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Body mass index trajectories and association with tuberculosis risk in a cohort of household contacts in Southern Africa

Leyla Larsson[1], Claire J. Calderwood[2,3], Edson T. Marambire[2], Kathrin Held[1,4,5,6], Denise Banze[7], Alfred Mfinanga[8], Karlos Madziva[2], Phoebe Walsh[3], Joseph Jacob[9,10], Francisco Trinchan Fernandez[11], Patrick Lungu[12], Anita Mesic[13,14], Celso Khosa[7,15], Lilian T. Minja[8], Junior Mutsvangwa[16], Madhavi Bhargava[17,18], Michael Lauseker[19], Rishi K. Gupta[9], Norbert Heinrich[1,4,§], Katharina Kranzer[1,2,20,§,] *On behalf of the ERASE-TB consortium*

[1] Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany; [2] The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe; [3] Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom; [4] German Center for Infection Research (DZIF), Partner site Munich, Munich, Germany; [5] Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany; [6] Unit Global Health, Helmholtz Zentrum München, German Research Centre for Environmental Health (HMGU), Neuherberg, Germany; [7] Instituto Nacional de Saúde (INS), Maputo, Mozambique; [8] National Institute for Medical Research- Mbeya Medical Research Centre, Mbeya, Tanzania; [9] UCL Respiratory, Division of Medicine, University College London, London, United Kingdom; [10] Centre for Medical Image Computing, University College London, London, UK; [11] Bulawayo City Health, Bulawayo, Zimbabwe; [12] East, Central, and Southern Africa-Health Community, Arusha, Tanzania; [13] Médecins Sans Frontières, Amsterdam, The Netherlands; [14] Unit of HIV & TB, Clinical Science Department, Institute of Tropical Medicine Antwerp, Antwerp Belgium; [15] Departments of Clinical Science and International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK; [16] Biomedical Research and Training Institute, Harare,

§ *equally contributing authors*

Corresponding author: Leyla Larsson, Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Leopoldstrasse 5, 80802 Munich, Germany, Mobile: +49 152 3467 0154, Email: leyla.larsson@med.uni-muenchen.de

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Zimbabwe; [17] Department of Community Medicine, Yenepoya Medical College, Mangalore, India; [18] Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore, India; [19] Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Ludwig Maximilian University, Munich, Germany; [20] Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Studies have demonstrated an inverse log-linear relationship between body mass index (BMI) and tuberculosis incidence. However, a person's BMI is dynamic and longitudinal changes may be more informative than cross-sectional assessments. We evaluate the association between cross-sectional and changing BMI and risk of tuberculosis and describe longitudinal trajectories in a high-risk cohort.

Methods: ERASE-TB was a prospective longitudinal cohort study of household contacts ≥10 years in Southern Africa (Zimbabwe, Tanzania, and Mozambique), with 6-monthly follow-up up to 24 months. Associations between BMI and tuberculosis were investigated based on baseline (including haemoglobin) and changing BMI, using logistic, Poisson, and Cox models. Prevalent tuberculosis was defined as diagnosis during <30 days after recruitment. Growth mixture modelling (GMM) was used to model longitudinal latent trajectories.

Results: Of 2,107 recruited household contacts (621 [29.5%] adolescents and 1,310 [62.2%] female), 520 (24.7%) were underweight. There were 21 and 41 people diagnosed with prevalent and incident tuberculosis, of whom 5/21 (23.8%) and 12/41 (29.3%) were underweight. Being underweight and anaemic (aHR: 3.77, 95% CI: 1.50-9.51) and >10% negative change in BMI during follow-up (aIRR: 2.27 (95% CI: 0.22-22.9) were associated with increased risk of incident tuberculosis. The association between continuous BMI-for-age Z-scores were non-linear, with increased risk of tuberculosis with lower BMI. Four latent groups were defined in the GMM: increasing, decreasing, and low/high stable BMI.

Conclusions: Declining BMI, regardless of absolute value, is a strong predictor of tuberculosis among household contacts. Longitudinal measurements should be considered in active case finding among tuberculosis-affected households.

Keywords: body mass index, tuberculosis, trajectories, undernutrition

INTRODUCTION

There is a complex cyclical relationship between undernutrition and tuberculosis (TB).[1-3] Undernutrition increases the risk of progression to TB among people with *Mycobacterium tuberculosis* (*Mtb*) infection due to impairment of cellular immunity;[4] whilst improved nutrition has been shown to decrease TB incidence.[5] In turn, TB can lead to appetite reduction, macro- and micronutrient malabsorption, and impaired metabolism, which can subsequently result in undernutrition and unintentional weight loss – a relationship historically reflected in the term

"consumption" (Figure 1).[6,7] The biological interaction between undernutrition and TB is overlaid by socioeconomic factors; with poverty, both as a cause and consequence of TB, resulting in malnutrition among people with TB and their households.[8]

Clinical assessment of nutritional status is typically performed using body mass index (BMI), because of its simplicity, low cost, and non-invasiveness, however it is a suboptimal measure of nutritional status.[9] Previous population-based cohort studies have demonstrated an inverse log-linear relationship between BMI and TB incidence; where overweight seems to have a protective effect against TB.[10,11] It is however important to note that a person's BMI is dynamic: rather than just investigating its absolute value, changes over time, whether positive or negative, may be more informative. Considering that unintended weight loss and decreased muscle mass are common consequences of TB, a downward sloping BMI trajectory may be an early indicator of TB. Studies investigating the relationship between BMI and TB risk have, to date, primarily used cross-sectional measurements without considering longitudinal changes.

Anaemia may further modify the relationship between undernutrition and TB as it may be an indication of possibly more severe undernutrition, especially amongst men. Anaemia is prevalent among people with TB and is typically associated with more severe disease manifestations, slower recovery, and higher mortality rates.

