolescents and was therefore assessed as a potential confounder[46;47].

2.2.2.5 Season

Due to the potential importance of season on food availability, season was considered as a potential confounder. The period when food availability is the lowest in each country, known as the lean season, was identified for each of the countries. In Zimbabwe the lean season falls between November and February, in southern Mozambique, between October and January, and in northern Tanzania, between October and December.

2.2.3 Bivariate analysis

Bivariate analysis was used in assessing the (non-a priori) covariates identified as potential confounders (HIV status and season). Mixed effect linear regression models that took into account clustering by household were used to assess associations with BMI z-score at baseline and change over time. Confounders were included in subsequent models if in bivariate analysis they were associated with the outcome at the $p<0.2$ level[48]. Neither HIV or recruitment in the lean season were associated with BMI z-score at baseline and change over time and so were not included in any further models.

2.2.4 Baseline multivariable analysis *(Objective 1)*

To explore whether BMI z-score was associated with SES, food insecurity and TB affected household breadwinner, mixed effect linear regression models were fitted with BMI z-score as the dependent variable and with household as a random effect. Firstly, country-specific SES was included as the predictor in country-specific models (adjusted for age and gender). Joint Wald tests of overall difference between the SES tertiles were carried out. This process was then repeated for food insufficiency and TB affected household breadwinner. Box plots showing baseline BMI z-score in each SES tertile were generated, and then repeated for food insufficiency and TB affected household breadwinner.

2.2.5 Longitudinal BMI analysis

2.2.5.1 Modelling trajectory of BMI z-scores *(Objectives 2 and 3)*

Line plots showing trajectories in BMI for each country were generated. To explore how BMI z-score changes over time, three country-specific linear mixed effect models were fitted with random effects for individual and household, to adjust for the fact the data consisted of repeated measures from people from the same households. Individuals were only included in the models if they had more than one follow-up visit. Age and gender were included as covariates in the models.

To explore differences in BMI z-score trajectory according to SES tertile, an interaction of SES tertile with time was fitted in each of the country-specific models. Joint Wald tests of differences amongst the slopes between SES tertiles were carried out. This was then repeated for food insufficiency and TB affected household breadwinner.

2.2.5.2 Change in BMI category *(Objective 4)*

In order to assess whether any changes in BMI z-score identified from the mixed effect models were clinically significant, an assessment of change in BMI category was carried out. Sankey plots were generated to show the number of adolescents that moved up and down a BMI category over the follow-up period, in each country. The plots only included adolescents who had at least one follow-up visit with available BMI data (n=391).

2.2.6 Missing data

Due to the rolling recruitment in this study, baseline data is available for 619 participants, with 6 month and 12 month data available for 391 and 221 participants, respectively. Detailed information of which participants are yet to be followed up and which participants have missing data or are lost-to-follow up is shown in Figure 2.1

2.2.7 Lost to follow-up analysis

To assess whether the adolescents who were lost to follow-up differed in terms of demographics and BMI z-score to those who remained in the study, baseline values were compared between the two groups (lost to follow-up and remaining). Additionally, a regression model with BMI z-score as the dependent variable and lost to follow-up as a binary predictor (accounting for household clustering) was carried out.

2.3 Ethics approval

This study was approved by the LSHTM MSc Research Ethics Committee (Ref:28671). Ethical approval for the ERASE-TB study was granted by the Medical Research Council of Zimbabwe (Ref:MRCZ/A/2618), the Ministry of Health Mozambique (Ref:541/CNBS/21) and the Ministry of Health Tanzania (TMDA-WEB0021/CTR/0004/05).

2.4 Reflexivity

As a white researcher from the UK with a good education and middle class background, I am aware that I am not familiar with the southern African context and am removed from the socioeconomic conditions that I am researching. I was able to visit Zimbabwe for this project, where I spent some time out in the field with the research team, and also discussed my results with researchers from each of the countries. However, I am acutely aware that these efforts are not a substitute for lived experience.

