Out of the

Center for International Health, Ludwig-Maximilians-Universität zu München

Substance use and its effect on quality of life, mental health, and adherence to anti-TB medication among tuberculosis patients in Southwest Ethiopia

Doctoral Thesis

for the awarding of a Doctor of Philosophy (Ph.D.)

at the Medical Faculty of

Ludwig-Maximilians-Universität, Munich

submitted by

Matiwos Soboka Daba

born in

Manasibu, Wollega, Ethiopia

submitted in 2021

Supervisors LMU:	Title, first name, last name
Habilitated Supervisor	Prof. Dr. Eva Grill
Direct Supervisor	PD Dr. med. Kristina Adorjan
3rd LMU Supervisor	
Supervisor External:	
Local Supervisor	Prof.Dr. Markos Tesfaye

Reviewing Experts:	
1st Reviewer	Prof. Dr. Eva Grill
2nd Reviewer	PD Dr. med. Kristina Adorjan

Dean:	Prof. Dr. med. Thomas Gudermann

Date of Oral Defense:	22 December 2021

Affidavit

Matiwos Soboka Daba

Name

Street

Jimma

Zip code, town

Ethiopia

Country

I hereby declare, that the submitted thesis entitled

Substance use and its effect on quality of life, mental health, and adherence to anti-TB medication among tuberculosis patients in Southwest Ethiopia

is the result of my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

The submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

I further declare that the electronic version of the submitted thesis is congruent with the printed version both in content and format.

Jimma, 17/01/2022

Place, Date

Matiwos Soboka

Signature of PhD Candidate

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dean's Office
Medical Faculty

MMRS

Confirmation of congruency between printed and electronic version of the doctoral thesis

Daba Matiwos

Surname, first name

Street

Jimma

Zip code, town

Ethiopia

Country

I hereby declare that the electronic version of the submitted thesis, entitled

Substance use and its effect on quality of life, mental health, and adherence to anti-TB medication among tuberculosis patients in Southwest Ethiopia

is congruent with the printed version both in content and format.

17/01/2022

Place, date

Matiwos Soboka

Signature doctoral candidate

Contents

Abstract

Background: Substance use disorders (SUDs) have a strong association with non-adherence to anti-tuberculosis (anti-TB) medication and contribute to the increasing multidrug-resistant tuberculosis (MDR-TB). Furthermore, SUDs may have a negative effect on the adherence, quality of life, and mental health of patients with tuberculosis, however, little is known about its effect on the adherence, quality of life, and mental health among tuberculosis patients in Southwest Ethiopia. Therefore, this study aims to address the existing scarcity of data on these issues in Ethiopia.

Methods: - A prospective cohort study was conducted among 268 patients with tuberculosis in Southwest Ethiopia between October 2017 and 2018. A structured questionnaire translated into the local language was used to assess SUD, adherence, mental distress, quality of life, and other potential risk factors. Patients were followed for six months and data were collected on three occasions (baseline, two-month and six-month follow-ups). The associations between SUD and quality of life, mental health, medication adherence, and other variables were explored by using a generalized mixed linear model and linear model.

Result: - The overall prevalence of non-adherence among patients with SUD was 16.4% (n=22), 41.7 % (n=48), and 45.7% (n=59) at baseline, two month, and six month respectively. The odds of non-adherence to anti-TB medications among patients with khat use was nearly four times that of patients who did not use khat (aOR 3.8, 95%CI=1.8-8.0).

Conclusions:-SUD predicts a greater likelihood of non-adherence to anti-TB medication. This implies that there is a need to integrate management for SUD into the existing tuberculosis treatment services. There was a high prevalence of mental distress and food insecurity. Health-related quality of life improved over the course of anti-TB treatment.

Keywords: Substance use disorder, quality of life, mental health, anti-TB adherence, tuberculosis, Ethiopia.

i. List of figures

ii. List of tables

iii. Abbreviations

TB: Tuberculosis

HIV: Human Immunodeficiency Virus

WHO: World Health Organization

SGDs: Sustainable Development Goals

MDR-TB: Multi-Drug Resistant Tuberculosis

NTCP: National Tuberculosis Control Programme

SUDs: Substance use disorders

DOT: Direct Oberved Therapy

MoH: Ministry of Health

HSTP: Health Sector Transformation Plan

QoL: Quality of Life

AUD: Alcohol Use Disorder

AUDIT: Alcohol Use Disorder Identification Test

FTND: Fagerstrom Test for Nicotine Dependence

SRQ-20: Self-Report Questionnaire-20

HFIAS: Household Food Insecurity Access Scale

BIC: Bayesian Information Criterion

DAG: Directed Acyclic Graph

1. Introduction

1.1 Global history of Tuberculosis

Tuberculosis (TB) is an infectious disease transmitted by bacteria called mycobacterium tuberculosis (1, 2). It is transmitted to a healthy person nearby when a sick person coughs and expel the agent into the air (3). This bacterium lived within this world since ancient times and thought to be originated 150 million years ago (1, 2). Three million years ago, mycobacterium thought to infect the earlier human being (hominids) in East Africa (4). Even though there is no confirmed evidence, skeletal deformities as a result of tuberculosis were found among Egyptian mummies dating back to 2400 BC (5, 6). The first written document about TB was found 3300 years ago in India, while 2300 years ago in China (2). TB mainly infects the lungs (pulmonary TB) and other organs of the body as well (extrapulmonary TB) (7). "One-third of the world's population carriers TB bacillus and are at risk for developing active disease"(3). Across the world, about 2 billion people were infected by TB (8). Every year approximately 10.4 million people are infected by TB worldwide (3). People living with human immunodeficiency virus (HIV) are at higher risk of being infected by TB. Likewise, males and productive age groups are mostly affected by TB (3, 9). Even though TB infects everybody, adults are mostly at higher risk (3). Tuberculosis remains a major global health problem and the first leading cause of mortality ranking above HIV (3). World Health Organization (WHO) has developed an ambitious target for 2020–2035, The End Tuberculosis Strategy, that was designed to reduce TB incidence by 20% and TB related death by 35% by 2020. Also in this strategy, the plan was to decrease new TB infection by 90% and death by 95% by 2035, in contrast to the level in 2015 (10). However, all countries, particularly, most WHO regions and high TB burden countries are not achieving the plan for 2020 of the End TB Strategy. The total reduction of TB incidence between 2015 and 2018 was only 6.3%, while the milestone target is 20% reduction between 2015 and 2020. Likewise, between 2015 and 2018, the cumulative TB death reduction number was 11%, but End TB Strategy target was 35% reduction by 2020 (3).

Across the globe, a total of 10 million people were infected by TB, and 1.5 million died in 2018 (3, 11). Of these, almost 1.2 million HIV free people were died, while 251, 000 deaths were among HIV-positive people (3, 11). Since 2000, a total of 54 million people died from TB despite the efforts to cut TB infection and death (12).

Tuberculosis is one of the prevalent diseases that cause enormous public health and economic burden in low-income countries (3). The morbidity and mortality related to TB are mainly noticeable in these countries where malnutrition, crowded living conditions, and lack of TB

control measures make the disease a serious public health burden (13-15). For example, more than 95% of TB related morbidity and mortality is in developing countries (3). Most of the estimated cases were found in Asia and the African region (11). In 2018, the highest TB cases were reported in the Western Pacific (18%), Africa (24%), and South-East Asia (44%). About two-thirds of the global TB cases are in eight countries namely: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%) (3). One of the global challenge is treatment coverage which remains below 64% (12). According to the Sustainable Development Goals (SGDs), TB new cases and mortality will decrease by 80% and 90% respectively by the end of 2030 (16). However, most countries across the world are not achieving the "2020 milestones of the End TB Strategy" (3). Because of poor adherence and treatment outcomes, worldwide the proportion of new cases with Multi-drug resistant tuberculosis (MDR-TB) remained to be 3.5% in 2013 (9).

1.2 History of tuberculosis in Ethiopia

In Ethiopia, for more than half a century, TB was the main public health challenge. For the first time, in the 1960s, Ethiopia established TB treatment centers in Addis Ababa, Asmara, and Harar to mitigate the expansion of the diseases. In 1976, the Central Office of the National Tuberculosis Control Programme (NTCP) was founded. As a pilot, the Directly Oberved Therapy (DOT) program was started in Arsi and Bale zones of Oromia Region to maximize the prevention and control program in the country (17).

According to the 2011 Ministry of Health (MoH) report, TB was the eighth leading cause of hospital admissions and the third leading cause of hospital deaths in Ethiopia (18). According to the WHO 2010 report, Ethiopia ranked third in Africa and 7th among the 22 countries in the world with a high burden of TB (19). In 2016, the estimated number of newly infected people by TB was 219,186, while the TB death was 48,910 (20). Likewise, in 2018, new TB cases in Ethiopia was 151 per 100,000 population (3). Most recently, Ethiopia has developed a five years Health Sector Transformation Plan (HSTP) which is a complement to the Sustainable Development Goals (SDGs) to halt Tb and other major diseases (21). DOT was introduced in Ethiopia mostly in hospitals and health centers (21). In Ethiopia, the prevalence of multidrug-resistant TB is increasing from time to time. A review of studies done by Biadglegne et al showed that the prevalence of MDR-TB varies from 3.3%-46.3% (22). Some of the main factors that determine MDR-TB are defaulting treatment, treatment failure, and non-adherence to anti-TB medications (23-26).

1.3 Adherence to anti-TB medications

Long-term adherence to standardized medication is the key to the successful treatment of TB, as non-adherence may lead to the emergence of multidrug-resistant TB (MDR-TB), which is an increasing global health threat (3). Non-adherence to anti TB medications could also lead to a lower treatment success rate, default, and death (27). Therefore, non-adherence to anti-TB medication is going to be a major global challenge to achieving the SD target to end TB by 2030 (3, 28). Improving adherence to anti-TB medication is important to increase the cure rate and halt poor outcomes such as drug resistance, relapse, and death.

Ethiopia has developed a national TB treatment guideline to ensure adherence through regular appointments and supervised drug administration, and to improve treatment outcomes (29) but the problem remained a big challenge. In Ethiopia, the pooled prevalence of non-adherence among TB patients is 21.3% which has been estimated to range from 10% in the Amhara region to 24% in Southern Nations and Nationalities of Ethiopia (30).

1.4 Mental distress among patients with Tuberculosis

Studies showed that the prevalence of mental illness among tuberculosis patients reaches up to 70% (31), and there is a strong association between mental disorders and tuberculosis (32). Also, mental illness was reported to affect patient adherence to anti-TB medications (31).

Mental distress is a type of mental health problem that includes symptoms of depression, anxiety, and somatic complaints which may not fall into standard diagnostic criteria (33, 34). Mental distress is associated with poorer adherence to anti-TB medications (35, 36), and TB treatment outcomes (37). A study done in South Africa among tuberculosis patients showed that the overall prevalence of common mental disorders was 32.9%. In Ethiopia, up to 67.6% of TB patients had symptoms of mental distress (38, 39). A study done in Oromia region of Ethiopia found that the prevalence of mental distress was 63.7% among TB/HIV co-infected patients. TB/HIV co-infected patients were 1.7 times more likely to experience mental distress than non-co-infected patients (40). Another study done in the same area among TB/HIV co-infected patients found that the prevalence of mental distress at baseline and end of 6 months was 54.4% and 41.2% respectively (41). A study done in Addis Ababa city administration found that a baseline psychological distress was associated with age greater than 35 years, previous history of treatment for tuberculosis, being diagnosed as TB/HIV co infection, being diagnosed as MDR-TB and low socio-economic status at the baseline. However, at 6 months after treatment initiation, only being a MDR-TB patient and having low economic status were associated with psychological distress (42). Older age, lower formal education, poverty, not being married, being

separated, being divorced/widowed, and being HIV positive were associated with mental distress(43). Furthermore, mental distress was found to be a predictor of tuberculosis treatment outcomes (39).