Therefore, in this study we investigated nutritional status among TB-affected households and evaluated the association between baseline and changing BMI and risk of TB and describe longitudinal BMI trajectories in the context of a household contact cohort study, ERASE-TB.[12]

METHODS

Study design

ERASE-TB was a prospective, non-interventional observational cohort study evaluating novel diagnostic tests for earlier detection of TB among household contacts aged ≥10 years.[12] The study enrolled 2,109 household contacts of people with microbiologically-confirmed pulmonary TB in three countries in East and Southern Africa (Zimbabwe, Mozambique, and Tanzania). Recruitment started in March, August, and September 2021 in Zimbabwe, Mozambique, and Tanzania, respectively, and continued until 700 household contacts were recruited per site. Participants were followed at 6-month intervals over a period of up to 24 months. Follow-up visits were conducted in person or telephonically if the participant was unable to attend the study facility.[12]

At enrolment, individual- and household-level information including socio-demographics, previous medical history, and TB history was recorded. At each visit, household contacts underwent physical examinations including height, weight, mid-upper arm circumference (MUAC), blood pressure and haemoglobin measurement, and were offered an HIV test. Detailed descriptions on how anthropometric measures were collected can be found in the Supplement.

TB screening was done using a combination of the World Health Organisation (WHO) symptom screening questionnaire (W4SS) and a chest X-ray (CXR). Anyone with a suggestive symptom screen or CXR underwent further microbiological testing using Xpert MTB/Rif Ultra® (Xpert Ultra; Cepheid, USA) followed by liquid and solid culture if the Xpert Ultra result had detected *Mtb* or was trace positive.[12] Participants were asked to contact the study team if they were unwell in the interval between study visits; this triggered an in-person or telephone review, including TB screening as above.

Nutritional status

For adults, the absolute BMI was calculated as the weight (in kilograms) divided by the square of height (in metres). For adolescents (<18 years), we used the R package *zscorer* (v0.3.1) which uses the WHO 2007 reference standard to generate BMI-for-age Z-scores (BAZ).[13] Nutritional status was categorised as underweight, mildly underweight, normal, overweight, and obese (Supplemental Table 1). Underweight was defined as being underweight or mildly underweight (i.e., BMI <18.5 or BAZ <-1 [to correspond with the adult threshold]). Sensitivity analyses were conducted using a BAZ cut-off of -2 to define underweight/thinness among adolescents as per WHO thresholds.[14] MUAC was also evaluated as a measure of nutritional status. Here, we used MUAC-for-age Z-scores based on a growth reference standard for children aged 5-19 years (Supplemental Table 1).[15] For all Z-score based analyses, all participants aged 19 and above were recategorized to be 19 years. The same nutritional categories were created for MUAC as for BMI. Stunting was defined as a height-for-age Z-score <-2 and was calculated for both adolescents and adults using similar procedures as for MUAC-for-age Z-scores (Supplemental Figure 1).

TB status

An independent endpoint review committee (ERC) classified TB as confirmed, likely, possible, and unlikely TB; in this analysis, the endpoint was either confirmed or likely TB (Supplemental Table 1). The ERC was asked to determine the earliest timepoint when a participant had evidence of TB. This timepoint was used to classify people into prevalent TB (TB diagnosed at baseline) and incident TB (TB diagnosed more than 30 days after the baseline visit) and was used for time-to-event analyses.

Analysis

Baseline nutritional status and weight loss were described by socio-demographic risk factors (food insecurity, etc.) and study outcome (prevalent TB, incident TB, no TB). The relationship between anaemia (using haemoglobin [Hb] measurements; Supplemental Table 1) and nutritional status or TB was explored through Chi-squared tests. The association between baseline BMI category and prevalent TB was evaluated using logistic regression adjusting for household clustering by incorporating a random effect on the household. TB incidence rates were calculated over the full duration of follow-up and the population attributable fraction for undernutrition was calculated using Levin's formula.[16] The association between nutritional status and incident TB risk was

investigated in two ways. Firstly, it was investigated based on baseline BMI using a Cox proportional hazard model (also with a random effect on the household in univariable models). The proportional hazards assumption for the Cox model was tested using the *cox.zph* function from the *survival* package in R. Participants were censored at TB diagnosis, loss to follow-up, death, or completion of follow-up. We then evaluated the association based on changes in BMI during follow-up. To do this, we fitted a Poisson model with a Lexis expansion based on follow-up time, with BMI change category (≥10% negative change, 0-10% change in either direction, or ≥10% positive change) between visits as the time-varying exposure. Multivariable analyses adjusted for site, age group, sex, HIV status, alcohol use (assessed using AUDIT-C)[17], and previous TB, as exemplified in a directed acyclic graph (DAG) (Figure 2). It was not possible to adjust for household clustering in the multivariable models as it would overparameterize the models due to the low numbers of outcomes in the study. In addition to the stratified regression analyses using categorical BMI data, we also evaluated the continuous associations between BAZ and prevalent and incident TB risk using crude and adjusted models with restricted cubic splines, with three knots.

Both the prevalent and incident analyses were repeated to include anaemia status with the exposure being either "underweight or anaemic" or "underweight and anaemic". Anaemia, defined as per WHO,[18] was included as it has been highlighted to increase the likelihood of progression from infection to disease, also by impairing the immune system.[19] Sensitivity analyses including i) multivariable adjustment for HbA1c (<6%, 6-6.5%, ≥6.5%; due to the known association between diabetes and tuberculosis and overweight and diabetes), ii) MUAC instead of BMI (to investigate MUAC as a potential alternative to BMI to assess anthropometric nutritional status), iii) BAZ cut-off of -2 for thinness (to match WHO criteria), and iv) investigating the association between weight (kg) and TB, adjusted for height, are found in the Supplement.

Growth mixture modelling (GMM) (R package *lcmm*) was used to model latent longitudinal trajectories. The Bayesian Information Criterion was used to determine the optimal number of latent groups. A Chi-squared test or ANOVA was used to test associations between socio-demographic characteristics and latent groups.

Ethics

ERASE-TB was approved by regulatory and ethical committees of the participating institutions (Medical Research Council in Zimbabwe [MRCZ/A/2618]; National Health Research Ethics Committee, Tanzania [TMDA-WEB0021/CTR/0004/03]; National Bioethics Committee for Health, Mozambique [541/CNBS/21]; London School of Hygiene & Tropical Medicine, United Kingdom [22 522–2] and Ludwig Maximilian University, Germany [20–0771]). Informed consent was obtained from all eligible adult household contacts; for minors (<18 years), informed consent was provided by guardians, with assent sought from minors, depending on local guidelines.