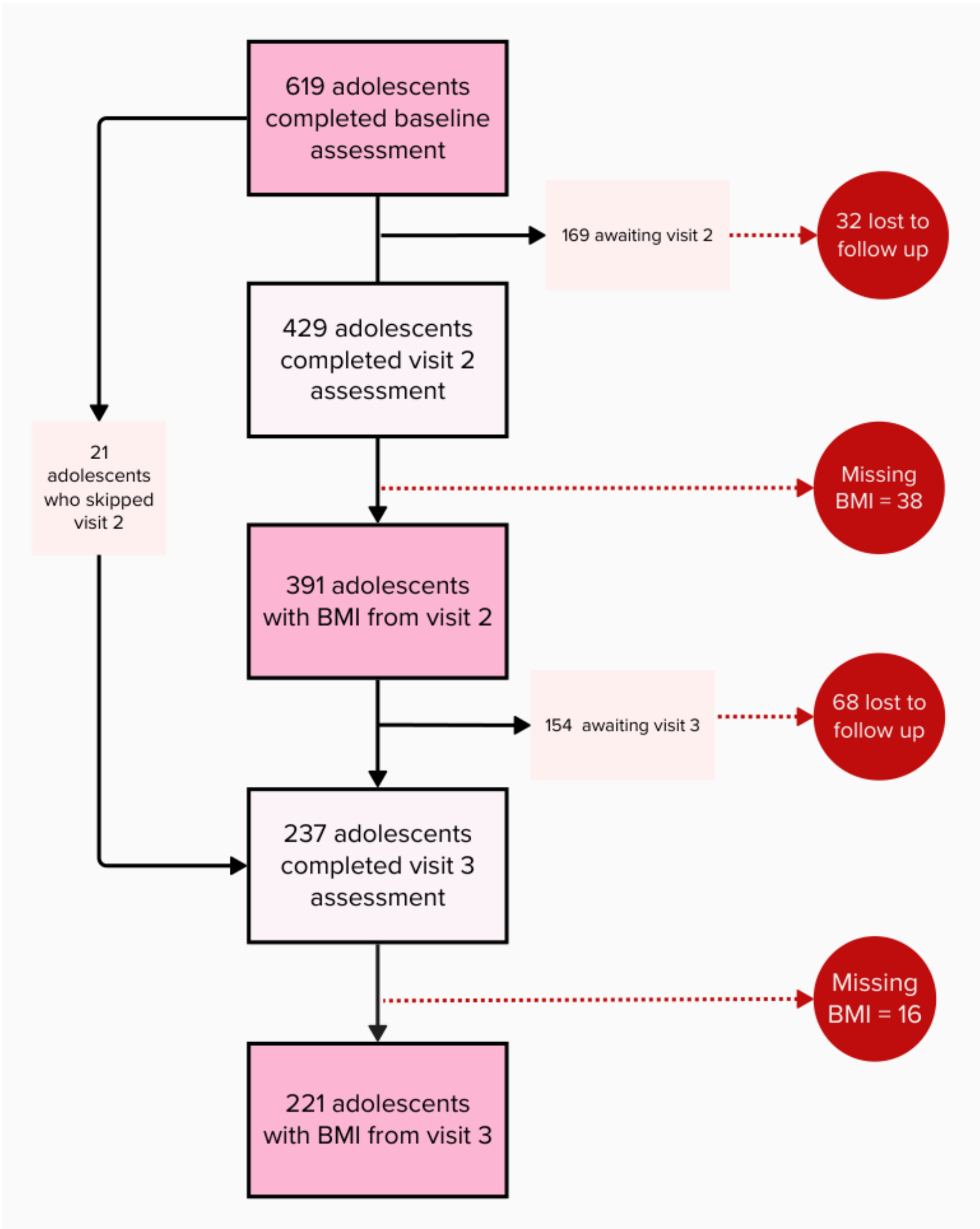

Figure 2.1: Adolescents included in the study sample

Chapter 3

Results

3.1 Sample characteristics

Table 3.1 shows baseline characteristics of all 619 adolescents and 401 households included in the study and stratified by country. The mean age was 13.8 years (SD 2.3) and 51.3% were female, which was similar across all countries. A high proportion of adolescents were in education and were negative for HIV across all three countries. A large proportion of the study sample was living below the poverty line, with the highest proportions of 80% observed in both Zimbabwe and Mozambique. However, there is a high proportion of missing poverty line data in Tanzania, which could be reflecting a lack of monetary income meaning the number living below the poverty line could be underreported. The total people in the household averaged 5.8 across all three countries. Baseline BMI z-score was -0.5 SD overall, with all countries having a mean z-score within the normal category. The lowest proportion of adolescents, 5.4%, in Tanzania reported having insufficient food compared to the overall average of 23.4%.

At baseline, there was no missing BMI data and a low proportion of missing food insecurity and demographic data.

3.2 Baseline multivariable analysis

Figure 3.1 demonstrates associations between BMI z-score and each of SES, insufficient food status and whether the person with TB was the household breadwinner. Those in the poorest tertile appeared to have a lower BMI z-score at baseline across all three countries. In Tanzania, BMI appeared to increase across all three SES groups. When examining this statistically, there was weak evidence for a difference in BMI z-score across tertiles (p=0.06) in Tanzania after adjusting for age and sex, and no evidence for a difference in Zimbabwe and Mozambique (Table 3.2). It is therefore likely that there is limited power to detect a difference in Zimbabwe and Mozambique with the reduced sample size from stratifying by country.

From examining the graphs (Figure 3.1), no differences in BMI z-score were apparent according to food insufficiency status and whether the person affected with TB was the household bread-

Table 3.1: Descriptive characteristics of the study sample at baseline

	Zimbabwe	Mozambique	Tanzania	Overall
Individuals	(N=194)	(N=223)	(N=202)	(N=619)
Households	(N=131)	(N=145)	(N=125)	(N=401)
Sex				
Male	93 (47.9%)	114 (51.1%)	95 (46.8%)	302 (48.7%)
Female	101 (52.1%)	109 (48.9%)	108 (53.2%)	318 (51.3%)
Age (years)				
Mean (SD)	13.8 (2.3)	14.1 (2.4)	13.5 (2.3)	13.8 (2.3)
Education				
Illiterate/No education	1 (0.5%)	2 (0.9%)	8 (3.9%)	11 (1.8%)
Primary school	101 (52.1%)	103 (46.2%)	124 (61.1%)	328 (52.9%)
Secondary school	92 (47.4%)	117 (52.5%)	71 (35.0%)	280 (45.2%)
College/Vocational	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)
HIV status				
Negative	190 (97.9%)	214 (96.0%)	188 (92.6%)	592 (95.5%)
Positive	2 (1.0%)	9 (4.0%)	7 (3.4%)	18 (2.9%)
Missing	2 (1.0%)	0 (0%)	8 (3.9%)	10 (1.6%)
BMI z-score				
Mean (SD)	-0.3 (1.1)	-0.6 (1.2)	-0.8 (1.2)	-0.5 (1.2)
BMI category				
Underweight <-2SD	12 (6.2%)	22 (9.9%)	18 (8.9%)	52 (8.4%)
Mildly underweight: <-1SD	33 (17.0%)	57 (25.6%)	69 (34.0%)	159 (25.6%)
Normal	122 (62.9%)	126 (56.5%)	106 (52.2%)	354 (57.1%)
Overweight: >1SD	27 (13.9%)	18 (8.1%)	10 (4.9%)	55 (8.9%)
Insufficient food				
No	139 (71.6%)	143 (64.1%)	192 (94.6%)	474 (76.5%)
Yes	55 (28.4%)	79 (35.4%)	11 (5.4%)	145 (23.4%)
Missing	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)
SES tertile*				
Poorest	50 (38.2%)	59 (40.7%)	49 (39.2%)	158 (39.4%)
Middle	50 (38.2%)	43 (29.7%)	36 (28.8%)	129 (32.2%)
Richest	31 (23.7%)	43 (29.7%)	40 (32.0%)	114 (28.4%)
Poverty line*				
>=1.90 USD	16 (12.2%)	8 (5.5%)	1 (0.8%)	25 (6.2%)
<1.90 USD	104 (79.4%)	117 (80.7%)	85 (68.0%)	306 (76.3%)
Missing	11 (8.4%)	20 (13.8%)	39 (31.2%)	70 (17.5%)
TB affected breadwinner*				
No	63 (48.1%)	94 (64.8%)	50 (40.0%)	207 (51.6%)
Yes	68 (51.9%)	50 (34.5%)	75 (60.0%)	193 (48.1%)
Missing	0 (0%)	1 (0.7%)	0 (0%)	1 (0.2%)
Total people in household*				
Mean (SD)	5.8 (2.4)	6.2 (2.3)	5.3 (2.0)	5.8 (2.3)
Household crowding*				
Not crowded	99 (75.6%)	109 (75.2%)	115 (92.0%)	323 (80.5%)
Crowded	32 (24.4%)	36 (24.8%)	10 (8.0%)	78 (19.5%)