1.5 Quality of life among patients with Tuberculosis

Quality of life (QoL) is a well-functioning of physical, mental, and social dimensions of life which is commonly used in the health care system to measure patient's subjective view of overall well-being. QoL is used both in a clinical trial and observational studies (44-46). Tuberculosis (TB) has a strong association with lower QoL, especially, patients with TB found to have poorer mental health components of QoL than the physical component (47-49). QoL among patients with tuberculosis is the worst compared to the general population (45, 50, 51). Even though after treatment TB patients have improved QoL, it remains lower than the general population in multiple areas (48, 50-53). TB significantly affects patients' quality of life and even after recovering from the disease their QoL remained lower than the general population (45). Studies showed that TB affects the physical and mental health summary of QoL. Also, tuberculosis-related symptoms affect a patient's role in society, and as a result, sometimes patients face stigma. Likewise, patients reported that they have a lower health-related quality of life as a result of continued stigma after treatment and lower emotional stability after declared cured of the disease (54-56). Physical symptoms of the disease also affect patients' activities including social activities which could lead to lower QoL (29, 50, 51, 57). Factors such as gender, marital status, education, job status, and place of residence (50, 51, 58, 59) have a significant impact on QoL among TB patients. Also, medication side effects, long duration of treatment, non-adherence to medications, access to health services, a complication of the disease, and comorbidities were found to affect QoL of life among patients with tuberculosis (50, 58-60). Also, psychological disturbance, low income, mental distress, comorbid diagnosis, and substance use were associated with lower QoL among patients with tuberculosis (48, 61-66).

1.6 Substance use and its effect on adherence, mental health, and quality of life

Psychoactive substance use such as khat, alcohol, and tobacco are identified to be associated with tuberculosis (15, 67-71), and decrease anti-TB treatment adherence (71-79). Also, these substances enhance susceptibility to infection including tuberculosis by modulating immunity (79, 80). Mental illness and substance use disorders, HIV, and TB are each major contributor to the global disease burden and are closely inter-related (75). Alcohol, tobacco/shisha, khat, cannabis, and other illicit drugs are commonly used psychoactive substances in African countries (75, 81-85) and it is responsible for poor health status, overall worse clinical outcomes (71), and

low QoL (49, 86-90). Also, substances use are common in persons with TB (91). Patients with TB are also at risk of increased morbidity and premature mortality due to substance use disorders (92).

Tobacco smoke contains thousands of different chemicals that might be cause lung cancer, Cardiovascular disease, and emphysema (84). Similarly, tobacco is responsible for an estimated 7% of deaths due to tuberculosis and 12% of deaths due to lower respiratory infections (78, 93-95). Tobacco use increases the risk of developing MDR-TB (96). In developing and middle-income countries, there is the highest morbidity and mortality related to tobacco use (93, 97). Also, smoking tobacco was associated with poor physical health summary of QoL (65).

Alcohol is a psychoactive substance that was used across the world for many centuries and is known for causing dependence (98). Alcohol use disorder (AUD) is a chronic relapsing brain disease that is characterized by affecting the physical and mental health of the users (99). There are factors such as genetic, psychosocial, peer pressure, and environment that determine alcohol use disorder among patients with tuberculosis (100, 101). Alcohol use share about 5.1% of all global burden of diseases and injuries, and every year AUD is responsible for the death of about 3 million people worldwide but the death highest among productive age groups (20-36 years). Because, alcohol use is associated with more than 200 diseases and injuries (98, 102). AUD is a major global health concern because of its detrimental effect on efforts towards reaching Sustainable Development Goals (SDGs) (98).

A systematic review done by *Simou et al* showed that consuming 10-20 mg of alcohol every day increases the risk of developing TB by 12% (103), and this could be related to the social gathering while consuming alcohol (104). Also, alcohol use has an association with the occurrence of tuberculosis (104) as well as worsening of the disease (105), because it has a negative impact on the immunity of the users (104, 106-108). Globally, approximately 10% of TB cases are related to alcohol use (108). The prevalence of alcohol use disorder among patients with TB varies from 31% to 62% in South Africa (109), while it is 10- 50% in Australia, Europe, and America(104). In Ethiopia, the lifetime and current prevalence of alcohol use among TB patients is 44.2% and 23.9% respectively (110).

Alcohol use disorder is also responsible for the development of MDR-TB (111) because it has an association with non-adherence to anti-TB medication (112, 113), missing DOT, and a higher rate of default (108). Likewise, patients who use alcohol were found to have higher treatment failure, relapse, loss to follow-up, transfer out, and delayed cultural conversion compared to

those who were sober (114, 115). Also, patients with TB who drink heavily had poor adherence, higher probability of an unfavorable clinical course and a higher probability of experiencing the most destructive forms of TB (116). Additionally, consuming a small amount of alcohol while taking medications causes interactions that could lead to adverse events (116). A study done among patients with MDR-TB showed that, patients who were using alcohol found to miss 18 and more intensive-phase doses compared to their counterparts (117). Moreover, alcohol use has a significant impact on the treatment outcomes of tuberculosis (91, 118-120) such as early death (121-123) because TB patients who use alcohol are at high risk of cerebrovascular, and liver disease (123).

In general, alcohol use disorder has an association with poor adherence (116), frequent default (124-126), and resistance to second-line injectable drugs (74). AUD is associated with mental distress among patients with TB (127). Likewise, alcohol use is found to affect QoL, for example, according to a study done in South Africa, the current use of 20 or more drinks has a major effect on the physical component of QoL (128). Also, another study done at the outpatient department in South Africa showed that alcohol dependence was associated with lower quality of life in three domains, namely, physical functioning, general health, and mental health (65).

Khat is an amphetamine-like natural stimulant with over 40 active compounds. Among these, the psychoactive alkaloids, cathinone, and cathine cause the stimulating effect, craving, and dependency (129). Khat has been chewed and enjoyed socially for centuries in the horn of Africa (130-132). Studies showed that khat use increases susceptibility to tuberculosis (133) and may be associated with poor TB treatment outcomes, prolonged duration of treatment (134), and high load of bacteria in TB patients (135). In Yemen, khat use has been shown to be associated with non-adherence to anti-tuberculosis medications (90), probably because khat disrupts patients' sleep patterns and causes them to miss their appointments (136). Another study done in Yemen showed that khat use also significantly affects the mental health component of quality of life among TB patients (86).

Ethiopia, like Yemen, counts among the few countries where khat use is legal. Khat use is an unrecognized threat to anti-TB medication adherence, mental health, and quality of life in Ethiopia.

Rationale and Objectives

Substance use disorder is responsible for different diseases including mental distress among tuberculosis patients. Also, substance use disorders have been found to play a dominant role in affecting adherence to anti-TB medications (120, 137-140). However, poor adherence to anti-TB medication increases the likelihood of developing MDR-TB.

SUD is associated with mental health problems such as anxiety and depression (141). Also, among patients with tuberculosis, substance use such as tobacco (38), khat, and alcohol use (142, 143) are associated with mental distress. On the other hand, mental distress has a negative effect on adherence to anti-TB medications (143) and treatment outcomes (144, 145). Therefore, screening substance use disorders and early intervention among tuberculosis patients is very crucial to reduce the probability of developing MDR-TB and achieving the sustainable development goal. However, in Ethiopia, there is no information regarding SUD and its effect on adherence to anti-TB medication, mental health, and quality of life among TB patients. Taking the importance of such information into account, this study attempts to fill the knowledge gap on substance use disorder and its effect on the QoL, mental health, and adherence to anti-TB medication. The finding of this study is important for health managers and policymakers to accommodate the needed services to improve patients' adherence to anti-TB medications, mental health, and quality of life. Moreover, having information on the magnitude of substance use disorder and its effect on adherence to anti-TB, mental health, and quality of life helps to focus on clients who need more attention. Generally, the findings of this study are very important to address sustainable developmental goals.

General objective

To assess substance use disorder and its effect on the quality of life, mental health, and adherence to anti-TB medication among tuberculosis patients in Southwest Ethiopia.

Specific objectives

1. To examine the prevalence of substance use disorders among tuberculosis patients in Southwest Ethiopia.
    a. To assess the magnitude of khat use and associated factors among TB patients in Southwest Ethiopia.
    b. To assess the prevalence of alcohol use disorders and associated factors among TB patients in Southwest Ethiopia.
    c. To assess the prevalence of nicotine use disorder and associated factors among TB patients in Southwest Ethiopia.
    d. To assess the magnitude of illicit drugs and associated factors among TB patients in Southwest Ethiopia.
2. To assess the effect of substance use disorders on adherence to anti-TB medication among tuberculosis patients in Southwest Ethiopia.
3. To assess the quality of life and associated factors among tuberculosis patients in Southwest Ethiopia.
4. To assess the prevalence of mental distress among tuberculosis patients in Southwest Ethiopia.
5. To assess the association between social support and adherence to anti-TB medication among tuberculosis patients in Southwest Ethiopia.
6. To assess food insecurity and associated factors among tuberculosis patients in Southwest Ethiopia.

2. Methods

2.1 Study area, period, design, and patients

This study was conducted using a prospective cohort study in Jimma zone and Jimma city special zone. Jimma city special zone is the capital city of Jimma zone and located in the Southwestern part of Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital and a zonal hospital, as well as four functional health, centers those currently providing services. Similarly, Jimma Zone has 18 districts and is located in the Southwest of Ethiopia. Overall, the zone has more than three million inhabitants. During the period of this study, Jimma Zone had 112 health centers and three hospitals. Out of these government's public health facilities, 91 health centers and all hospitals were providing services to TB patients. In this study, data was collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma city, we randomly selected 2 health centers and one hospital. We also randomly selected 20 health centers and three hospitals from the Jimma Zone (excluding Jimma City). Patients were included if they had initiated anti-TB treatment within a month of starting the study at the selected health centers and hospitals between October 2017 and October 2018.

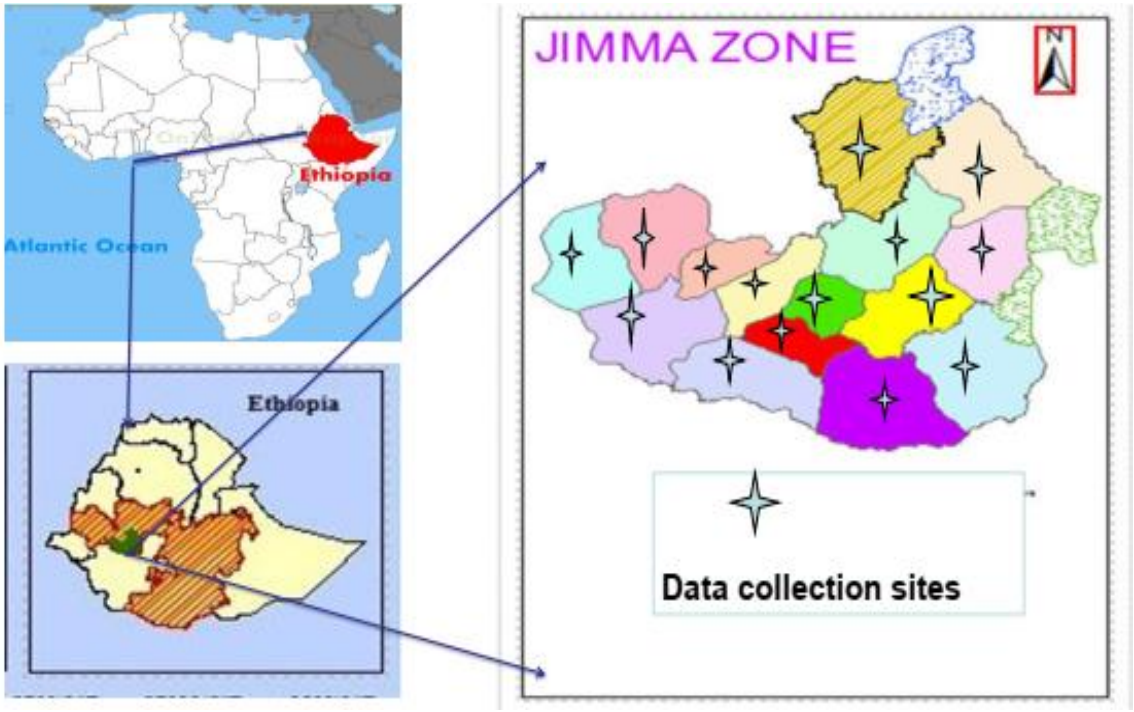

Figure 1: Study sites of Jimma Zone, 2017/18

Study Design:-This study is a multicenter prospective cohort study.

2.2 Study population

A sample of all tuberculosis patients aged 18 years and above who came for a follow-up to 22 health centers and four hospitals in Jimma zone and town during the study period.