RESULTS

This study included 2,107 household contacts: 699 in Zimbabwe from 268 households, 710 in Mozambique from 277 households, and 698 in Tanzania from 277 households. The median number of people recruited per household was 2 (IQR:1-3), the median follow-up time was 23.8 months (IQR:21.8-26.3), and the median time between visits was 6.0 months (IQR:5.5-6.6).

Among participants included in the study (n=2,107), 1,310 (62.2%) were female and the median age was 27 years (IQR:16-42), with 621 (29.5%) being adolescents (10-17 years). Almost two-thirds of adolescents were underweight (61.8%, 384/621), compared to 136/1,486 (9.2%) of adults. A total of 543 (36.6%) adults were classified as overweight or obese (Supplemental Figure 3;Table 1). There was evidence of household-level dual burden of malnutrition, with coexistence of overweight and underweight in 19%, 14%, and 17% of the Zimbabwean, Mozambican, and Tanzanian households (Figure 3).

Table 1: Socio-demographic characteristics of the cohort stratified by endline tuberculosis status.

	Total (N= 2,107)	Prevalent TB at baseline# (n=21)	Incident TB# (n=41)	No TB (n=2,045)
Age*				
10-14 years	405 (19.2%)	1 (0.2%)	4 (1.0%)	400 (98.8%)
15-17 years	216 (10.3%)	1 (0.5%)	5 (2.3%)	210 (97.2%)
18-25 years	403 (19.1%)	5 (1.2%)	11 (2.7%)	387 (96.0%)
26-35 years	338 (16.0%)	5 (1.5%)	7 (2.1%)	326 (96.4%)
>35 years	745 (35.4%)	9 (1.2%)	14 (1.9%)	722 (96.9%)
Sex*				
Female	1,310 (62.2%)	9 (0.7%)	24 (1.8%)	1,277 (97.6%)
Male	797 (37.8%)	12 (1.5%)	17 (2.1%)	768 (96.4%)
Site				
Zimbabwe	699 (33.2%)	11 (1.6%)	14 (2.0%)	674 (96.4%)
Mozambique	710 (33.7%)	4 (0.6%)	17 (2.4%)	689 (97.0%)
Tanzania	698 (33.1%)	6 (0.9%)	10 (1.4%)	682 (97.7%)
HIV status*				
Negative	1,772 (84.1%)	14 (0.8%)	31 (1.8%)	1,726 (97.4%)
Positive	335 (15.9%)	7 (2.1%)	10 (3.0%)	319 (95.2%)
On ART (baseline)	*276 (82.4%)*	*4 (1.4%)*	*9 (3.3%)*	*263 (95.3%)*
Not on ART (baseline)	*14 (17.6%)*	*3 (21.4%)*	*0 (0.0%)*	*11 (78.6%)*
CD4 count (median)	*562 (390 – 746)*	*236 (219 – 476)*	*437 (334 – 583)*	*572 (394 – 763)*
Previous TB*				

No	1,970 (93.5%)	18 (0.9%)	34 (1.7%)	1,918 (97.3%)
Yes	129 (6.1%)	3 (2.3%)	7 (5.4%)	119 (92.2%)
BMI categories[1]				
Underweight	156 (7.4%)	1 (0.6%)	4 (2.6%)	150 (96.8%)
Mildly underweight	364 (17.3%)	4 (1.1%)	8 (2.2%)	349 (96.7%)
Normal	1,022 (48.5%)	14 (1.4%)	24 (2.3%)	988 (96.3%)
Overweight	351 (16.7%)	2 (0.6%)	2 (0.6%)	346 (98.9%)
Obese	214 (10.2%)	0 (0.0%)	3 (1.4%)	212 (98.6%)
Self-reported weight loss[2]				
Yes	2,071 (98.3%)	15 (0.7%)	39 (1.9%)	2,018 (97.4%)
No	36 (1.7%)	6 (16.7%)	2 (5.6%)	28 (77.8%)
Diabetes (HbA1c)*				
< 6%	1,289 (61.2%)	9 (0.7%)	26 (2.0%)	1,254 (97.3%)
6 – 6.5%	563 (26.7%)	5 (0.9%)	10 (1.8%)	548 (97.4%)
≥ 6.5%	154 (7.3%)	2 (1.3%)	3 (1.9%)	149 (96.8%)
Anaemia				
Non-anaemia	1,653 (78.5%)	11 (0.7%)	24 (1.5%)	1,618 (97.8%)
Mild	248 (11.8%)	3 (1.2%)	8 (3.2%)	237 (95.6%)
Moderate	120 (5.7%)	4 (3.3%)	6 (5.0%)	110 (91.7%)
Severe	13 (0.6%)	0 (0.0%)	0 (0.0%)	13 (100.0%)
Education*				
Up to primary	961 (45.6%)	6 (0.6%)	12 (1.2%)	943 (98.1%)
At least secondary	1,146 (54.4%)	15 (1.3%)	29 (2.5%)	1,102 (96.2%)
Employment*				
Full-time (formal)	768 (36.4%)	7 (0.9%)	11 (1.4%)	750 (97.7%)
Full-time (informal)	80 (3.8%)	2 (2.5%)	4 (5.0%)	74 (92.5%)
House man/housewife	224 (10.6%)	3 (1.3%)	5 (2.2%)	216 (96.4%)
Retired	13 (0.6%)	0 (0.0%)	0 (0.0%)	13 (100.0%)
Student	730 (34.6%)	4 (0.5%)	15 (2.1%)	711 (97.4%)
Unemployed	277 (13.1%)	5 (1.8%)	6 (2.2%)	266 (96.0%)
Household income/day*				
USD median (IQR)	0.5 (0.3 - 1.0)	0.7 (0.5 - 1.2)	0.6 (0.3 - 1.2)	0.5 (0.3 - 1.0)
Residence area[3]				
Peri-Urban	690 (32.7%)	5 (0.7%)	18 (2.6%)	667 (96.7%)
Rural	311 (14.8%)	3 (1.0%)	1 (0.3%)	307 (98.7%)
Urban	1,105 (52.4%)	13 (1.2%)	22 (2.0%)	1,070 (96.8%)
Food insecurity[4]				
No	1,306 (62.0%)	8 (0.6%)	27 (2.1%)	1,271 (97.3%)
Yes	798 (37.9%)	13 (1.6%)	14 (1.8%)	771 (96.6%)
Smoking status*				