* denotes variables which were collected at the household level
SD - Standard deviation

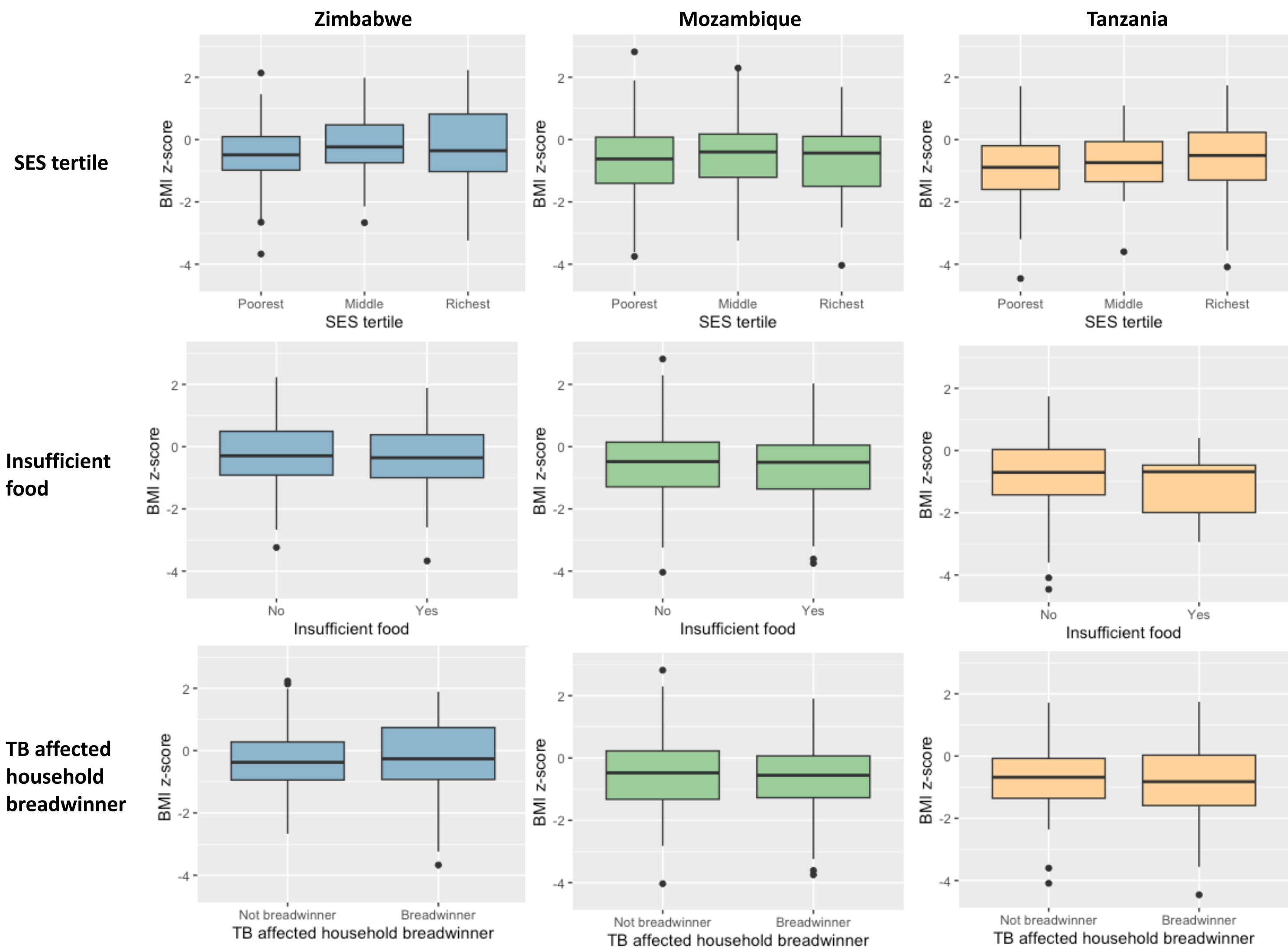

Figure 3.1: BMI score by SES tertile, insufficient food and TB affected household breadwinner in each of the three countries. Figures are generated using the raw data.