2.3 Sample size assumptions and sampling procedure

The prevalence of non-adherence among khat user TB patients from previous studies was found to be 62.4% (146). The prevalence of non-adherence among non-khat user TB patients was 43.6% (146). We needed to study 111 exposed (using substance) and 111 unexposed (not using substance) individuals to detect a difference of non-adherence to the anti-tuberculosis medication at an alpha level of 0.05 and with a power of 80% using the corrected Fleiss sample size calculation [EPInfo^{TM}]. The total sample size took into account a 20% drop out. Thus, the final sample size was 134 in each group which totals 268 TB patients.

Sampling procedure

All eligible adult TB patients who were on a follow-up to 22 health centers and four hospitals in Jimma zone and town during the study period were consecutively invited to participate in the study. We included all TB patients who were registered for tuberculosis treatment in the selected health facilities within a month prior to the data collection. Patients with severe medical and mental illness who have difficulty participating in the first data collection were excluded from the study. Also, patients who had a plan to be transferred out to other health facilities were excluded. Informed written consent was obtained from all study participants. Participants of the study were followed up for a period of six months and data were collected on three occasions.

2.4 Instruments and measures

Exposure variables

Alcohol use disorders (AUDs):- To gather data regarding alcohol use disorder, Alcohol use disorder identification test (AUDIT) was used (147). The AUDIT was developed by World Health Organization and measures AUDs in developing and developed countries, particulary among patients attending primary health care. The sensitivity and specificity of AUDIT for AUDs at a cut-off score of eight or more were 0.90 and 0.80, respectively (147). With some modification to questions number two and three, AUDIT was used in Ethiopian context (148). For local alcohols, the volume has been measured in milliliters and converted to a standard drink

(148). The minimum score of AUDIT is zero, while the maximum is 40. In this study, a total score of AUDIT 8 or more was used to declare AUDs (147).

Nicotine dependence: To collect data regarding tobacco dependence, Fagerstrom test for nicotine dependence (FTND) was used. The FTND score range from 0-10 to measure tobacco use disorder. Out of the total score, a score of $\geq$ 5 was used to declare tobacco dependence (149). At this cut-off, the sensitivity and specificity of FTND were 0.75, and 0.80 respectively. A total FTND score of five indicates moderate nicotine dependence, a score of 6-7 indicates high nicotine dependence, and a score of 8-10 indicates very high nicotine dependence (149).

Khat use:- khat use was assessed by a self-reported questionnaire. Since there is no standardized questionnaire for khat use, patterns and causes of khat use were assessed by using a structured questionnaire which was developed through a literature review. Any consumption of khat in the last one month was considered as current khat use. In this study, frequent khat use (using khat daily and 2–3 times per week) and using more than one bundle of khat per day was considered as khat use disorder.

Cannabis smoking: Cannabis use was assessed by one single question. Any consumption of cannabis in the last one month was considered as current cannabis use.

Outcome variables

Adherence: The adherence status of tuberculosis patients was assessed by Direct Observed Treatment (DOT), pills counts, and self-report. In this study, adherence is defined as taking the medication regularly and attending follow-up according to appointments and national guidelines for tuberculosis in Ethiopia (150). Non-adherence was defined as missing at least one follow-up appointment during DOT. Also, non-adherence during the intensive phase was defined as missing at least one dose of the prescribed anti-Tb medication and noted separately.

*TB treatment Outcomes***:** Defaulted, interrupted, treatment failure, treatment completed, transfer out, cured, or death (150).

Quality of life: Quality of life was assessed by using Medical Outcomes Study Short Form-36 (SF-36). SF-36 has thirty-six items, and a low score indicates poor quality of life (151). SF-36 has eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain,

general health (152). SF-36 has been translated into Amharic and validated for use in Ethiopia (151).

Mental distress: Self-report questionnaire-20 (SRQ-20) which was prepared by WHO was used to assess mental distress. SRQ-20 has 20 questions with 'yes' or 'no' responses. SRQ-20 has been adapted and validated in the Ethiopian setting with an established cut-off where values below 7 indicate the absence of mental distress and values of 7 and above indicate mental distress (64).

Explanatory variables

Socio-demographic variables: Age, sex, marital status, level of education, religion, ethnicity, income, household size, occupation, place of residence, living conditions,

Health institutions related factors: Distance of the patient from health institute, availability of drugs, counseling status.

Disease-related factors: Type of TB diagnosis (smear-positive, smear-negative, extrapulmonary TB, MDR-TB)

Type of treatment: New treatment, re-treatment

Comorbidities: HIV, previous mental illness, hypertension, diabetes mellitus.

Patients' related factors (i.e getting improvement, forgetfulness to take medication). A self-reported questionnaire was used to assess patients' related factors.

Patient type: Data regarding the type of patients (i.e new, return after default, and relapse) was collected from the patients' chart.

Social support: Data regarding social support were collected using Oslo Social Support Scale (The Oslo 3-items). While the minimum score of Oslo-3 scale is 3, the maximum score is 14. The Oslo-3 total score of 3-8 indicates poor social support, 9-11 indicates moderate social support and 12-14 indicates strong social support (153).

Food insecurity: Data regarding food insecurity in the previous month were collected using the Household Food Insecurity Access Scale (HFIAS). Endorsing non of the HFIAS items indicate food security, while endorsing any of the itms 1, 2, 3, and/or 4 but not the items 5 to 9 indicate mild food insecurity. Moderate food insecurity if respondent endorsed items 5 and/or 6 but not

the items 7 to 9, while endorsing 7, 8 and/or 9 indicate severe food insecurity (154). This tool was validated in Ethiopia among people living with HIV (155, 156).

2.5 Data collection procedures

Patients were interviewed on three occasions:

1. *Baseline:* Tuberculosis patients were interviewed for their substance use disorders, mental distress, and quality of life. Also, data on socio-demography, distance from health institutions, food insecurity, and social support were collected. Simultaneously, patients' records were reviewed for circumstances of diagnosis, anti-TB medication types, and in case of an HIV infection, a regimen of ART. Adherence was measuered by reviewing the DOT attendance at the health institutions.
2. *Second visit:* At the end of the intensive phase (the first two months) directly observed treatment (DOT) was used to measure patients' adherence to anti-TB medication adherence. Patients were interviewed for reasons of not attending the DOT regularly, substance use disorders, mental distress, social support, quality of life, and food insecurity. On the second visit number of anti-TB tablets prescribed on that day was documented along with the expected number of days for which they are prescribed. Patients were then be advised to come with all the remaining drugs. They were strictly advised not to take and bring leftovers from an old prescription.
3. *Third visit:* The third visit took place at the end of six months. Medication leftovers were counted to assess patients' adherence to anti-Tb medications. Patients were asked for current reasons why they missed to take doses of anti-TB. Also, AUDIT, FTND, Oslo-3, SRQ-20, and SF-36 were administered for patients in order to identify whether the patient has alcohol use disorder, nicotine dependence, social support, mental distress, and quality of life. Data on comorbid medical or psychiatric illness and tuberculosis treatment outcomes were collected. Also, household food insecurity was assessed at the end of six months.

2.6 Data processing and analysis

Data were entered into Epi Data (version 3.1) and analyzed using R (1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. A generalized linear model was used to examine the longitudinal effect of substance use disorders on medication adherence and mental distress, while a linear model was used to assess the association between substance use disorder and QoL.

Model fit was examined with the Bayesian Information Criterion (BIC). Lower BIC indicates a better model fit. The covariate selection was based on a directed acyclic graph (DAG). DAG is an analytical method for visualizing hypotheses about causal relationships between exposure (substance use) and outcome (adherence) (48, 49). This approach has been shown to yield valid adjustment sets of variables and to avoid bias (50).

2.7 Ethical Considerations

The study was conducted after an ethical clearance is obtained from the ethical review board of Jimma University and Ludwig-Maximilians-Universität. Written informed consent translated into local languages was obtained from the study subjects. The privacy of the participants was ensured during the data collection. The anonymity of the participants was kept at every stage of data analysis and interpretation. The findings of the study was be given to the hospitals, Oromia region, and other concerned bodies to avail information and make use of its intervention and for further studies in the field.

3. Results

3.1 Socio-demographic and clinical characteristic

In this prospective cohort study, a total of 268 patients (50% with substance use disorders) were recruited. Out of the total participants, 60.1% (n=161) were male with an age range of 18 to 80 years, and mean age 32·4, SD 14·4. More than one-third of the participants were under 25 years (34.5%, n=93). The majority (58.6%, n=157) of the study participants were married and Islam religion followers (61.6%, n=165). Also, two-third (63.1%, n=169) of them did not attend formal education. More than half (52.6%, n=141) of the participants were living in urban areas (see table 1).

3.2 Clinical characteristics and non-adherence

Among the total participants, 40.3 % (n=108), 32.5 % (n=87), and 27.2 % (n=73) were diagnosed with smear positive, smear negative, and extra pulmonary TB respectively. At baseline, 3.7% (n=10) patients were diagnosed with HIV, and 7.1% (n=19) with other comorbidities. The prevalence of non-adherence to TB medication at baseline was 9.7 % (n=26). This percentage increased to 26.1% (n=70) at two month assessment, and 27.6% (n=74) at the six month assessment.

3.3 Substance use disorders

The prevalence of non-adherence among patients with substance use disorder was 16.4% (n=22), 41.7 % (n=48), and 45.7% (n=59) at baseline, first, and second follow up respectively. The majority of patients with substance use disorder were male (58.4% at baseline, ~50.0% at first follow-up, and 52.2% at second follow-up). The baseline prevalence of substance use disorder among divorced/widowed was 71.4% (See table 1).

Table 1: Socio-demographic characteristics and substance use disorder among a cohort of patients on anti-tuberculosis treatment in Southwest Ethiopia, 2017/18 (n=268).

Variables		**Total %(N)**	**Substance use disorder**		
			Baseline N (%)	**First follow-up N (%)**	**2nd follow up N (%)**
Gender	Female	39·9 (107)	40(37·4)	35(32·7)	45(42·1)
	Male	60·1 (161)	94(58·4)	80(49·7)	84(52·2)
Age	18-24	34·7 (93)	42(45·2)	31(33·3)	38(40·9)

	25-34	32·5 (87)	35(40·2)	34(39·1)	35(40·2)
	35-44	13·4 (36)	23(63·9)	20(55·6)	22(61·1)
	45-54	10·1 (27)	17(63·0)	16(59·3)	18(66·7)
	55-64	9·3 (25)	17(68·0)	14(56·0)	16(64·0)
Occupation	Merchant	10·8(29)	23(79·3)	19(65·5)	20(69·0)
	Farmer	34·3(92)	57(62·0)	51(55·4)	57(62·0)
	Government employee	39·2(105)	37(35·2)	29(27·6)	33(31·4)
	Daily laborer	15·7(42)	17(40·5)	16(38·1)	19(45·2)
Education	No formal education	63·1(169)	68(40·2)	59(34·9)	62(36·7)
	Literate	36·9(99)	66(66·7)	56(56·6)	67(67·7)
Annual income in Birr	<14568	76·9(206)	108(52·4)	92(44·7)	104(50·5)
	≥14568	14·9(40)	16(40·0)	17(42·5)	18(45·0)
Marital	Single	36·2(97)	85(54·1)	76(48·4)	87(55·4)
	Married	58·6(157)	39(40·2)	32(33·0)	34(35·1)
	Divorced/widowed	5·2(14)	10(71·4)	7(50·0)	8(57·1)
Religion	Orthodox	30·6(82)	43(52·4)	27(32·9)	43(52·4)
	Muslim	61·6(165)	89(53·9)	86(52·1)	82(49·7)
	Protestant/others	7·8(21)	2(9·5)	2(9·5)	4(19·0)
Ethnicity	Amhara	22·0(59)	27(45·8)	17(28·8)	29(49·2)
	Oromo	61·6(165)	83(50·3)	82(49·7)	79(47·9)
	Tigre/Gurage	16·4(44)	24(54·5)	16(36·4)	21(47·7)
Family size	Less than five	67·5(181)	89(49·2)	76(42·0)	89(49·2)
	Five or greater	32·5(87)	45(51·7)	39(44·8)	40(46·0)
Residence	Rural	47·4(127)	72(56·7)	59(46·5)	68(53·5)
	Urban	52·6(141)	62(44·0)	56(39·7)	61(43·3)

Type of tuberculosis	Smear positive,	40·3(108)	54(50·0)	43(39·8)	46(42·6)
	Smear negative	32·5(87)	43(49·4)	39(44·8)	46(52·9)
	Extra pulmonary	27·2(73)	37(50·7)	33(45·2)	37(50·7)

3.4 Prevalence of alcohol use disorder and associated factors

Out of the total patients who participated in the study, 10.8% (n=29) of them had alcohol use disorder (AUD) at baseline, while it was 16.0% (n=43) at the first and second follow-up. The prevalence of AUD among male participants was 11.8% (n=19), 17.4% (28), 18.0% (29) at baseline, first and second follow-up respectively. Likewise, the prevalence of AUD among HIV positive patients was 10.0% (n=1), 30.0% (n=3), and 40.0% (n=4) at baseline, first and second follow-up respectively. Amongst patients with AUD, 11.0% (n=18), 18.6% (n=19), 13.6% (n=8) had mental distress at baseline, first and second follow-up respectively (See table 2).