Non-smoker	1,948 (92.5%)	19 (1.0%)	36 (1.9%)	1,893 (97.1%)
Smoker (current/former)	158 (7.5%)	2 (1.3%)	5 (3.2%)	151 (95.6%)
Alcohol use (AUDIT-C)				
Negative or no use	1,812 (86.0%)	16 (0.9%)	32 (1.8%)	1,764 (97.3%)
Positive	295 (14.0%)	5 (1.7%)	9 (3.1%)	281 (96.5%)

*denotes missingness, one person missing HIV status

[#] Someone is diagnosed as "prevalent TB" if they were diagnosed at their baseline visit and as "incident TB" if they were diagnosed at a subsequent visit or outside of the study (minimum 30 days from baseline)

[§] p-value calculated through Chi-squared testing with study outcome (prevalent TB, incident TB, remained healthy)

[1] Nutrition categories are defined as follows: underweight (BMI < 16 for adults and BMI-for-age Z-scores < -2 for adolescents), mildly underweight (BMI between 16-18.5 for adults and BMI-for-age Z-scores between -2 and -1 for adolescents), normal (BMI between 18.5 and 24.9 for adults and BMI-for-age Z-scores between -1 and 1 for adolescents), and overweight (BMI over 25 for adults and BMI-for-age Z-scores over 1 adolescents).

[2] Self-reported weight loss collected as part of the WHO four symptom screen at baseline

[3] Residence area is strongly associated with site and the association with TB is thus probably confounded by site and should not be interpreted as higher risk of TB in urban areas

Abbreviations: SES: socioeconomic status, BMI: body mass index, TB: tuberculosis, HIV: human immunodeficiency virus, AUDIT-C: , USD: United States Dollar, SD: standard deviation

[4] Food insecurity is defined as either having reported eating < 3 meals per day or if one reported having had insufficient food at any time in the previous six months

Twenty-one participants (1.0%) across 21 households were diagnosed with prevalent TB and 41 (1.9%) participants across 39 households were diagnosed with incident TB, with a median time to diagnosis among incident events of 12.8 months after enrolment (IQR: 9.0-22.1). This resulted in an overall incidence rate of 13.2 (95% CI: 9.5-17.9) per 1,000 person-years.

Among the 21 participants with prevalent TB, five (23.8%) were underweight (Table 1). Baseline underweight had an aOR of 0.94 for prevalent TB (95% CI: 0.28-2.73, p=0.916). When anaemia was included (i.e., underweight and anaemic), the effect estimate increased (aOR: 4.83, 95% CI: 1.03-16.8, p=0.022) (Table 2).

Table 2: Univariable and multivariable associations between indicators of nutritional status (baseline BMI, and combination of BMI and anaemia) and prevalent or incident TB.

			Crude[§]		Adjusted[#]	
Prevalent TB						
Logistic regression	**N**	**n**	OR (95% CI)	*p**	OR (95% CI)	*p**
Baseline BMI						
Overweight	565	2	0.26 (0.06 – 1.13)	0.073	0.27 (0.04 – 1.03)	0.091
Normal	1022	14	1		1	
Underweight	520	5	0.71 (0.25 – 1.97)	0.509	0.94 (0.28 – 2.73)	0.916
Baseline BMI or anaemia						
Underweight or anaemic	809	9	1.40 (0.57 – 3.45)	0.469	1.70 (0.63 – 4.48)	0.282
Neither	1242	10	1		1	
Baseline BMI and anaemia						
Underweight and anaemic	92	3	3.93 (1.13 – 13.6)	0.031	4.83 (1.03 – 16.8)	0.022

Not underweight and anaemic	1998	17	1		1	
Incident TB						
Cox proportional hazards	**PY**	**n[1]**	HR (95% CI)	*p**	HR (95% CI)	*p**
Baseline BMI						
Overweight	929	6	0.39 (0.15 – 1.02)	0.055	0.42 (0.15 – 1.16)	0.083
Normal	1482	20	1		1	
Underweight	553	14	0.98 (0.48 – 1.98)	0.906	1.06 (0.49 – 2.26)	0.900
Baseline BMI or anaemia						
Underweight or anaemic	1031	22	1.50 (0.79 – 2.85)	0.179	1.43 (0.73 – 2.80)	0.271
Neither	2998	16	1		1	
Baseline BMI and anaemia						
Underweight and anaemic	85	6	3.68 (1.47 – 9.21)	0.005	3.77 (1.50 – 9.51)	0.005
Not underweight and anaemic	2023	35	1		1	
Poisson regression[2]	-	-	IRR (95% CI)	*p**	IRR (95% CI)	*p**
BMI change category						
≥ 10% negative change	-	-	2.20 (0.22 – 21.5)	0.498	2.27 (0.22 – 22.9)	0.488
0-10% change (either)	-	-	1			
≥ 10% positive change	-	-	1.54 (0.33 – 7.23)	0.586	1.66 (0.34 – 8.06)	0.532

Nutrition categories are defined as follows; underweight (BMI < 18.5 for adults and BMI-for-age Z-scores < -1 for adolescents), normal (BMI between 18.5 and 24.9 for adults and BMI-for-age Z-scores between -1 and 1 for adolescents), and overweight (BMI over 25 for adults and BMI-for-age Z-scores over 1 adolescents).

Abbreviations: BMI: body mass index, HR: hazard ratio, CI: confidence interval, PY: person-years

n[1] Number of people with TB (events); the total number of incident TB in the study is 40, though some were not included in analyses involving change in BMI as subsequent weight and height measurements were not always available (e.g. participant diagnosed outside of study)

§ Crude models are adjusting for household clustering by including a random effect on the household

Adjusted for age at baseline, sex, site, HIV status, previous TB, and alcohol use. The model did not adjust for household clustering due to overparameterization

[2] Poisson regression includes a lexis expansion based on follow-up time and includes a random effect on the individual

* p-value calculated with a likelihood ratio test

Among participants who were underweight at baseline, the TB incidence rate was 25.3 (95% CI:13.8-42.4) per 1,000 person-years compared to 14.2 (95% CI: 8.8-21.6) in the normal BMI category and 6.5 (95% CI:2.4-14.1) in the overweight/obese category. aHR were 1.06 (95% CI: 0.49-2.26, p=0.900) and 0.42 (95% CI: 0.15-1.16, p=0.083) comparing underweight and overweight/obese with normal BMI at baseline (Table 2, Supplemental Figure 5). Including anaemia again strengthened the association (aHR: 3.77, 95% CI: 1.50-9.51). The association between continuous BAZ in the restricted cubic spline models were non-linear, with increased risk of TB with lower BMI and steeper increases below Z-scores of 0, demonstrating an inverse log-linear relationship between BMI and TB (Figure 4). The PAF of underweight (both underweight and mildly underweight) for incident TB was 17.3%.