Table 3.2: Association of baseline BMI z-score with SES, food insecurity and TB affected household breadwinner

	SES					Insufficient food				Breadwinner with TB			
	Group	β	95% CI	*p* value	*p* value for difference	Group	β	95% CI	*p* value	Group	β	95% CI	*p* value
Zimbabwe	1	—	—	—									
	2	0.23	-0.13, 0.61	0.2	0.2	No	—	—	—	No	—	—	—
	3	0.33	-0.07, 0.75	0.1		Yes	-0.19	-0.53, 0.15	0.3	Yes	-0.04	-0.36, 0.28	0.8
Mozambique	1	—	—	—									
	2	0.20	-0.21, 0.61	0.3	0.6	No	—	—	—	No	—	—	—
	3	0.06	-0.36, 0.47	0.8		Yes	-0.12	-0.45, 0.2	0.5	Yes	-0.16	-0.52, 0.21	0.4
Tanzania	1	—	—	—									
	2	0.29	-0.13, 0.72	0.2	0.06	No	—	—	—	No	—	—	—
	3	0.47	0.07, 0.87	0.02		Yes	-0.45	-1.2, 0.3	0.3	Yes	-0.19	-0.55, 0.16	0.3

β are shown for change in BMI z-score from a) the poorest SES tertile, b) the no insufficient food group and c) the group where the TB affected person was not the household breadwinner. Regression models results are adjusted for age and sex. For SES, a *p* value from a joint Wald test for a difference across all tertiles is included.

winner. This was confirmed statistically, with no evidence for any difference in each country according to insufficient food status (p>0.25, all countries) and whether the person with TB was the household breadwinner (p>0.30, all countries), adjusted for age and gender.

All models showed very little change between base and models adjusted for age and gender (data not shown), indicating minimal confounding.

3.3 Longitudinal BMI analysis

3.3.1 Modelling trajectory of BMI z-scores

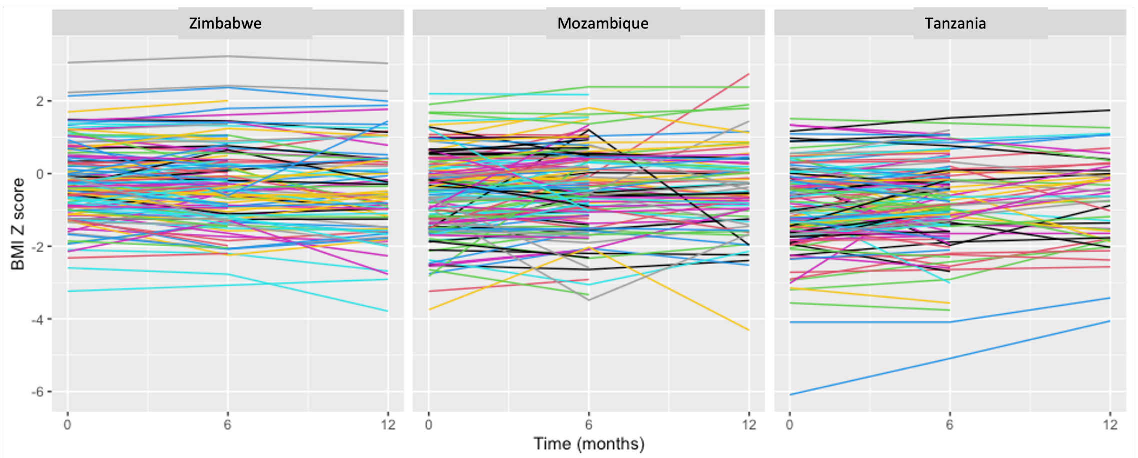

Figure 3.2: Spaghetti plots illustrating BMI z-score trajectories for each individual from each of the three countries

BMI trajectories in each country are illustrated in the spaghetti plots in Figure 3.2. Table 3.3 shows fitted increases in BMI z-score over time in each individual country. There was quite strong evidence (p=0.02) for a decrease in BMI z-score in Zimbabwe, whereby an average decrease of -0.07 (95% CI -0.013 to -0.01) was observed per 6 months (or between each visit). There was quite strong evidence (p=0.01) for an increase in BMI z-score per 6 months of 0.08

Table 3.3: Regression model results for the mean change in BMI over time in each country

	β	95% CI	*p* value
Zimbabwe	-0.07	-0.13, -0.01	0.02
Mozambique	0.08	0.02, 0.14	0.01
Tanzania	0.15	0.08, 0.22	<0.001

β represents the fitted change (with 95% confidence intervals) and *p* values in BMI z-score per 6 months between each visit. Results are shown for country individually and adjusted for age and gender.

(95% CI 0.02 to 0.14) in Mozambique and very strong evidence (p<0.001) for an increase of 0.15 (95% CI 0.08 to 0.22) in Tanzania.

There was no evidence for effect modification by SES, insufficient food status and whether the person affected by TB was the household breadwinner (Table 3.4), across any countries, apart from weak evidence (*p*=0.07) for effect modification by SES tertile in Zimbabwe whereby those in the poorest group had a steeper downward BMI trajectory.