After adjusting for potential confounders using a generalized linear mixed model, male gender, and being educated were associated with AUD. However, age, marital status, income, occupation, ethnicity, residence, HIV status, social support, khat use, and food insecurity were not associated with AUD.

The odds of having AUD among male patients was about two times higher than that of female participants (aOR=1.8, 95%CI=1.1, 3.1). Also, Islam religion followers were 60% times less likely to have AUD compared to Orthodox Christians (aOR=0.4, 95%CI=0.2, 0.8) (See table 3).

Table 2: Magnitude of alcohol use disorder among patients with tuberculosis in Southwest Ethiopia, 2017/2018 (n=268).

Variables		Alcohol use disorder		
		Baseline	First follow-up (end 2nd month)	Second follow-up (end of six months)
		N (%)	N (%)	N (%)
Gender	Male	19(11.8%)	28(17.4)	29(18.0)
	Female	10(9.3%)	15(14.0)	14(13.1)
Age	18-24	9(9.7%)	9(9.7)	12(12.9)
	25-34	3(3.4%)	14(16.1)	8(9.2)
	35-44	5(13.9%)	8(22.2)	10(27.8)
	45-54	4(14.8%)	7(25.9)	9(33.3)
	55-64	8(32.0%)	5(20.0)	4(16.0)
Annual income in Eth Birr	<14,568	22(10.7%)	35(17.0)	30(14.6)
	≥14,568	5(12.5%)	6(15.0)	9(22.5)
Marital status	Single	6(6.2%)	8(8.2)	11(11.3)
	Married	19(12.1%)	32(20.4)	30(19.1)
	Divorced/widow	4(28.6%)	3(21.4)	2(14.3)
Religion	Orthodox	22(26.8%)	12(14.6)	31(37.8)
	Muslim	6(3.6%)	31(18.8)	10(6.1)
	Protestant and others	1(4.8%)	0(0.0)	2(9.5)
Ethnicity	Amhara	14(23.7%)	6(10.2)	21(35.6)

	Oromo	4(2.4%)	29(17.6)	12(7.3)
	Tigre/Gurage	11(25.0%)	8(18.2)	10(22.7)
Occupation	Merchant	2(6.9%)	8(27.6)	4(13.8)
	Farmer	10(10.9%)	20(21.7)	14(15.2)
	Government Employee	13(12.4%)	12(11.4)	16(15.2)
	Daily laborer	4(9.5%)	3(7.1)	9(21.4)
Family size	Less than 5	19(10.5%)	29(16.0)	31(17.1)
	5 and more	10(11.5%)	14(16.1)	12(13.8)
Residence	Rural	13(10.2%)	23(18.1)	19(15.0)
	Urban	16(11.3%)	20(14.2)	24(17.0)
HIV	Positive	1(10.0%)	3(30.0)	4(40.0)
	Negative	28(10.9%)	40(15.5)	39(15.1)
Mental distress	No	11(10.6%)	24(14.5)	35(16.7)
	Yes	18(11.0)	19(18.6)	8(13.6)

Table 3: Factors associated with alcohol use disorder among patients with tuberculosis in Southwest Ethiopia, 2017/18 (n=268).

Variables		Intercept only (empty model)		Model1		Model2 (Model 1 including mental distress)		Model3 (Full model)		
		OR	P-Value	OR	P-Value	aOR	P-Value	aOR	P-Value	95%CI
Gender	Female	Reference								
	Male	-	-	-	-	-	-	1.8	**0.02**	**1.1, 3.1**
Age	18-24	Reference								
	25-34	-	-	-	-	-	-	0.7	0.30	0.4, 1.4
	35-44	-	-	-	-	-	-	1.0	0.93	0.5, 2.2
	45-54	-	-	-	-	-	-	1.7	0.20	0.8, 3.7
	55-64	-	-	-	-	-	-	0.8	0.69	0.3, 2.1
Marital status	Single							0.6	0.05	0.3, 1.0
	Married	Reference								
	Divorced/widowed	-	-	-	-	-	-	1.0	0.95	0.4, 2.5
Annual Income in Ethiopian birr	<14,568	Reference								
	>14,568	-	-	-	-	-	-	1.1	0.7	0.6, 2.1
Occupation	Merchant	Reference								
	Farmer	-	-	-	-	-	-	1.0	0.9	0.4, 2.3
	Government Employee	-	-	-	-	-	-	0.8	0.61	0.4, 1.8
	Day laborer	-	-	-	-	-	-	0.8	0.57	0.3, 1.9
Religion	Orthodox	Reference								
	Muslim		-	-	-	-	-	0.4	**0.006**	**0.2,0.8**
	Protestant/other		-	-	-	-	-	0.2	**0.010**	**0.1, 0.7**
Ethnicity	Amhara	-	-	-	-	-	-			
	Oromo	-	-	-	-	-	-	0.5	0.07	0.2, 1.1
	Tigre/G	-	-	-	-	-	-	1.7	0.12	0.9, 3.2

	uragie									
Education	No formal education	-	-	-	-	-	-			
	Primary/ secondary	-	-	-	-	-	-	2.8	**<0.001**	**1.6, 5.1**
	Tertiary	-	-	-	-	-	-	3.0	**0.002**	**1.5, 5.9**
Residence	Rural	-	-	-	-	-	-			
	Urban	-	-	-	-	-	-	0.9	0.60	0.5, 1.6
HIV	No	-	-	-	-	-	-			
	Yes	-	-	-	-	-	-	1.6	0.24	0.7, 3.8
khat	No									
	Yes	Reference	-	1.0	0.95	1.0	**0.95**	1.03	0.90	0.6, 1.7
Social support	Good	Reference								
	Moderate	-	-	-	-	0.94	0.83	0.6	0.1	0.3, 1.1
	Poor	-	-	-	-	1.10	0.83	0.8	0.52	0.5, 1.5
Food insecurity	No	Reference								
	Mild/moderate	-	-	-	-	1.03	0.91	1.2	0.64	0.6, 2.2
	Severe	-	-	-	-	0.92	0.75	1.4	0.25	0.8, 2.5
Time		1.3	0.08	1.25	0.08	1.23	0.10	1.3	0.10	0.96, 1.6
BIC		669.7		676.4		702.7		735.3		

3.5 Magnitude of khat use and associated factors

The prevalence of khat use was 39.2% (n=105) at baseline and after two months, and 37.3% (n=100) at the end of six months. Amongst khat users, 24.8% (n=26), 46.7% (n=49), and 37.0% (n=37) chewed khat daily at baseline, first follow up and second follow up respectively. Likewise, 55.2% (n=58), 46.7% (n=49) and 32.0% (n=32) chewed it 2-3 times per week. Males were found to use khat more than women at baseline (46.6% versus 28.0%, $p<0.05$), at second month (46.6% versus 28.0%, $p<0.001$), and sixth month (41.6% versus 30.8%). The majority of khat users were merchants (72.4%, n=21), followed by farmers (51.1%, n=47), and being educated till the tertiary level (53.6%, n=15) at baseline (see table 4). The majority of khat users (77.1%, n=81) believed that khat can reduce medication side effects or reduce symptoms of tuberculosis (96.2%, n=101).

After adjusting for potential confounders, being male (aOR=7, 95%CI= 2.2, 22.2) and AUD (aOR=20.0, 95%CI=6.0, 38.1) were positively associated with khat use. Being government employee (aOR=0.03, 95%CI=0.01, 0.2), daily laborer (aOR=0.1, 95%CI=0.01, 0.6), and protestant (aOR=0.01, 95%CI=0.01, 0.3) were negatively associated with khat use. However, age, income, and mental distress were not associated with khat use (See table 5).

Table 4: Magnitude of khat use among patients with TB in Southwest Ethiopia, 2017/18 (n=268).

Variables		Khat use		
		Baseline	First follow-up (end 2nd month)	Second follow-up (end of six months)
		N (%)	N (%)	N (%)
Gender	Male	75(46.6)	75(46.6)	67(41.6)
	Female	30(28.0)	30(28.0)	33(30.8)
Age	18-24	33(35.5)	30(32.3)	28(30.1)
	25-34	32(36.8)	30(34.5)	32(36.8)
	35-44	18(50.0)	20(55.6)	15(41.7)
	45-54	13(48.1)	13(48.1)	13(48.1)
	55-64	9(36.0)	12(48.0)	12(48.0)
Annual income in Eth Birr	<14,568	86(41.7)	85(41.3)	83(40.3)
	≥14,568	11(27.5)	15(37.5)	13(32.5)
Marital status	Single	33(34.0)	30(30.9)	26(26.8)
	Married	66(42.0)	70(44.6)	68(43.3)
	Divorced/widow	6(42.9)	5(35.7)	6(42.9)
Religion	Orthodox	21(25.6)	19(23.2)	20(24.4)
	Muslim	83(50.3)	84(50.9)	78(47.3)
	Protestant and others	1(4.8%)	2(9.5)	2(9.5)
Ethnicity	Amhara	13(22.0)	12(20.3)	12(20.3)
	Oromo	79(47.9)	79(47.9)	74(44.8)
	Tigre/Gurage	13(29.5)	14(31.8)	14(31.8)
Occupation	Merchant	21(72.4)	7(58.6)	17(58.6)
	Farmer	47(51.1)	47(51.1)	49(53.3)
	Government Employee	24(22.9)	26(24.8)	21(20.0)
	Daily laborer	13(31.0)	15(35.7)	13(31.0)
Education	No formal education	15(32.5)	56(33.1)	46(27.2)
	Primary/secondary	35(49.3)	34(47.9)	36(50.7)
	Tertiary	15(53.6)	15(53.6)	18(64.3)
Family size	Less than 5	70(38.7)	37(42.5)	66(36.5)
	5 and more	35(40.2)	8(37.6)	34(39.1)
Residence	Rural	59(46.5)	57(44.9)	55(43.3)
	Urban	46(32.6)	48(34.0)	45(31.9)
HIV	Positive	6(60.0%)	7(58.3)	8(42.1)
	Negative	99(38.4)	98(38.3)	92(36.9)
Mental distress	No	36(34.6)	55(33.1)	77(36.8)
	Yes	69(42.1)	50(49.0)	23(39.0)

Table 5: Factors associated with khat use among patients with tuberculosis in Southwest Ethiopia, 2017/18 (n=268).