Association between BMI trajectories and tuberculosis

Among people with incident TB who also had repeated anthropometric measurements (n=34/41), 22 (64.7%) lost weight during their time in the study, of whom 7/22 (31.8%) lost over 10% of their baseline BMI. Of note, 8/22 participants with weight loss and 4/7 participants with substantial weight loss (>10% BMI) reported weight loss as a symptom. Adults who lost weight tended and

developed incident TB to start off overweight and thus their BMI was categorised as normal or even overweight at time of TB diagnosis, whilst adolescents tended to be already underweight at baseline (Figure 6B).

Poisson regression including time-varying BMI change category (exposure) and TB (outcome) demonstrated an aIRR of 2.27 (95% CI: 0.22-22.9; p=0.488) among those with 10% negative change in BMI compared to those in whom BMI was stable. There was no evidence for a difference in TB risk among those with increasing BMI, compared to those in whom it was stable.

Models adjusting for HbA1c; those using MUAC; or those using WHO thresholds for adolescent thinness showed similar results (Supplemental Tables 3-6).

We identified four latent groups in the GMM based on the observed longitudinal patterns. We named these decreasing, low stable, high stable, and increasing BMI (Figure 6). Most participants were allocated to the stable groups (n [low stable]=988; n [high stable]=638) with the remainder allocated to the increasing (n=178) and decreasing (n=52) groups. TB outcome was associated with latent group allocation (p=0.005); 3/52 (5.8%) of participants in the decreasing BMI group developed TB compared to 13 (1.3%), 5 (0.8%), and 0 (0.0%) participants in low stable, high stable, and increasing groups (Supplemental Table 7). The groups with decreasing weight had higher baseline median BMIs (median BMI: 30.6) compared to low and high stable and increasing groups (median BMI: 19.6, 25.0, and 25.7).

DISCUSSION

Our study reiterates the strong relationship between undernutrition and TB[10,20,21] with a log-linear association between baseline BMI and incident TB risk, when modelled with BMI as a continuous variable. Declining BMI, regardless of absolute value, is associated with an increased risk of TB. When including anaemia in the exposure, this relationship is further strengthened. Many participants who experienced extreme changes in BMI however did not report any weight loss when asked about symptoms of weight loss and would have thus been classified as being asymptomatic. While many participants with incident TB had lost weight prior to diagnosis, the majority of them had a baseline BMI exceeding 22.5kg/m^2. Consequently, weight loss over 10% preceding a TB diagnosis meant the BMI would have been categorised as normal at the time of diagnosis. Our latent class analysis identified four different BMI trajectories: increasing, high stable, low stable, and decreasing. Those in the latter group had the highest risk of developing tuberculosis.

The association between BMI trajectory during TB treatment and treatment outcome is well-known, highlighting the usefulness of BMI as a 'biomarker' of treatment response.[22-24] Other than our study, only one study has investigated BMI trajectories prior to TB diagnosis (i.e., BMI trajectory as a 'biomarker' of disease), in a Tanzanian cohort of people living with HIV.[25] This

study, like ours, found that people who have a declining BMI, regardless of the absolute value, are at higher risk of developing TB. The underlying biochemical and immunological processes are likely to be complex: declining BMI may reflect early pathogenesis or a decreasing health status which is increasing the risk of TB.[26] In fact, the progressive immunological and pathological disturbance occurring during early TB states may cause this weight loss, via altered metabolic processes, including increasing energy requirements and loss of appetite (Figure 1). Only measuring BMI however falls short in the pursuit of disentangling the complex causal relationship between nutritional status and TB as it does not provide enough detailed information on underlying physiological changes. The stronger association when anaemia was included points to the existence of a macro- and micronutrient pathway; though anaemia is a coarse marker and micronutrient measurements are needed.

In many settings, symptom screening serves as the primary TB triage tool due to its low cost and ease of use; although its limitations, such as low sensitivity for TB, are well recognised.[27] Our study highlights the particular limitation of self-reported weight loss as a component of this assessment: among these TB household contacts very few reported having lost weight despite objective evidence of sometimes extreme weight loss (>10% of BMI) over time. This may reflect both the person not noticing they had lost weight and potential social desirability bias in reporting of stigmatised symptoms, especially in Southern Africa where weight loss remains associated with advanced HIV.[28] Recent TB prevalence surveys have estimated that one in two individuals with microbiologically-confirmed TB did not report symptoms (termed asymptomatic TB).[29] Herein, over half of the incident asymptomatic TB events had preceding weight loss. Thus, cross-sectional classification of asymptomatic TB may not reflect ground truth; earlier TB states may instead reflect absence of traditional subjective, insensitive and self-reported symptoms, or the presence of milder symptoms below the threshold at which an individual is willing, or considers it important to, report these to a health provider.[30,31]

Screening for undernutrition and provision of nutritional support for people with TB is recommended by the WHO.[32] Our findings highlight the potential added value of nutritional assessment as a TB screening tool, particularly among household contacts, a population at high risk of TB, or for targeting TB preventative therapy. BMI, MUAC, and haemoglobin are quick and easy to measure using non- or minimally invasive (finger pricks) tests and therefore could be used alongside conventional symptom screening and chest X-ray to identify high-risk individuals during active case finding and prioritise these for confirmatory testing and/or TB prevention (e.g. TB preventive therapy and/or food supplementation). In fact, BMI has been previously used in clinical prediction tools aiming to stratify risk among household contacts in Peru, though these have not yet been validated in our setting.[33,34] Using tools which require little-to-no additional infrastructure ensures these can be delivered at household- or community-level where diagnostic capacity is scarce. In many households in low-income settings, even measurement of BMI is challenging due to the requirement for scales and a stadiometer, and lack of a level surface on which to site these.[35]