Table 3.4: Regression model results for effect modification by SES, insufficient food and TB affected household breadwinner

	SES					Insufficient food					Breadwinner with TB				
	Group	β	95% CI	*p* value	*p* value for interaction	Group	β	95% CI	*p* value	*p* value for interaction	Group	β	95% CI	*p* value	*p* value for interaction
Zimbabwe	1	-0.12	-0.21, -0.03	0.008	0.07										
	2	0.04	-0.07, 0.17	0.4		No	-0.07	-0.13, -0.01	0.03	0.7	No	-0.06	-0.13, 0.01	0.1	0.6
	3	-0.09	-0.16, -0.02	0.02		Yes	-0.09	-0.14, 0.09	0.07		Yes	-0.09	-0.16, 0.02	0.02	
Mozambique	1	0.07	-0.05, 0.19	0.3	0.9										
	2	0.09	-0.03, 0.20	0.1		No	0.09	-0.01, 0.19	0.05	0.7	No	0.09	0.01, 0.19	0.03	0.5
	3	0.09	-0.06, 0.24	0.2		Yes	0.07	-0.05, 0.18	0.25		Yes	0.04	-0.09, 0.17	0.5	
Tanzania	1	0.17	0.05, 0.28	0.006	0.6										
	2	0.07	-0.08, 0.22	0.3		No	0.14	0.06, 0.21	<0.001	0.9	No	0.13	-0.00, 0.26	0.05	0.9
	3	0.14	0.02, 0.25	0.02		Yes	0.12	-0.14, 0.38	0.37		Yes	0.14	0.05, 0.23	0.002	

β represents the fitted change (with 95% confidence intervals and *p* values) in BMI z-score per 6 months between each visit. Results are shown stratified by country and by SES tertile, insufficient food status and whether the TB affected person was the household breadwinner. Regression models results are adjusted for age and sex. A *p* value for interaction from joint Wald tests are also displayed.

3.3.2 Change in BMI category

The Sankey plots in Figure 3.3 demonstrate changes in BMI category in each country. In Zimbabwe, 10% of those with BMI data for both the first and second visits move to an underweight category in the first 6 months, compared to 5% in Mozambique, 7% in Tanzania. When looking at those who have the second and third visit, 2% move down in Zimbabwe, compared to 5% in Mozambique and 7% in Tanzania.

3.4 Lost to follow up analysis

Baseline statistics remained largely similar among those lost to follow compared to those remaining in the study (Appendix 1). The majority of those lost to follow up were in Zimbabwe

(61%). BMI z-scores averaged -0.3 in those lost to follow up compared to -0.6 in those remaining in the study, however there was no evidence for a difference (p=0.4).

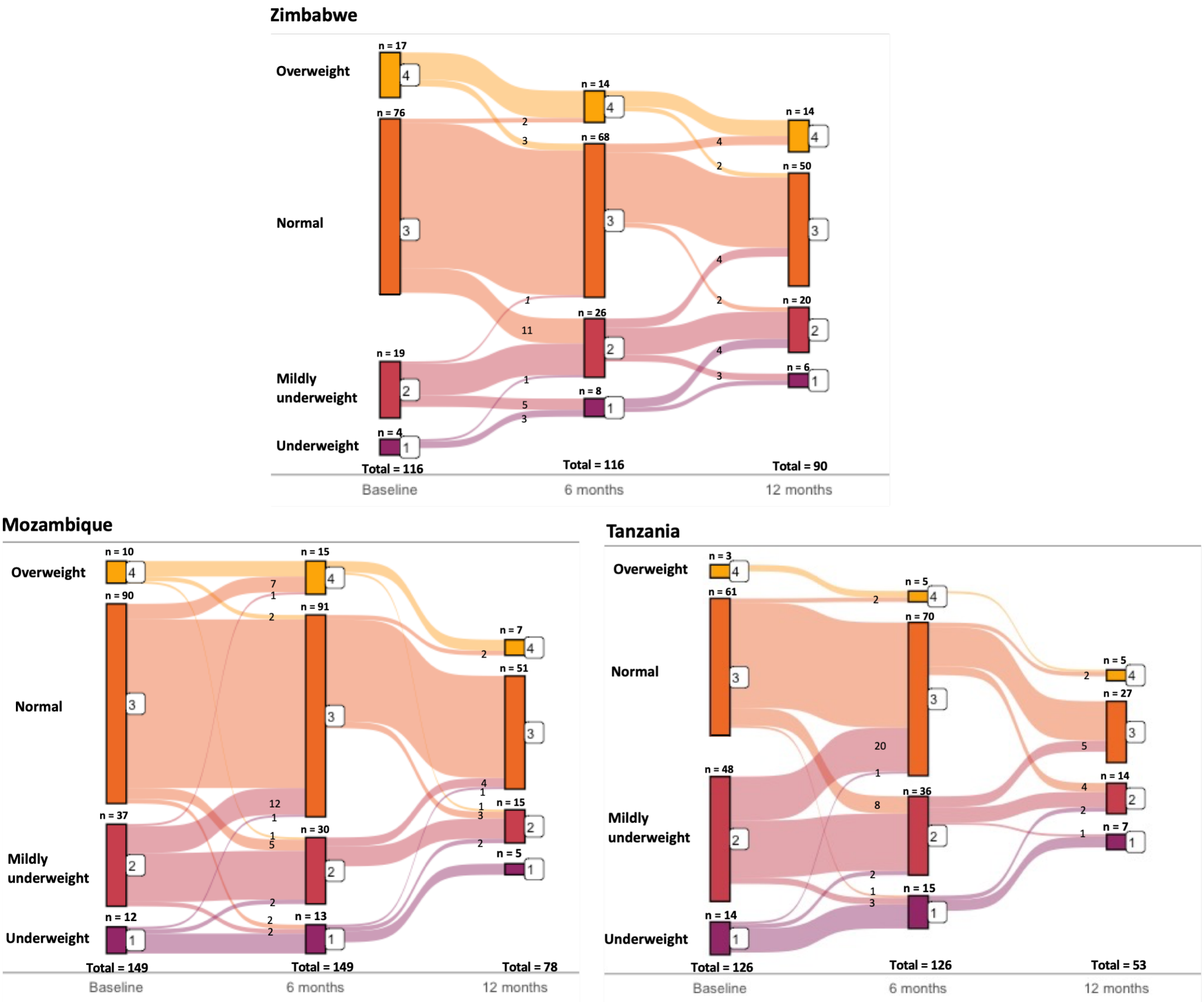

Figure 3.3: Sankey plots showing BMI category changes over 12 months for adolescents with BMI data available for two at least visits.