Variables		Intercept only (empty model)			Model1 (Socio-demography)			Model2 (Model 1 including mental distress)			Model3 (Full model)		
		OR	P-Value	95% CI (upper, lower)	aOR	P-Value	95%CI (upper, lower)	aOR	P-Value	95%CI (upper, lower)	aOR	P-Value	95%CI (upper, lower)
Gender	Female	Ref.											
	Male	-	-		5.9	**0.01**	2.0,17.7	5.9	**0.01**	2.0,17.7	7.0	**0.001**	2.2,22.2
Age	18-24	Ref.											
	25-34	-	-		0.9	0.83	0.2,3.2	0.9	0.83	0.2,3.2	0.9	0.83	0.2.3.4
	35-44	-	-		1.8	0.50	0.3,10.1	1.8	0.49	0.3,10.1	2.0	0.47	0.3,12
	45-54	-	-		1.1	0.91	0.2,7.4	1.1	0.92	0.2,7.4	1.3	0.82	0.2,9.2
	55-64	-	-		0.5	0.41	0.1,3.0	0.5	0.42	0.1,3.0	0.5	0.47	0.1.3.5
Annual Income in Ethiopian birr	<14,568	Ref.											
	≥14,568	-	-		0.4	0.19	0.1,1.6	0.4	0.19	0.1,1.6	0.3	0.16	0.8,1.5
Occupation	Merchant	Ref.											
	Farmer	-	-		0.2	0.08	0.04,1.2	0.2	0.08	0.04,1.2	0.2	0.05	0.02,1.0
	Government Employee	-	-		0.04	**0.001**	0.01,0.3	0.04	**0.001**	0.01,0.3	0.03	**0.001**	0.01,0.2

	Day laborer	-	-		0.1	0.03	0.01,0.8	0.1	**0.02**	0.02,0.8	0.1	**0.01**	0.01,0.6
Religion	Orthodox	Ref.											
	Muslim		-		3.3	**0.04**	1.0,10.6	3.3	**0.04**	1.0,10.6	2.6	0.3	0.8,8.6
	Protestant		-		0.03	**0.01**	0.01,0.5	0.03	**0.01**	0.01,0.5	0.01	**0.01**	0.01,0.3
AUD	No	Ref.											
	Yes		-	-	-	-	-	-	-	-	20	**0.001**	6.0,38.1
Mental distress	No	Ref.											
	Yes		-	-	-	-	-	1.0	0.96	0.5,2.0	1.0	0.94	0.7,5.2
Time		0.9	0.48	0.7,1.2	0.8	0.2	0.6,1.1	0.8	0.25	0.6,1.2	0.9	0.47	0.6,1.3
BIC		819.0			815.2			821.9			815.7		

*Ref=Reference

3.6 Tobacco and cannabis use disorders

Tobacco and cannabis use was assessed but we could not get patients who were using these substances. So, we have no data regarding these substances.

3.7 The effect of substance use disorders on adherence to anti-TB medication

The intercept only model (model 0) showed a significant decrease in the percentage of adherence over time (BIC= 642.5). Adding alcohol and khat use disorders (model 1) improved model fit (BIC=627.6): Patients with khat use disorder had a significantly higher probability of non-adherence over time (OR= 4·2, 95%CI=2.1-8.6). The odds of non-adherence among patients with alcohol use disorder (AUDs) was 3.3 times that of patients free of AUDs (OR=3.3, 95%CI=1.6-6.6). Adding covariates did not substantially change this association (OR= 2.8, 95%CI=2.0-3.8) and further improved model fit (BIC= 642.2). In the final model khat use disorder (aOR= 3.8, 95%CI=1.8-8.0), or AUD (aOR= 3.2, 95%CI=1.6-6.6), being educated (aOR=4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI= 1.2-30.8) were associated with decreasing adherence (See table 6). Patients with khat use disorder were 3.8 times more likely to be non-adherent to anti-TB medications than patients without khat use disorder. Also, participants whose occupation was merchant were 6.1 times more likely to be non-adherent to anti-TB medications compared to daily laborers (See table 6).

Table 6: Predictors of non-adherence to anti TB medications among patients with tuberculosis in Southwest Ethiopia, 2017/2018 (n=268).

Variables		**Model 0 (Intercept only)**		**Model 1 (khat and alcohol including age and gender)**		**Full model**	
		OR	**95%CI**	**OR**	**95%CI**	**aOR**	**95%CI**
Khat use	No	Reference					
	Yes	-	-	4.2	2.1-8.6	**3.·8**	**1.8-8.0**
AUD	No	Reference					
	Yes	-	-	3.3	1.6-6.6	**3.2**	**1.6-6.6**
Age	18-24	Reference					
	25-34	-	-	1.2	0.4-3.2	-	-
	35-44	-	-	1.8	0.5-6.4	-	-
	45-54	-	-	0.9	0.2-4.0	-	-

	≥55	-	-	1.2	0.3-5.1	-	-
Gender	Female	Reference					
	Male	-	-	1.6	0.7-3.6	-	-
Education	No formal education	Reference					
	Read and write/literate	-	-	-	-	**4.4**	**1.7-11.3**
Social support	Good	Reference					
	moderate	-	-	-	-	0.5	0.2-1.2
	Poor	-	-	-	-	0.8	0.3-1.9
Occupation	Daily laborer	Reference					
	Farmer	-	-	-	-	2.1	0.5-8.0
	Government employee	-	-	-	-	2.1	0.6-8.0
	Merchant	-	-	-	-	**6.1**	**1.2-30.8**
Time T2		2.7	2.0-3.6	2.7	2.0-3.6	2.8	2.0-3.·8
BIC		642.5		672.6		642.2	

3.8 Quality of life and associated factors

Overall the quality of life was improved over time. At baseline, the highest mean score of quality life was observed on social functioning (60.1+SD30.7) and bodily pain (59.6+SD30.5) while the lowest was on role limitations due to physical health (43.3+SD43.1), and emotional (43.8+SD 44.9) problems. During the first follow up the highest mean of quality of life was observed on Bodily pain is missed (71.1+27.7) followed by physical functioning (64.8+29.1) and general health (63.1+27.9) while the lowest was energy/fatigue (63.1+27.9). At the end of follow up the highest mean score of quality of life was social functioning (77.1+28.5) followed by bodily pain (75.5+29.5) and physical functioning (72.3+31.3) but energy/fatigue (54.9+23.9) the lost one. The overall mean quality of life was improved during the follow-ups in all components (See table 7).

Physical functioning

After adjusting for potential confounders using linear regression, age group of 45-54 (β =-8.1, 95%= -15.1,-1.0) and 55-64 (β =-10.4, 95%= -17.9,-3.0), single (β =-6.7, =95%= -11.2,-2.2), and illiterate (β =-6.2=95%= -10.0,-2.3), interact with time to negatively predict physical functioning

score. But being widowed/divorced was positively affect physical functioning (β =, 14.8=95%= 6.5, 23.1). Also, being government employee interact with physical functioning (β =11.6, =95%= 5.2, 18.1). As mental distress increase by one unit, physical functioning (β= -32.2=95%= -33.9,-26.4) decease by about 32 times compared to patients free of mental distress. Likewise, for every one-unit increase in poor social support, physical functioninging (β=-8.6, 95%CI=-13.2,-3.9) decreases by about nine times compare to having good social support.

Role limitation due to physical functioning

But being widowed/divorced was positively affect role limitation due to physical functioning (β =15.7, =95%= 1.7, 29.8) scores. Also, being a government employee interacts with role limitation due to physical functioning (β =27.9=95%= 17.0, 38.7) over time. As mental distress increase by one unit role limitations due to physical functioning (β-11.4, =95%CI=-17.6,-5.1), decreases by about 11 times compared to patients free of mental distress. Likewise, for every one-unit increase in poor social support, quality of life in role limitation due to physical functioning (β=-9.0, 95%CI=-13.5,-4.4), decreases by about two, times compare to having good social support.

Role limitations due to personal or emotional problems and emotional well-being

After adjusting for potential confounders using linear regression being farmer (β=13.4, 95%CI=4.2, 22.7) and government employee (β=18.3, 95%CI=8.7, 28.0), a diagnosis of HIV positive (β=13.3, 95%CI=1.0, 25.7) and mental distress (β=-45.2, 95%CI=-50.8,-39.6) were associated with role limitation component of quality of life. Age group 55-64 (β=-5.1, 95%CI=-10.1,-0.002), poor (β=-13.5, 95%CI=-16.6,-10.5) and moderate (β=-6.1, 95%CI=-9.3-2.8) social support of QoL negatively affect emotional wellbeing of HQoL component. As mental distress increase by one unit, emotional wellbeing (β=-14.6, 9CI=-17.0,-12.1), decease by about 15 times.

Social functioning and Energy/fatigue

Also, being in the age group 55-64 (β=-12.9, 95%CI=-21.2,-4.6), poor (β=-12.3, 95%CI=-17.3,-7.3), moderate (β=-11.1, 95%CI=-16.4,-5.8) social support were negatively associated with the social functioning of QoL. However, being a government employee was positively associated with a social functioning (β=16.5, 95%CI=9.4, 23.7). Age group 45-54 (β =-8.3, 95%CI=-14.7,-1.9), mental distress (β =--3.4, 95%=-6.8,-0.03), and poor (β=-16.3, 95%CI=-20.4,-12.1) and moderate (β=-9.6, 95CI=-13.9,-5.2) social support, diagnosis of smear-negative TB (β=, -5.7,

95CI=-9.4,-1.9) were negatively affect energy/fatigue components of QoL while being farmer (β=10.6, 95CI=5.0,16.2), government employee (β=15.4, 95CI=9.6,21.2) and diagnosis of extra-pulmonary TB (β=5.1, 95CI= 1.1,9.0) were positively predict it.

Bodily pain and general health

Male gender (β=5.7, 95%CI=2.8, 10.4), being widowed/divorced (β=12.3, 95%CI=3.8, 20.7), and government employee (β=13.0, 95%CI=6.5, 19.6) were positively associated with body pain component of QoL. Likewise, government employees (β=5.8 95%CI=1.3, 10.3) and being farmers (β=12.8, 95%CI=8.2, 17.5) were positively associated with the general health component of QoL.

For every one-unit increase in poor social support, body pain (β=-5.3, 95%CI=-10.1,-0.9), general health (β=-10.3, 95%CI= -16.5,-10.0) decreases by about five and ten times respectively compare to having good social support. Likewise, as moderate social support increases by one unit, body pain (β=-9.0, 95%CI=-13.9,-4.2) decreases by nine compared to having good social support (See table 8).

Table 7: Change in quality of life among patients with tuberculosis in Southwest Ethiopia, 2017/2018 (n=268).

Component of quality of life	Baseline	First follow-up	Second follow-up
	Mean(SD)	Mean(SD)	Mean(SD)
Physical functioning	56.06(30.4)	64.8(29.1)	72.3(31.3)
Role limitations due to physical health problems	43.3(43.1)	56.3(44.7)	70.2(41.9)
Role limitations due to personal or emotional problems	43.8(44.9)	57.1(44.7)	68.5(42.2)
Emotional well-being	55.8(20.2)	59.2(19.5)	61.4(18.5)
Social functioning	60.1(30.7)	61.7(25.7)	77.1(28.5)
Energy/fatigue	45.1(24.7)	49.4(23.5)	54.9(23.9)
Bodily pain	59.6(30.5	71.1(27.7)	75.5(29.5)
General health perceptions	54.8(20.5)	63.1(27.9)	68.8(16.9)

Table 8: Factors associated with the component of quality of life among patients with tuberculosis in Southwest Ethiopia, 2017/2018 (n=268).

Variables		Physical functioning									Role limitations due to physical functioning								
		Model1			Model2			Full model			Model1			Model2			Full model		
		β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI
Current khat use	No	Ref.			Ref.			Ref.			Ref.								
	Yes	0.3	2.2	-4.1,4.7	3.3	1.9	-0.5,7.0	4.1	2.0	0.2,7.9	-1.1	3.2	-7.5,5.3	0.6	3.2	-5.7,6.8	5.4	3.3	-1.1,12.0
AUD	No	Ref																	
	Yes	-3.5	3.1	-9.7,2.6	-4.6	2.6	-9.7,0.6	-3.2	2.6	-8.2,1.9	-0.6	4.5	-9.4,8.2	-1.1	4.4	-9.8,7.6	0.8	4.4	-7.8,9.4
Gender	Male							5.8	1.9	**2.0,9.5**							2.4	3.2	-3.9,8.8
	Female	Ref			Ref.			Ref.			Ref.								
Age	18-24	Ref						Ref.			Ref.								
	25-34							4.0	2.4	-0.6,8.6							-0.8	4.0	-8.6,6.9
	35-44							-4.0	3.3	-10.5,2.5							-11.0	5.6	**-22.0,-0.1**
	45-54							-8.1	3.6	**-15.1,-1.0**							-6.3	6.1	-18.2,5.6
	55-64							-10.4	3.8	**-17.9,-3.0**							-11.0	6.4	-23.5,1.6
Marital status	Single							-6.7	2.3	**-11.2,-2.2**							-4.7	3.9	-12.3,2.9
	Married																		
	Widowed/divorced							14.8	4.2	**6.5,23.1**							15.7	7.1	**1.7,29.8**
Occupation	Merchant				Ref.			Ref.			Ref.								
	Farmer							9.6	3.2	**3.4,15.8**							11.1	5.3	0.7,21.5
	Government Employee							11.6	3.3	**5.2,18.1**							**27.9**	**5.5**	**17.0,38.7**
	Daily laborer							-5.5	3.6	-12.7,1.6							-6.0	6.1	-18.0,6.1
Education	Illiterate	Ref			Ref.			-6.2	1.9	**-10.0,-2.3**	Ref.						-2.5	3.3	-8.9,3.9
	literate																		
Type of TB	Smear positive	Ref.																	
	Smear negative							-1.7	2.1	-5.9,2.5							-6.2	3.6	-13.2,0.8
	Extrapulmonary							5.7	2.2	**1.3,10.1**							6.8	3.8	-0.6,14.2
HIV	Yes				6.4	4.2	-1.9,14.	7.3	4.2	-0.9,15.6				2.1	7.1	-11.9,16.	4.3	7.1	-9.6,18.2