The dual burden of malnutrition was present in households in our study: while 17% had at least one member who was underweight, 29% had members who were overweight, and both conditions coexisted in about a fifth of households. This is a phenomenon which has been found in many low- and middle-income countries.[36] Nutritional supplementation will benefit people who are underweight,[37,38] but may increase weight in those who are overweight or obese. While overweight increases the risk of non-communicable disease such as diabetes, in the specific context of TB it appears protective.[10,39]

Strengths of this study include a large and well-characterised longitudinal cohort of household contacts in three high TB burden settings. To our knowledge, this is the first study which investigated longitudinal BMI trajectories and their association with TB and provides novel insight into physiological changes pre-diagnosis. Repeated BMI measurement allowed investigation of nutritional status longitudinally prior to TB diagnosis. We were able to characterise both group- and individual-based trajectories of a diverse population spanning three countries displaying varying levels of nutritional status. Limitations include the small number of prevalent and incident TB diagnoses, resulting in large confidence intervals. Residual confounding is likely given that adjustment was limited to a few key variable to avoid overparamerization of the model. Whilst findings may be specific to the three sites we were recruiting from and not generalisable to other high TB burden settings (such as India), in an era where many countries experience a growing dual burden of malnutrition, we may find similar patterns elsewhere, such as in other Southern African countries. Lastly, in this study, we were not able to draw upon results from biochemical markers beyond haemoglobin, which would have provided insight on micronutrient deficiencies. BMI is prone to misclassification due to measurement error which we aimed to mitigate with repeated measures, and has low sensitivity for diagnosing malnutrition due to the delayed effect of decreased food intake on weight and weak correlation with micronutrient deficiency as measured by biochemical markers.[40] This in turn may have resulted in misclassification of malnutrition.[41,42]

In conclusion, our study confirms the strong association between underweight and TB risk and further highlights their complex cyclical relationship. We underscore the importance of considering the underlying population in designing intersecting TB/nutrition interventions in the face of the growing dual burden of malnutrition. We show that nutritional trajectories are especially important in determining risk of future TB and that longitudinal measurements of BMI should be considered in active case finding among TB-affected households.

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Contributions

NH, KK, KH, JM, CK, LTM conceptualised and acquired the funding for the ERASE-TB study. LL, CJC, ETM, DB, AM, LTM, KM, CK, JJ, HE, DY, FTF, PL, AM, and KK contributed to study implementation, data collection and curation. LL undertook the analysis with input from CJC, RKG, CK, ML, and KK. LL and CJC had access to and reviewed the source data. LL wrote the first draft with input from KK, CJC, and RKG. All authors reviewed and contributed to subsequent drafts. All authors read and approved the final manuscript.

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Data availability

Data to replicate this analysis will be made available at the time of publication.

Conflicts of interest: The authors declare no conflicts of interest

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Figure 1: Conceptual framework of the complex cyclical relationship between undernutrition and tuberculosis

Abbreviations: BMR: basal metabolic rate

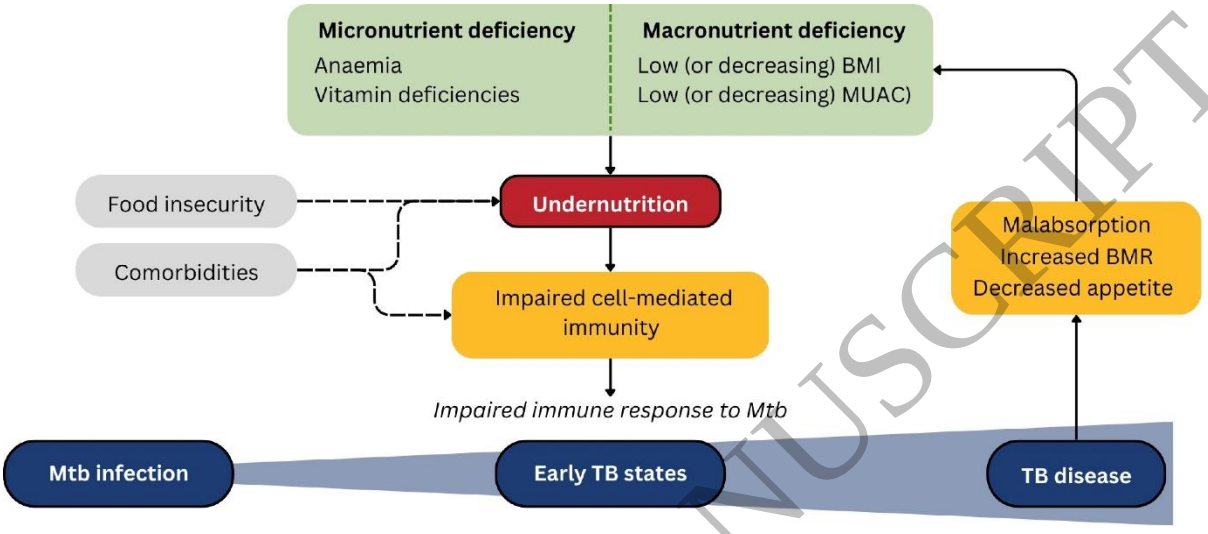


Figure 2: Directed Acyclic Graph (DAG) for the relationship between undernutrition (as measured through body mass index) and tuberculosis

The variables highlighted in yellow refer to confounders which are included in the minimally adjusted variable set. Undernutrition (red) is the exposure and TB disease (blue) is the outcome. Grey variables are not confounders.