Chapter 4

Discussion

4.1 Main findings

This project found evidence of weight loss following a TB diagnosis in the household in Zimbabwe and evidence of a weight gain in Tanzania and Mozambique. There was some evidence in all countries (although there was insufficient power to achieve statistical significance) that those in the poorest tertile had a lower BMI z-score at baseline and in Zimbabwe, a steeper weight loss trajectory. The measures of food insecurity, or whether the TB affected person was the breadwinner, were not associated with differences in weight loss trajectory, or with adolescents' weight at baseline.

It is important not to overstate the change in BMI observed in this study; the mean weight loss in Zimbabwe was small (a 0.07 decrease in BMI z-score per 6 months) and therefore the clinical significance is unclear. However, when looking at changes in BMI category, a considerable proportion of adolescents in Zimbabwe do appear to move into an underweight category, especially in the first 6 months.

This study found differences between countries in the change in BMI observed among household contacts. Although a decrease was observed in Zimbabwe, an overall increase in BMI was observed in Mozambique and Tanzania. A very recent randomised controlled trial in India, the RATIONS trial, looking at nutritional supplementation as a TB preventative treatment in household contacts, demonstrated similar findings to ours with respect to the weight gain observed in Mozambique and Tanzania[36]. As well as an increase in weight observed in the intervention group, individuals aged 6-17 years in the control group experienced a more modest increase in weight 6 months following a TB diagnosis in the household, with the caveat that only absolute weight gain was reported rather than BMI. This is important because children and adolescents will have grown during follow-up making it difficult to interpret the absolute weight. However, even among adult household contacts in the RATIONS trial, there was a gain in weight both in the control and intervention arm following TB diagnosis. This weight gain is supportive of our hypothesis that catastrophic expenditures and subsequent impact on BMI are greatest immediately following a TB diagnosis, with an observable impact on baseline BMI among adolescent household contacts. The BMI increase over the 6 months following a TB diagnosis in the household observed in the RATIONS trial and in this study could be interpreted as some recovery from an initial decrease in weight.

The fact that adolescents in Zimbabwe do not gain weight, or even appear to be losing weight, in the 6 months after the initial financial shock indicates a significant and sustained socioeconomic impact. The high level of poverty across the three countries in this cohort, predisposes households to catastrophic costs as a result of the TB diagnosis. Recent national cost surveys found that that 80% of people face TB-related catastrophic costs in Zimbabwe[15], compared to 45% of people in Tanzania[18] (although it is important to note these are national surveys which may not be completely generalisable to the geographically small recruitment area in this study). The higher proportion reported to be facing catastrophic costs in Zimbabwe could be due to the harsh economic conditions in the country over the past two decades[49]. The following sections will further discuss contributing factors to the observed weight loss in Zimbabwe, with respect to the socioeconomic factors considered in the analysis (loss of income, food insecurity and socioeconomic status).

4.2 Loss of income

Income loss has been shown to be one of the most impactful socioeconomic consequences of a TB diagnosis[16;50;51]. The Zimbabwean National Statistics Agency estimates a national unemployment rate of 19.1%[52] and, although the World Bank estimates a lower rate, the Zimbabwean unemployment rate is significantly higher than that of Tanzania and Mozambique (Figure 4.1). Zimbabwe also has extremely high numbers of people working in the informal economy, with most recent estimates placing the figure at 76%[53]. These people in precarious employment could be most at risk for catastrophic costs and could be one reason behind the increased weight loss among adolescents in Zimbabwe.

Whether the person affected by TB was the household breadwinner was not associated with adolescent weight loss. It was assumed that the income loss a household experienced would be more severe if the person affected by TB was the main breadwinner. However, income loss due to TB at baseline and during follow-up was not measured directly. Additionally, even if the person affected by TB was not the main breadwinner or did not contribute to the household income, large income losses may have been experienced because other members may have lost their income and/or employment due to caring responsibilities[55]. Furthermore, income is usually not the sole source of financial support. In the context of Zimbabwe, family and friends living outside the country often contribute to household income and provide support especially in times of dire need[56].

4.3 Food insecurity

Another potential factor underpinning the observed changes in BMI could be national variability in food availability. In this study, high numbers of people reported having insufficient food in