							7									0			
	No																		
Mental distress	Yes				-32.2	1.9	**-35.9,-28.5**	-30.1	1.9	**-33.9,-26.4**				-18.0	3.2	**-24.2,-11.7**	-11.4	3.2	**-17.6,-5.1**
	No																		
Social support	poor				-8.6	2.4	**-13.2,-3.9**	-9.0	2.3	**-13.5,-4.4**				-2.5	4.0	**-10.4,5.3**	-4.2	3.9	**-11.9,3.4**
	moderate				-10.2	2.5	**-15.1,-5.3**	-8.6	2.4	**-13.4,-3.8**				-4.2	4.2	**-12.5,4.0**	-1.1	4.1	**-9.1,7.0**
	Good																		

Continuation of table 8

Variables		Role limitation-emotional									Energy fatigue								
		Model 1			Model 2			Full model			Model 1			Model 2			Full model		
		β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI
Current khat use	No	Ref						Ref			Ref						Ref		
	Yes	-6.4	3.3	-12.8,0.04	-2.5	2.8	-8.0,2.9	-1.8	2.9	-7.5,4.0	-2.4	1.8	-5.8,1.1	-1.3	1.7	-4.6,2.1	1.2	1.8	-2.3,4.7
AUD	No	Ref						Ref			Ref						Ref		
	Yes	2.3	4.5	-6.6,11.2	0.7	3.9	-7.0,8.3	1.1	3.9	-6.5,8.7	1.2	2.4	-3.6,6.0	0.9	2.4	-3.7,5.5	2.6	2.3	-2.0,7.2
Gender	Male							6.1	2.9	0.5,11.7							0.1	1.7	-3.3,3.5
	Female	Ref						Ref			Ref						Ref		
Age	18-24	Ref						Ref			Ref						Ref		
	25-34							-0.8	3.5	-7.7,6.1							1.1	2.1	-3.0,5.3
	35-44							-9.2	4.9	-18.9,0.5							-4.4	3.0	-10.2,1.5
	45-54							-7.1	5.4	-17.7,3.4							-8.3	3.3	**-14.7,-1.9**
	55-64							-8.5	5.7	-19.6,2.6							-5.3	3.4	-12.1,1.4
Marital status	Single							-5.9	3.4	-12.6,0.8							-2.4	2.1	-6.5,1.7
	Married																		
	Widowed/divorced							10.6	6.3	-1.9,23.0							3.1	3.8	-4.5,10.6
Occupation	Merchant	Ref						Ref			Ref						Ref		
	Farmer							13.4	4.7	**4.2,22.7**							10.6	2.9	**5.0,16.2**
	Government Employee							18.3	4.9	**8.7,28.0**							15.4	3.0	**9.6,21.2**
	Daily laborer							-4.9	5.4	-15.6,5.8							6.1	3.3	-0.4,12.5
Education	Illiterate	Ref						Ref			Ref						Ref		
	Literate							-4.1	2.9	-6.1,5.3							-0.2	1.8	-3.7,3.2
Type of TB	Smear positive	Ref						Ref									Ref		
	Smear negative							-0.3	3.2	-6.6,5.9							-5.7	1.9	**-9.4,-1.9**
	Extrapulmonary							7.5	3.3	1.0,14.1							5.1	2.0	**1.1,9.0**
HIV	Yes				10.5	6.2	-	13.3	6.3	**1.0,25.7**				4.2	3.8		5.2	3.8	-2.3,12.6

							1.7,22.6												
	No																		
Mental distress	Yes				-48.3	2.8	**-53.7,-48.2**	-45.2	2.8	**-50.8,-39.6**				-6.4	1.7	-9.8,-3.1	-3.4	1.7	**-6.8,-0.03**
	No																		
Social support	poor				3.4	3.5	-3.4,10.2	3.2	3.5	-3.6,10.0				-15.4	2.1	**-19.6,-11.3**	-16.3	2.1	**-20.4,-12.1**
	moderate				0.1,3.7		-7.1,7.3	2.1	3.6	-5.1,9.2				-11.1	2.2	**-15.5,-6.7**	-9.6	2.2	**-13.9,-5.2**
	Good																		

Continuation of table 8

Variables		Emotional wellbeing									Social functioning								
		Model 1			Model 2			Full model			Model 1			Model 2			Full model		
		β	SE	95%CI	β	SE	P value	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI
Current khat use	No	Ref						Ref			Ref						Ref		
	Yes	-3.4	1.4	-6.2,-0.6	-1.6	1.3	-4.1,0.8	-1.4	1.3	-4.0,1.2	-4.0	2.1	-8.2,0.2	-3.0	2.1	-7.1,1.1	-0.7	2.2	-5.0,3.6
AUD	No	Ref						Ref			Ref						Ref		
	Yes	-01.4	2.0	-4.3,3.4	-0.7	1.7	-4.1,2.7	-0.4	1.8	-3.9,3.0	-1.4	2.9	-7.2,4.4	-1.6	2.9	-7.3,4.1	-1.3	2.9	-6.9,4.4
Gender	Male							1.7	1.2	-0.9,4.2							1.8	2.1	-2.4,6.0
	Female	Ref						Ref			Ref						Ref		
Age	18-24	Ref						Ref			Ref						Ref		
	25-34							2.7	1.6	-0.5,5.8							-1.3	2.6	-6.4,3.8
	35-44							2.6	2.2	-1.9,7.0							-1.0	3.7	-8.2,6.2
	45-54							-0.7	2.4	-5.5,4.1							-5.6	4.0	-13.5,2.3
	55-64							-5.1	2.6	**-10.1,-0.002**							-12.9	4.2	**-21.2,-4.6**
Marital status	Single							-2.3	1.6	-5.4,0.7							-6.4	2.5	**-11.4,-1.4**
	Married																		
	Widowed/divorced							2.8	2.9	-2.8,8.5							11.2	4.7	**2.0,20.5**
Occupation	Merchant	Ref						Ref			Ref						Ref		
	Farmer							1.9	2.1	-2.3,6.1							7.2	3.5	0.4,14.1
	Government Employee							4.9	2.2	0.6,9.3							16.5	3.6	**9.4,23.7**
	Daily laborer							-4.7	2.5	-9.5,0.2							-4.0	4.0	-11.9,3.9
Education	Illiterate	Ref						Ref			Ref						Ref		
	Literate							-1.4	1.3	-4.0,1.2							-1.2	2.2	-5.5,3.0
Type of TB	Smear positive	Ref						Ref									Ref		
	Smear negative							2.5	1.4	-0.3,5.3							-3.4	2.4	-8.0,1.2
	Extrapulmonary							2.3	1.5	-0.7,5.3							0.6	2.5	-4.3,5.4
HIV	Yes				2.8	2.8	-2.6,8.3	2.4	2.9	-3.2,8.0				1.1	4.6	-8.0,10.2	-0.8	4.7	-10.0,8.3
	No																		
Mental distress	Yes				-14.6	1.3	**-17.0,-12.1**	-13.8	1.3	**-16.3,-11.3**				-6.1	2.1	**-10.2,-2.0**	-2.9	2.1	-7.0,1.3
	No																		
Social support	poor				-14.0	1.6	**-17.1,-10.9**	-13.5	1.6	**-16.6,-10.5**				-12.1	2.6	**-17.2,-6.9**	-12.3	2.6	**-17.3,-7.3**
	moderate				-7.4	1.7	**-10.7,-4.2**	-6.1	1.7	**-9.3-2.8**				-13.5	2.7	**-18.9,-8.1**	-11.1	2.7	**-16.4,-5.8**
	Good																		

Continuation of table 8

Variables		Bodily pain									General health								
		Model 1			Model2			Full model			Model 1			Model2			Full model		
		β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI	β	SE	95%CI
Current khat use	No	Ref						Ref			Ref						Ref		
	Yes	-3.8	2.2	-8.1,0.4	-1.5	1.9	-5.2,2.3	-0.6	2.0	-4.5,3.4	-3.3	1.4	-6.1,-0.6	-2.6	1.4	-5.3,0.1	-0.6	1.4	-3.4,2.2
AUD	No	Ref						Ref			Ref						Ref		
	Yes	2.9	3.0	-3.0, 8.8	1.7	2.6	-3.5,6.9	1.8	2.6	-3.4,6.9	-1.3	1.9	-5.1,2.3	-1.4	1.9	-5.1,2.3	-0.7	1.9	-4.4,3.0
Gender	Male							5.7	1.9	**2.8,10.4**							3.6	1.4	0.8,6.3
	Female	Ref						Re			Ref						Ref		
Age	18-24	Ref						Ref			Ref						Ref		
	25-34							3.0	2.3	-1.7,7.6							2.0	1.7	-1.3,5.4
	35-44							2.1	3.4	-4.5,8.6							-1.2	2.4	-5.9,3.5
	45-54							-1.4	3.6	-8.6,5.7							2.6	2.6	-2.5,7.7
	55-64							-8.0	3.8	-15.2,-0.4							-3.6	2.8	-9.0,1.9
Marital	Single							-2.8	2.3	-7.4,1.7							-0.1	1.7	-3.3,3.2
	Married																0.4	3.1	-5.6,6.4
	Widowed/divorced							12.3	4.3	**3.8,20.7**									
Occupation	Merchant	Ref						Ref			Ref						Ref		
	Farmer							6.1	3.2	-0.1,12.4							5.8	2.3	**1.3,10.3**
	Government Employee							13.0	3.3	**6.5,19.6**							12.8	2.4	**8.2,17.5**
	Daily laborer							-5.6	3.7	-12.9,1.6							4.5	2.6	-0.6,9.7
Education	Illiterate	Ref						Ref			Ref						Ref		
	Literate							-2.0	2.0	-4.9,2.8							-1.4	1.4	-4.2,1.4
Type of TB	Smear positive	Ref						Ref									Ref		
	Smear negative							-3.0	2.2	-7.1,1.3							-0.6	1.5	-3.6,2.4
	Extrapulmonary							0.6	2.3	-3.8,5.1							1.7	1.6	-1.4,4.9
HIV	Yes				8.6	4.2	0.2,16.9	7.0	4.3	-1.3,15.4				0.5	3.0	-5.1,6.7	1.5	3.0	-4.5,7.5
	No																		
Mental distress	Yes				-27.6	1.9	-31.4,-23.9	-25.4	1.9	**-29.1,-21.6**				-3.1	1.4	-5.8,-0.4	-1.3	1.4	-4.0,1.4
	No																		
Social support	poor				-5.0	2.4	-9.7,-0.3	-5.3	2.5	**-10.1,-0.9**				-12.4	1.7	-15.7,-9.1	-10.3	1.8	**-16.5,-10.0**
	moderate				-10.5	2.5	-15.4,-5.6	-9.0	2.3	**-13.9,-4.2**				-11.3	1.6	-14.8,-7.9	-13.2	1.7	**-13.7,-6.8**
	Good																		

*Ref= Reference

3.9 Magnitude of mental distress and associated factors

The prevalence of mental distress at baseline, the second month and end of the sixth month was 61.2 % (n=164), 38.1 % (n=10.2), 22.0% (n=59) respectively. Out of patients with mental distress, the majority of them were in the age group of 55-64 years at baseline (76.0%) and first follow-up (56.0) while it was 32.0% in the second follow-up. Also, about 3/4th (77.3%) of patients with mental distress were suffering from severe food insecurity at baseline but it dropped to 64.6% and 46.0% in the second and sixth months respectively. Of patients with mental distress, 71.4% of them were either divorced or widowed. The prevalence of alcohol use disorder among patients with mental distress was 62.1%, 44.2%, and 18.6% at baseline, first follow up and second follow up respectively, while 65.7%, 47.6, 23.0% of them were using khat at baseline, first, and second follow-up respectively (See table 9).