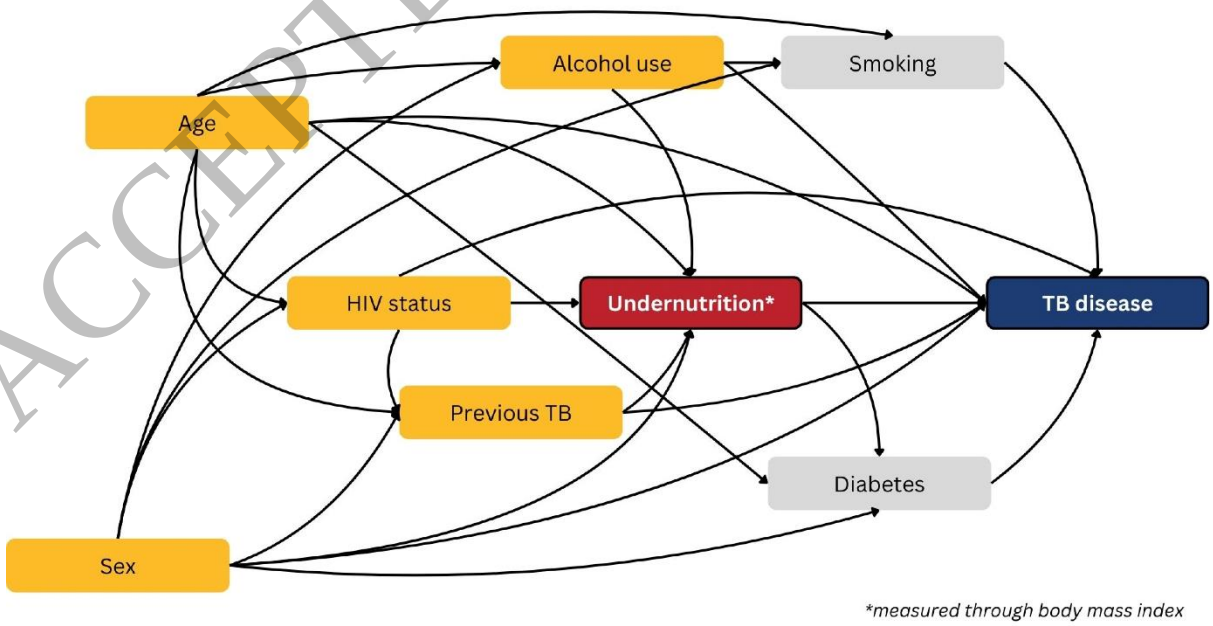


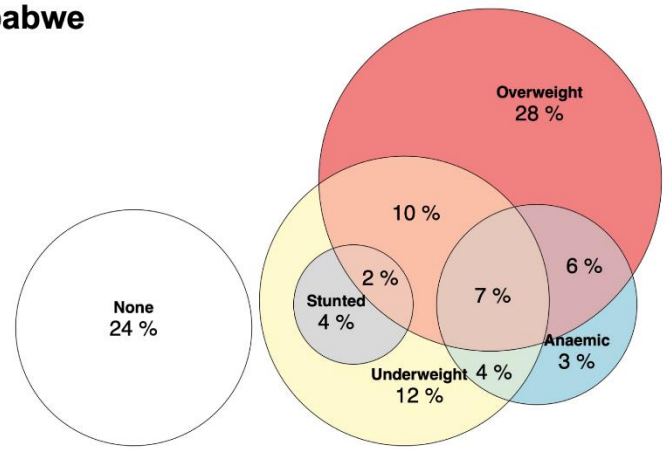
Figure 3: Household-level dual burden of malnutrition exemplified by the overlap of underweight, overweight, and anaemia by site

Proportions refer to the number of households with at least one member being categorised in any of the nutritional categories shown.

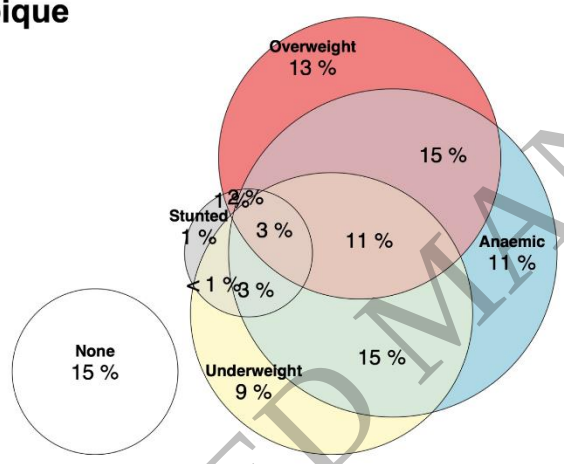
Underweight is defined as a body mass index (BMI) < 18.5 for adults and a BMI-for-age Z-score < 1 standard deviation (SD) for adolescents (< 18 years). Overweight is defined as BMI > 25 for adults and a BMI-for-age Z-score > 1 SD for adolescents. Anaemia is anyone with mild, moderate, or severe according to definitions in Supplemental Table 1. Stunting is defined as having a weight-for-height Z-score < -2.

ERASE-TB recruited in Harare, Zimbabwe (altitude: 1483m), Mbeya, Tanzania (altitude: 1700m), and Maputo, Mozambique (altitude: 47m). Whilst all countries have malaria, both Harare and Mbeya are at high altitude and malaria exclusively occurs among returning local/regional travellers. The increase in prevalence of anaemia in Mozambique is likely due to the prevalence of malaria in the city.

Zimbabwe



Mozambique



Tanzania

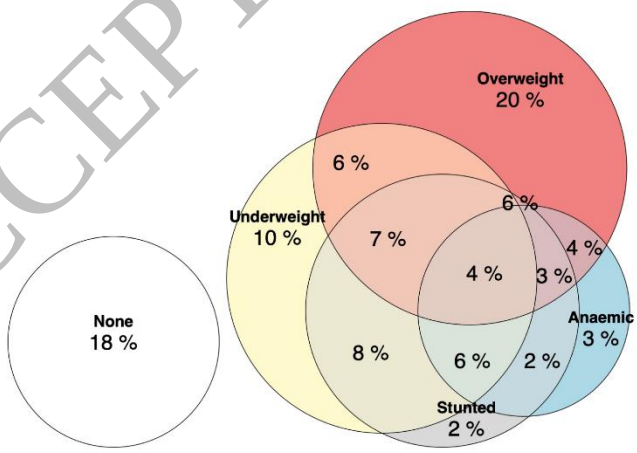


Figure 4: Restricted cubic spline modelling of BMI-for-age Z-score and weight adjusted for height with prevalent (A) and incident (B, C, D) TB as outcome.