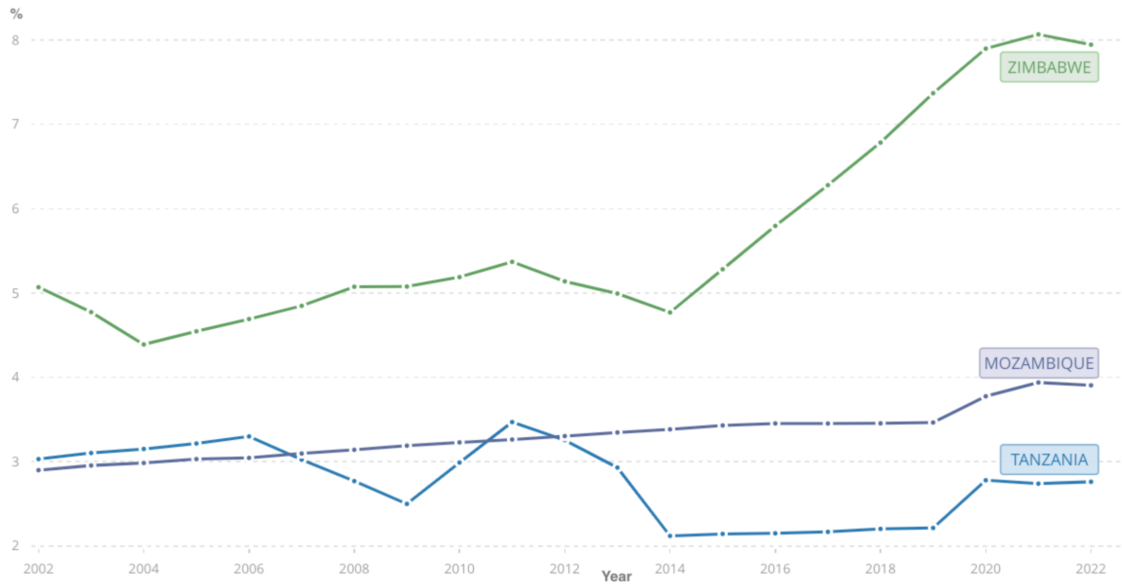

Figure 4.1: Unemployment rates in Zimbabwe, Mozambique and Tanzania. Figure taken from The World Bank[54].

Zimbabwe (28.2%) compared to Tanzania (2.4%), with the highest levels observed in Mozambique (35.2%). This is in contrast to the World Food Programme estimates with 35%, 16% and 13% of the population in Zimbabwe, Mozambique and Tanzania respectively as risk of food insecurity[24]. Zimbabwe's high level of food insecurity has been attributed to recent levels of high inflation and rising food prices[57]. Importantly though, recruitment for the Zimbabwean cohort took place in the capital city, Harare, where levels of food insecurity are lower[58], which may account for the lower levels reported in this study. The very low levels of reported food insecurity in Tanzania in this study are likely due to the population living from subsistence farming with lower levels of food insecurity than people living in urban or peri-urban areas.

Although differences were observed in level of insufficient food between the three countries, there was no association with adolescent weight loss in Zimbabwe, Mozambique or Tanzania. The fact that there was also no association between insufficient food and BMI z-score at baseline is perhaps an indication that this self-reported measure at one time point is not a reliable indicator of food insecurity over prolonged period of time. An ideal food security indicator should capture all the four food security dimensions (availability, access, utilisation and stability) and components (quantity, quality, safety and preference)[59]. However, there are logistical, and time constrains when conducting research interviews and hence the number of questions which can be asked about one topic (i.e. food security) is usually limited.

Previous research on self-reported food insecurity measures has found complex patterns of both economic and social desirability bias, whereby participants either overstate food insecurity in order to be included in any potential food insecurity programme, or understate to avoid shame and protect pride[60]. In order to reduce bias, methods such as list experiment designs or a composite index measure could be used[60].

Food insecurity was also only measured at baseline and so does not capture any longer term impact of the TB diagnosis. Although we hypothesised that a TB diagnosis could have already caused food insecurity due to the high costs associated with diagnosis and initiation of treatment, longer term impacts of a TB diagnosis on food security and on any subsequent weight loss would not have have been captured in this study.

4.4 SES status

This study found some evidence for a difference in weight loss by SES, but analysis stratified by country had limited power due to small sample sizes. Although no other studies have assessed weight loss in TB affected households, previous research has demonstrated a gradient by SES in TB-associated catastrophic costs, whereby the poorest households have a greater risk of experiencing catastrophic costs[15;16;61;62;63]. The poorest households have less resilience to deal with financial shocks, such as the high costs associated with a TB diagnosis. Besides the limited power, a further explanation for the lack of strong evidence for a social gradient observed in this study is the high level of poverty in this cohort, with an average of over 75% of people living under the poverty line. Therefore, it is likely that even the richest tertile will still be experiencing considerable poverty that may be affecting food security and weight loss.

The results observed in this study could also be due to limitations in the methodology used to create the SES index. Efforts were made to ensure the accuracy of the SES measure, by using asset based measures that were country specific to reflect the different value of assets in rural compared to urban settings. However, there are limitations to the principle component analysis approach used, such as a when there is a lack of variability in assets between households[42]. Additionally, although country specific approaches were used, these fail to take into account variability within a country, which is especially important in Tanzania and Mozambique where recruitment took place from both urban and rural regions.

SES was also only measured at baseline, meaning any change as a result of a household TB diagnosis would not have been captured in this study. In contrast to food insecurity which is more sensitive enough to financial shocks, SES is unlikely to have been impacted by the TB diagnosis at the baseline visit. It would therefore be interesting to assess the longer term impact of the TB diagnosis on SES and assess the relationship with weight loss.

4.5 Strengths and limitations

4.5.1 Strengths

A major strength of this study is its novelty, as very few studies have been conducted on the impact of TB-associated socioeconomic decline on the nutritional status of the household. Using a study of household contacts offers a unique opportunity to assess the wider socioeconomic impact of TB, over and above that of the direct medical consequences of the disease. This study is one of the only studies to examine the longer lasting effects of a TB diagnosis using quantitative methodologies and longitudinal data.

There are also few studies on the effects of a household TB diagnosis on adolescents; an important group when considering the wider impacts of TB in the household at this age such as education disruption and stigma[19], but also the importance of nutrition at this important stage of development[37;38].

This study also used a large cohort that spanned three southern African countries and included a mixture of rural and urban areas. This increases the generalisability to other countries in southern Africa with high TB burden.