After adjusting for potential confounder using a generalized linear mixed model, severe food insecurity (aOR=4.7, 95%CI=2.4, 9.4), and being a government employee (aOR=0.3, 95%CI=0.1, 0.9) were associated with mental distress (See table 10).

Table 9: Magnitude of mental distress at the three-time points among patients with tuberculosis in Southwest Ethiopia, 2017/18 (n=268).

Variables		Mental distress					
		Baseline		First follow-up		Second follow-up	
		Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)
Gender	Male	104(64.6)	57(35.4)	66(41.0)	95(59.0)	45(28.0)	116(72.0)
	Female	60(56.1)	47(43.9)	36(33.6)	71(66.4)	14(13.1)	93(86.9)
Age	18-24	47(50.5)	46(49.5)	26(28.0)	67(72.0)	18(19.4)	75(80.6)
	25-34	52(59.8)	35(40.2)	33(37.9)	54(62.1)	17(19.5)	70(80.5)
	35-44	26(72.2)	10(27.8)	16(44.4)	20(55.6)	10(27.8)	26(72.2)
	45-54	20(74.1)	7(25.9)	13(48.1)	14(51.9)	6(22.2)	21(77.8)
	55-64	19(76.0)	6(24.0)	14(56.0)	11(44.0)	8(32.0)	17(68.0)
Occupation	Merchant	24(82.8)	5(17.2)	12(41.4)	17(58.6)	7(24.1)	22(75.9)
	Farmer	68(73.9)	24(26.1)	45(48.9)	47(51.1)	23(25.0)	69(75.0)
	Government Employee	43(41.0)	62(59.0)	23(21.9)	82(78.1)	14(13.3)	91(86.7)
	Daily laborer	29(69.0)	13(31.0)	22(52.4)	20(47.6)	15(35.7)	27(64.3)

Education	No formal education	55(57.3)	41(42.7)	35(36.5)	61(63.5)	21(21.9)	75(78.1)
	Educated	109(63.4)	63(36.6)	67(39.0)	105(61.0)	38(22.1)	134(77.9)
Marital status	Single	48(49.5)	49(50.5)	26(26.8)	71(73.2)	20(20.6)	77(79.4)
	Married	106(67.5)	51(32.5)	71(45.2)	86(54.8)	35(22.3)	122(77.7)
	Divorced/widow	10(71.4)	4(28.6)	5(35.7)	9(64.3)	4(28.6)	10(71.4)
Family size	Less than 5	103(56.9)	78(43.1)	74(40.9)	107(59.1)	44(24.3)	137(75.7)
	5 and more	61(70.1)	26(29.9)	28(32.2)	59(67.8)	15(17.2)	72(82.8)
Residence	Rural	93(73.2)	34(26.8)	48(37.8)	79(62.2)	24(18.9)	103(81.1)
	Urban	71(50.4)	70(49.6)	54(38.3)	87(61.7)	35(24.8)	106(75.2)
Type of tuberculosis	Smear positive	63(58.3)	45(41.7)	37(34.3)	71(65.7)	18(16.7)	90(83.3)
	Smear negative	62(71.3)	25(28.7)	41(47.1)	46(52.9)	27(31.0)	60(69.0)
	Extra pulmonary	39(53.4)	34(46.6)	24(32.9)	49(67.1)	14(19.2)	59(80.8)
Social support	poor	49(52.7)	44(47.3)	37(43.5)	48(56.5)	37(26.4)	103(73.6)
	moderate	77(68.1)	36(31.9)	45(40.5)	66(59.5)	19(25.7)	55(74.3)
	Good	38(61.3)	24(38.7)	20(27.8)	52(72.2)	3(5.6)	51(94.4)
Food insecurity	No	69(50.7)	67(49.3)	36(24.8)	109(75.2)	18(11.1)	144(88.9)
	Mild/moderate	37(64.9)	20(35.1)	13(31.7)	28(68.3)	12(27.9)	31(72.1)
	Severe	58(77.3)	17(22.7)	53(64.6)	29(35.4)	29(46.0)	34(54.0)
AUD	No	146(61.1)	93(38.9)	83(36.9)	142(63.1)	51(22.7)	174(77.3)
	Yes	18(62.1)	11(37.9)	19(44.2)	24(55.8)	8(18.6)	35(81.4)
Khat use	No	95(58.3)	68(41.7)	52(31.9)	111(68.1)	36(21.4)	132(78.6)
	Yes	69(65.7)	36(34.3)	50(47.6)	55(52.4)	23(23.0)	77(77.0)

Table 10: Factors affecting mental distress among patients with tuberculosis in Southwest Ethiopia, 2017/2018 (n=268).

Variables	Intercept only (Model0)				Model 1			Model 2			Full model		
	cOR		95%CI		aOR	95%CI		aOR	95%CI		aOR		
			Upper	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Gender	Female	Ref.			Ref			Ref			Ref		
	Male	-	-	-	-	-	-	-	-	-	1.8	0.9	3.3
Age	18-24	Ref			Ref			Ref			Ref		
	25-34	-	-	-	-	-	-	-	-	-	0.9	0.5	2.1
	35-44	-	-	-	-	-	-	-	-	-	1.5	0.5	4.4
	45-54	-	-	-	-	-	-	-	-	-	1.2	0.4	3.9
	55-64	-	-	-	-	-	-	-	-	-	1.8	0.5	6.3
Occupation	Merchant	Ref			Ref			Ref			Ref		
	Farmer	-	-	-	-	-	-	-	-	-	0.9	0.3	2.6
	Government Employee	-	-	-	-	-	-	-	-	-	**0.3**	**0.1**	**0.9**
	Daily laborer	-	-	-	-	-	-	-	-	-	0.8	0.3	2.8
Annual income	<14568 Eth Birr	Ref			Ref			Ref			Ref		
	≥14568 Eth Birr	-	-	-	-	-	-	-	-	-	1.9	0.8	4.3
Marital status	Married	Ref						Ref			Ref		
	Single	-	-	-	-	-	-	-	-	-	0.8	0.4	1.7

	Widowed/ divorced	-	-	-	-	-	-	-	-	-	0.9	0.2	3.5
Type of TB	Smear positive	Ref			Ref								
	Smear negative	-	-	-	-	-	-	-	-	-	1.8	0.9	3.6
	Extra pulmonary	-	-	-	-	-	-	-	-	-	0.9	0.4	1.9
AUD	No	Ref			Ref			Ref			Ref		
	Yes	-	-	-	-	-	-	1.2	0.7	2.2	1.0	0.6	2.0
Khat use	No	Ref			Ref			Ref					
	Yes	-	-	-	-	-	-	1.5	0.9	2.6	1.1	0.6	1.9
Social support	Good	Ref			Ref			Ref			Ref		
	moderate	-	-	-	-	-	-	-	-	-	1.3	0.7	2.4
	poor	-	-	-	-	-	-	-	-	-	1.2	0.6	2.2
Food insecurity	No	Ref			Ref								
	Mild/Moderate	-	-	-	2.0	1.0	3.9	2.0	1.0	3.8	1.7	0.9	3.3
	Severe	-	-	-	7.3	3.7	14.2	7.0	3.6	13.7	**4.7**	**2.4**	**9.4**
BIC		912.3			886.6			896.4			955.3		

*Ref=Reference

3.10 Social support and its association with adherence to anti-TB medications

Out of the total participants, 42.9% (n=115) and 33.6% (n=90) of them had poor and moderate social support respectively, while 23.5% (n=63) had strong social support. The prevalence of poor social support at baseline, first and second follow-up was 34.7%, 41.4%, and 52.4% respectively, while strong social support was 23.1%, 26.9%, and 20.1% respectively (see figur1).

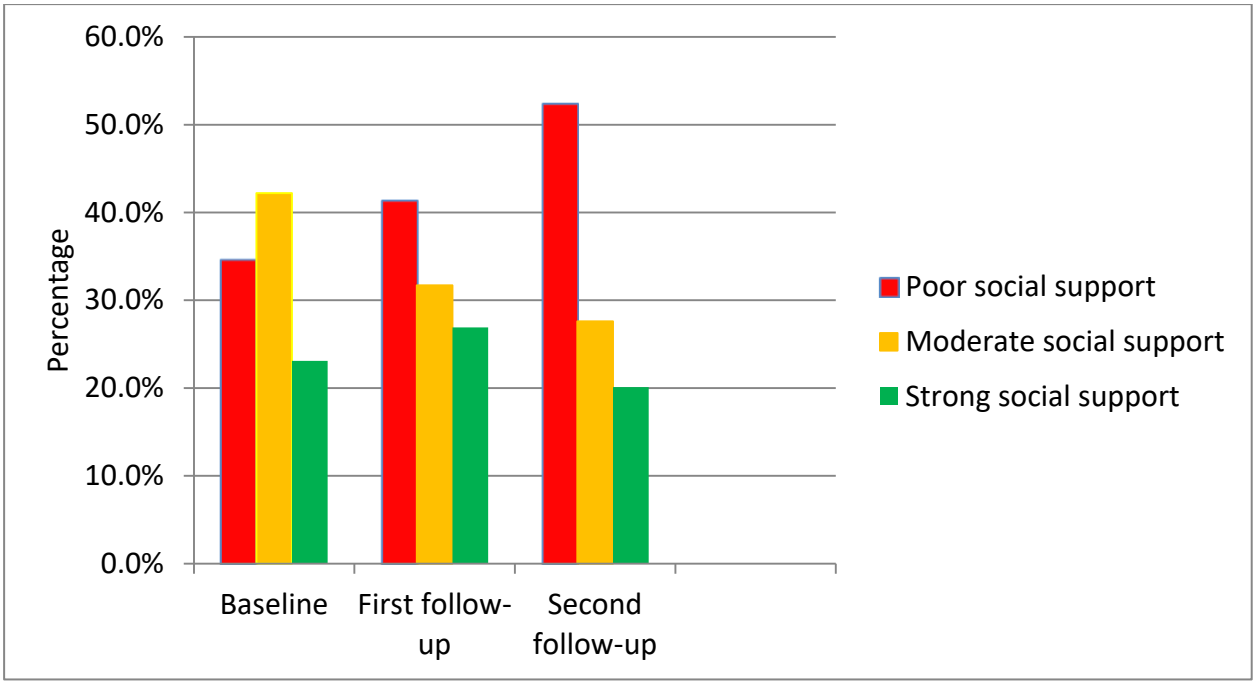

Figure 2: Magnitude of social support at different time interval among patients with TB in Southwest Ethiopia

Among patients with poor social support, 44.7% (n=120) were not adherent to anti-Tb medications. Also, the prevalence of non-adherence among patients with moderate social support was 31.0% (n=83). While 42.7% of patients with poor social support had mental distress, only 19.1% of those with strong social support found to have mental distress. Similarly, 44.0% of patients with poor social support use khat, while 24.0% of them had alcohol use disorder (See table2). At baseline (28.0%, n=30) and second follow-up (29.0%, n=31) about 1/3 of females had strong social support, while 43.0% (46) of them had poor social support as a first follow-up. The prevalence of poor social support among single patients was 36.1% (n=35), while it was 63.1% (n=9) among those who were divorced/ widowed. Among patients with a family member of less than five, the prevalence of poor social support was 70.1% (n=188), whereas it was 29.8% (n=80) among those who had five or more than a family member. While 66.8% (n=179) of patients who were living in an urban area had poor social support, only 33.2% (n=89) who were living in a rural area had poor social support.

Social support was not associated with adherence to anti-TB medications, after controlling for factors such as khat use, alcohol use disorder, and mental distress (Model2), however, model fit was improved (BIC=658.7). After adjusting for all covariates in the final model, the association between social support and adherence to anti-TB medication remained unchanged but the model fit was further improved (BIC=607.0). In the final model, khat use (aOR=3.0, 95%CI=1.7,7.4), alcohol use disorder (aOR=3.1, 95%CI=1.5,6.3), and being educated (aOR=4.3, 95%CI=1.6, 12.9) were associated with non-adherence to anti-TB medications (See table 11).

Table 11: The association between social support and anti-TB medication adherence among patients with tuberculosis in Southwest Ethiopia, 2017/2018 (n=268).