Restricted cubic spline model for baseline A. BMI-for-age Z-scores for prevalent TB, B. Weight adjusted for height for incident TB, C. BMI-for-age Z-scores for incident TB, D. BMI-for-age Z-scores for incident TB on the log scale

Optimal number of knots (n=3) was determined using the Bayesian Information Criterion (BIC)

Adjusted models are adjusted for age, sex, site, and HIV status

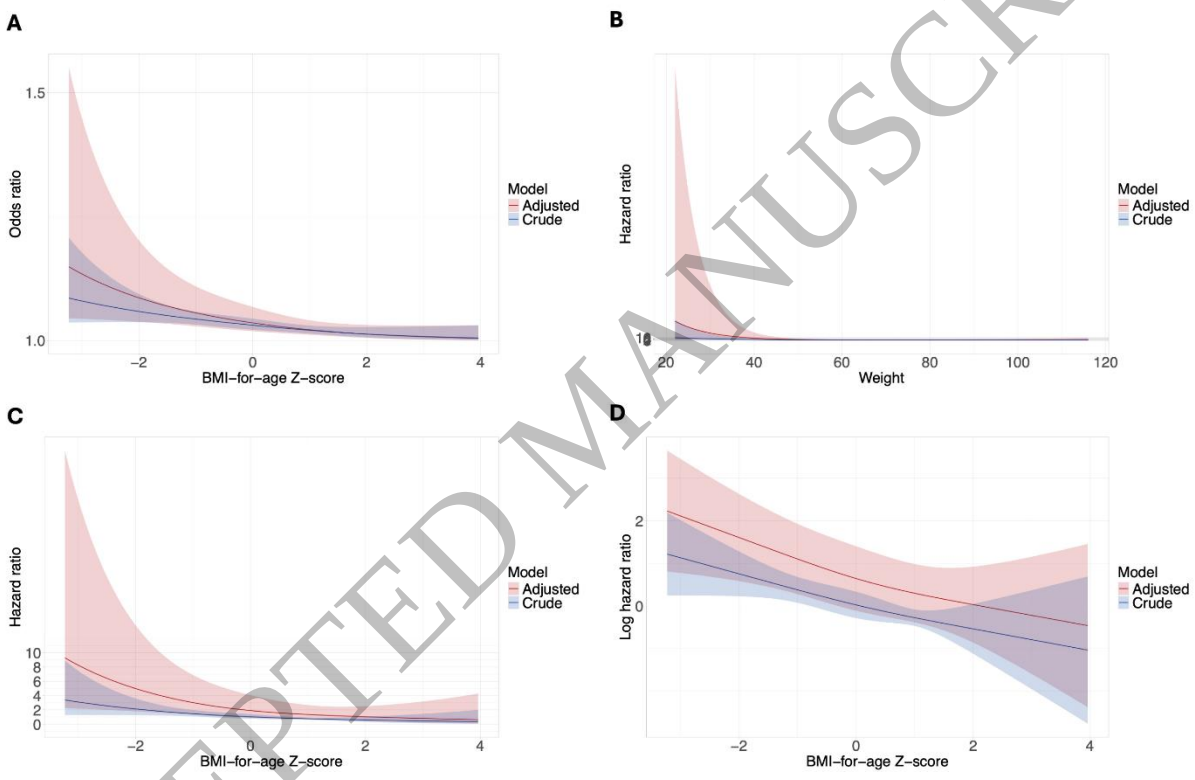


Figure 5: Longitudinal movement between nutritional categories throughout the study for adults and adolescents.

Adults: A, adolescents: B

Nutrition categories are defined as follows; underweight (BMI < 16 for adults and BMI-for-age Z-scores < -2 for adolescents), mildly underweight (BMI between 16-18.5 for adults and BMI-for-age Z-scores between -2 and -1 for adolescents), normal (BMI between 18.5 and 24.9 for adults and BMI-for-age Z-scores between -1 and 1 for adolescents), and overweight (BMI over 25 for adults and BMI-for-age Z-scores over 1 adolescents).

Abbreviations: TB: tuberculosis, BMI: body mass index

Decrease in number over time are due to loss to follow up or early study exit

Most participants who started the study underweight had an increase in BMI over time (369/472 [78.2%]). The median increase in BMI among 117 underweight adults was 0.4kg/m2 (IQR: -0.3-1.1), while underweight adolescents (n=205) had a median BMI increase of 1.2kg/m2 (IQR:0.4-2.3). 723/2,107 (34.3%) participants lost weight during the study, of whom 67 (9.3%) lost over 10% of their baseline BMI. 130/723 (18.0%) of the participants who lost weight and 15/67 (22.4%) of those who lost over 10% of their BMI were adolescents.

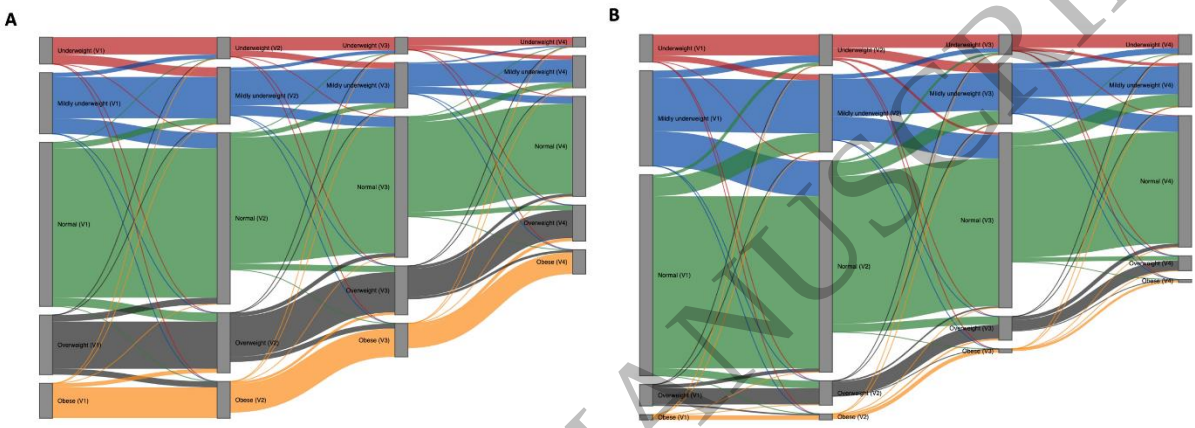


Figure 6: Grouped and individual body mass index trajectories defined by A) latent groups generated by a growth mixture model and B) individual BMI-for-age Z-scores prior to diagnosis

Abbreviations: BMI: body mass index (kg/m^2)