4.5.2 Limitations

This study has a number of limitations. Firstly, a major limitation is the lack of a control group against which adolescents living in TB-affected households can be compared to, or any data available on the adolescents before the household TB diagnosis. It is therefore unclear whether the TB diagnosis has impacted upon the baseline BMI measurement, as hypothesised. Additionally, this means that the socioeconomic impact of TB cannot be discerned over and above any other external factors that may be causing weight loss. In Zimbabwe, for example, the rising inflation and high food prices[57] may be impacting on the weight of adolescents across the country, regardless of a TB diagnosis. Similarly, it is plausible that in the agricultural regions of Tanzania, variability in the harvest from year to year may impact the weight of all adolescents. In the period between March to May 2023, for example, a good rainfall had a positive impact on crop harvest[64], which may account for the overall weight gain in the population.

A second limitation is the considerable proportion of adolescents that had not yet reached follow-up, resulting in missing data for the longitudinal analyses. Once a more complete dataset is achieved, it would be important to expand upon the longitudinal analysis to explore the clinical significance of the observed changes in BMI. Logistic regression to formally test whether adolescents are moving into an underweight category, would be useful in this regard.

A further limitation is the use of BMI as the outcome measure. Although being quick and relatively easy to measure, BMI is a rather crude measurement of undernutrition as it does not provide information regarding specific micronutrient deficiencies. This is especially important as individuals may have abnormal underlying nutritional deficiencies related to food insecurity whilst their BMI remains normal, a so called ”hidden hunger”[65]. Additionally, nutrient deficiencies are likely to be apparent prior to any change in BMI and may be more sensitive to detect the socioeconomic impact of TB at very early stages. Moreover, the 6 or 12 month follow up in this study may not be adequate for any impact on BMI to be observed.

There was likely a degree of weight and height measurement error present in this study, with some adolescents’ BMI z-scores fluctuating between categories from one time point to the next. Although this only occurred in a minority of cases, this could have had an impact on the results from the linear mixed effects models. Evidence also suggests BMI-based criteria for weight categories fail to take ethnicity into account, as cut-offs have often been developed using white populations[66].

MUAC is a anthropometric measurement that has been shown to be less affected by measurement error, requires limited resources and may be suitable across multiple populations[67;68;69]. Although MUAC measurements were available for the adolescents in this study, there is currently no internationally accepted reference for MUAC scores in 5 to 18-year-olds and creating one suitable for this population was beyond the scope of this project.

Other limitations surrounding the use of baseline, self-reported food insecurity and SES measures have already been discussed in relation to their specific sections.

Chapter 5

Recommendations and conclusion

5.1 Recommendations

TB disproportionally affects the most vulnerable in any society who are most at risk from the wider socioeconomic consequences of the disease, therefore perpetuating a cycle of poverty. It is important that interventions aimed at mitigating the impact of TB go beyond a purely biomedical approach, and tackle the wider determinants and consequences of a TB diagnosis. This study supports the theory that a TB diagnosis can lead to an increase in food insecurity as a result of TB-related catastrophic costs. Interventions that intercept the TB-poverty cycle through alleviating poverty and/or food insecurity should be considered an area of interest for policy makers.

Recent evidence from the RATIONS trial strongly supports nutritional support for TB households[70]. As well as demonstrating a positive impact on weight, the RATIONS trial demonstrated a 40% reduction in TB incidence among household contacts. This reduction in TB incidence is particularly striking as it is comparable to the effect of preventive therapy which requires the daily (or weekly) adherence to anti-TB drugs[70]. It is important to note that this trial was carried out in an Indian population with a high prevalence of undernutrition and so further research will need to establish whether nutritional support would result in a similar effect in other settings.

A recent review of both financial and nutritional support interventions for TB affected households identified several key barriers to implementation[35]. Although the majority of studies assessed outcomes in the TB affected person only, several issues were identified that would also be applicable to interventions targeted at household contacts. These include logistical challenges in transferring funds to recipients and the distribution of food parcels, as well as a lack of political will and sustainable long-term funding.

As a first step towards evidence based policy, better process and implementation evaluations must be carried out to identify the type of social protection that may be successful in preventing malnutrition (and specifically weight-loss) among adolescents in a TB affected household in southern Africa. This work should build upon research already conducted in Zimbabwe, that found that cash transfers lead to an increase in food intake by all members of the household[71].

5.2 Conclusion

The findings of this study demonstrate that a TB diagnosis in the household may lead to weight loss among adolescent members of the household in certain country contexts. In order to meet WHO's target to minimise the impact of catastrophic costs associated with a TB diagnosis, effective ways to deliver poverty alleviating or nutritional support interventions to TB affected households, alongside existing TB treatment regimes, need to be investigated.

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Appendix A

Appendices

A.1 Appendix 1

Table A.1: Comparative baseline statistics of those lost to follow up

	Not LTFU (N=519)	LTFU (N=100)
Site		
Zimbabwe	132 (25.4%)	62 (61.4%)
Mozambique	202 (38.9%)	21 (20.8%)
Tanzania	185 (35.6%)	18 (17.8%)
Sex		
Male	255 (49.1%)	47 (46.5%)
Female	264 (50.9%)	54 (53.5%)
Age (years)		
Mean (SD)	13.8 (2.3)	14.1 (2.3)
HIV status		
Negative	495 (95.4%)	97 (96.0%)
Positive	16 (3.1%)	2 (2.0%)
BMI category		
Underweight: <-3SD	44 (8.5%)	8 (7.9%)
Mild underweight: <-2SD	142 (27.4%)	17 (16.8%)
Normal	293 (56.5%)	61 (60.4%)
Overweight: >1SD	40 (7.7%)	15 (14.9%)
BMI Z score		
Mean (SD)	-0.6 (1.2)	-0.3 (1.2)

LTFU - Lost to follow up