Variables		**Model 0(Intercept only)**		**Model 1**		**Model2**		**Full model**	
		OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**aOR**	**95%CI**
Social support	Good	Reference							
	moderate	-	-	0.5	2.2, 4.1	0.5	0.2,1.2	0.4	0.2,1.1
	Poor	-	-	0.8	0.02,0.1	0.8	0.4,1.9	0.8	0.4,2.2
Khat UD	No	Reference							
	Yes	-	-			**4.6**	**2.3,9.3**	3.0	**1.7,7.4**
AUD	No	Reference							
	Yes	-	-			**3.3**	**1.7,6.6**	3.1	**1.5,6.3**
Mental distress	No	Reference							
	Yes	-	-			0.8	0.4,1.6	0.7	0.4,1.6
Age	18-24	Reference				-	-		
	25-34	-	-			-	-	1.1	0.3, 2.9
	35-44	-	-			-	-	1.6	0.3, 5.1
	45-54	-	-			-	-	0.9	0.2, 4.3
	≥55	-	-					1.1	0.2, 4.8

Gender	Female	Reference							
	Male	-	-		-	-	-	2.4	0.8, 4.7
Education	No formal education	Reference							
	Read and write/literate	-	-	-	-	-	-	4.3	**1.6, 12.9**
Occupation	Merchant	Reference							
	Farmer	-	-	-	-	-	-	0.3	0.9, 1.3
	Government employee	-	-	-	-	-	-	0.4	0.8, 1.3
	Daily laborer	-	-	-	-	-	-	0.4	0.1, 1.2
Time T2		3.0	2.2, 4.1	2.9	2.2, 4.1	2.5	1.8,3.5	2.7	1.8, 3.8
BIC		672.0		680.9		658.7		607.0	

3.11 Food insecurity and associated factors

The total prevalence of food insecurity at baseline, second month and six month was 49.3 %(n=132), 45.9 %(n=123), and 39.6 %(n=106) respectively. The prevalence of severe food insecurity was 28.0% at baseline but declined to 23.5% second follow-up (See figure 2).

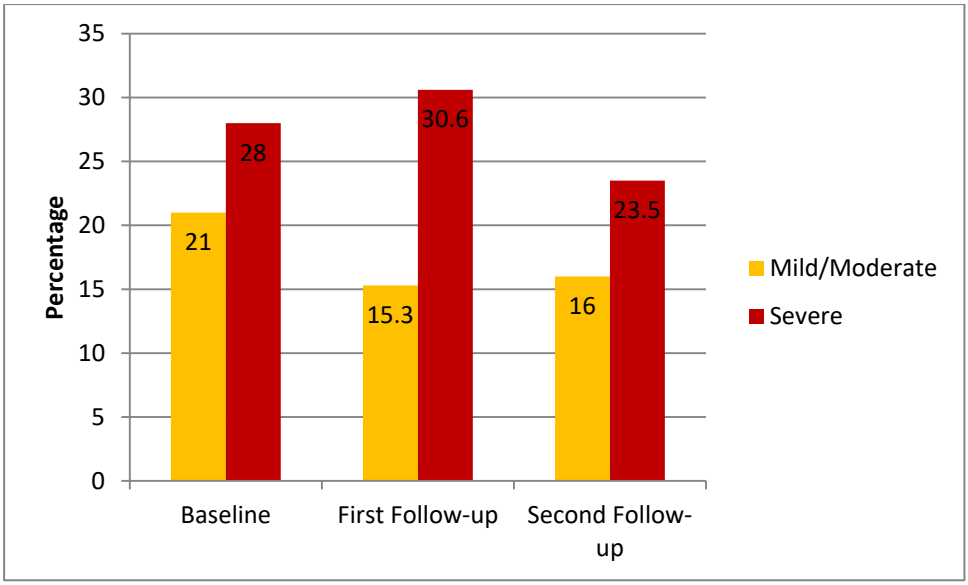

Figure 3: Magnitude of food insecurity at different time interval among patients with TB in Southwest Ethiopia

The prevalence of severe food insecurity among female participants was higher than their counterparts at baseline (31.8%vs25.5%), and at first, follow up (34.6%vs28.0%). The prevalence of severe food insecurity among daily laborers was 59.5%, while it was 12.4% among government employees at baseline. Half of divorced/widowed patients (50.0%, n=7) reported severe food insecurity at baseline which declined to 21.4% at the end of six months. At baseline, about a quarter of patients who chew khat (25.7%, n=27) and with alcohol use disorder (24.1%, n=7) reported mild/moderate food insecurity. Out of the total participants with food insecurity 40.7% and 36.0%, of them were in the age group of 45-54 and 55-64 respectively (See table 12).

After adjusting for potential confounders using generalized linear mixed model male gender (aOR=0.407, 95%CI=0.40, 0.414), being farmer (aOR=-0.82, 95%CI=-0.84, -0.81), being government employee (aOR=-1.0, 95%CI=-1.01, -0.99), being daily laborer (aOR=-1.6, 95%CI=-1.60, -1.58), mental distress (aOR=-0.84, 95%CI=-0.85, -0.83) being in the age group of 35-44 (aOR=-0.11, 95%CI=--0.122, -0.10), being in the age group of 45-54 (aOR=0.22, 95%CI=0.20, 0.23), having more than five family member (aOR=-0.35, 95%CI=-0.353, -0.34), having annual income less than 14568 Eth Birr (aOR=1.1, 95%CI=1.11, 1.12), being widowed/divorced (aOR=0.09, 95%CI=0.08, 0.11), and khat use (aOR=-0.84, 95%CI=-0.85, -0.83) were associated with food insecurity. The odds of having severe food insecurity were 60% times less likely among male patients compared to their counterparts (aOR=0.407, 95%CI=0.40, 0.414). Also, having family members five or more was 65% times less likely to have food insecurity compared to those who had family members less than 5 (aOR=-0.35, 95%CI=-0.353, -0.340). However, the odds of having food insecurity among patients who earn an annual income of less than 14568 Eth Birr was about one times higher than that of those who earn an annual income of more than 14568 Eth Birr (aOR=1.1, 95%CI=1.11, 1.12) (see table 13).

Table 12: Magnitude of food insecurity among patients with tuberculosis in Southwest Ethiopia, 2017/2018 (n=268).

Variables		Food insecurity							
		Baseline		First follow-up			Second follow-up		
		Mild/moderate insecurity N (%)	Severe insecurity N (%)	Food secure	Mild/moderate insecurity N (%)	Severe insecurity N (%)	Food secure	Mild/moderate insecurity N (%)	Severe insecurity N (%)
Gender	Male	33(20.5)	41(25.5)	94(58.4)	22(13.7)	45(28.0)	95(59.0)	27(16.8)	39(24.2)
	Female	24(22.4)	34(31.8)	51(47.7)	19(17.8)	37(34.6)	67(62.6)	16(15.0)	24(22.4)
Age	18-24	23(24.7)	21(22.6)	57(61.3)	12(12.9)	24(25.8)	60(64.5)	15(16.1)	18(19.4)
	25-34	17(19.5)	23(26.4)	44(50.6)	16(18.4)	27(31.0)	56(64.4)	14(16.1)	17(19.5)
	35-44	10(27.8)	11(30.6)	18(50.0)	7(19.4)	11(30.6)	18(50.0)	9(25.0)	9(25.0)
	45-54	4(14.8)	11(40.7)	13(48.1)	3(11.1)	11(40.7)	15(55.6)	2(7.4)	10(37.0)

	55-64	3(12.0)	9(36.0)	13(52.0)	3(12.0)	9(36.0)	13(52.0)	3(12.0)	9(36.0)
Occupation	Merchant	8(27.6)	9(31.0)	14(48.3)	6(20.7)	9(31.0)	14(48.3)	7(24.1)	8(27.6)
	Farmer	24(26.1)	28(30.4)	46(50.0)	16(17.4)	30(32.6)	54(58.7)	15(16.3)	23(25.0)
	Government Employee	19(18.1)	13(12.4)	74(70.5)	12(11.4)	19(18.1)	78(74.3)	16(15.2)	11(10.5)
	Daily laborer	6(14.3)	25(59.5)	11(26.2)	7(16.7)	24(57.1)	16(38.1)	5(11.9)	21(50.0)
Education	No formal education	16(16.7)	28(29.2)	50(52.1)	17(17.7)	29(30.2)	59(61.5)	16(16.7)	21(21.9)
	Educated	41(23.8)	47(27.3)	95(55.2)	24(14.0)	53(30.8)	103(59.9)	27(15.7)	42(24.4)
Marital status	Single	18(18.6)	24(24.7)	58(59.8)	11(11.3)	28(28.9)	61(62.9)	14(14.4)	22(22.7)
	Married	36(22.9)	44(28.0)	81(51.6)	27(17.2)	49(31.2)	92(58.6)	27(17.2)	38(24.2)
	Divorced/ widow	3(21.4)	7(50.0)	6(42.9)	3(21.4)	5(35.7)	9(64.3)	2(14.3)	3(21.4)
Religion	Orthodox	14(17.1)	14(17.1)	54(65.9)	9(11.0)	19(23.2)	58(70.7)	11(13.4)	13(15.9)
	Muslim	40(24.2)	57(34.5)	74(44.8)	31(18.8)	60(36.4)	89(53.9)	29(17.6)	47(28.5)
	Protestant and others	3(14.3)	4(19.0)	17(81.0)	1(4.8)	3(14.3)	15(71.4)	3(14.3)	3(14.3)
Ethnicity	Amhara	7(11.9)	14(23.7)	35(59.3)	7(11.9)	17(28.8)	39(66.1)	7(11.9)	13(22.0)
	Oromo	40(24.2)	55(33.3)	80(48.5)	28(17.0)	57(34.5)	91(55.2)	29(17.6)	45(27.3)
	Tigre/Gurage	10(22.7)	6(13.6)	30(68.2)	6(13.6)	8(18.2)	32(72.7)	7(15.9)	5(11.4)
Family size	Less than 5	33(18.2)	51(28.2)	55(54.7)	25(13.8 %)	57(31.5)	112(61.9)	23(12.7)	46(25.4)
	5 and more	24(27.6)	24(27.6)	46(52.9)	16(18.4)	25(28.7)	50(57.5)	20(23.0)	17(19.5)
Residence	Rural	35(27.6)	32(25.2)	70(55.1)	24(18.9)	33(26.0)	77(60.6)	23(18.1)	27(21.3)
	Urban	22(15.6)	43(30.5)	75(53.2)	17(12.1)	49(34.8)	85(60.3)	20(14.2)	36(25.5)
Type of TB	Smear positive	24(22.2)	26(24.1)	61(56.5)	13(12.0)	34(31.5)	67(62.0)	18(16.7)	23(21.3)
	Smear negative	15(17.2)	34(39.1)	41(47.1)	13(14.9)	33(37.9)	49(56.3)	10(11.5)	28(32.2)
	Extra pulmonary	18(24.7)	15(20.5)	43(58.9)	15(20.5)	15(20.5)	46(63.0)	15(20.5)	12(16.4)
HIV	Seronegative	55(21.3)	73(28.3)	140(54.3)	39(15.1)	79(30.6)	157(60.9)	39(15.1)	62(24.0)
	Seropositive	2(20.0)	2(20.0)	5(50.0)	2(20.0)	3(30.0)	5(50.0)	4(40.0)	1(10.0)
Social support	poor	14(15.1)	31(33.3)	58(52.3)	9(8.1)	44(39.6)	79(56.4)	17(12.1)	44(31.4)
	moderate	31(27.4)	36(31.9)	38(44.7)	20(23.5)	27(31.8)	41(55.4)	16(21.6)	17(23.0)
	Good	12(19.4)	8(12.9)	49(68.1)	12(16.7)	11(15.3)	42(77.8)	10(18.5)	2(3.7)
Khat use	No	30(18.4)	49(30.1)	94(57.7)	24(14.7)	45(27.6)	106(63.1)	25(14.9)	37(22.0)
	Yes	27(25.7)	26(24.8)	51(48.6)	17(16.2)	37(35.2)	56(56.0)	18(18.0)	26(26.0)
AUD	No	50(20.9)	69(28.9)	120(53.3)	36(16.0)	69(30.7)	137(60.9)	35(15.6)	53(23.6)
	Yes	7(24.1)	20.7(20.7)	25(58.1)	5(11.6)	13(11.6)	25(58.1)	8(18.6)	10(23.3)

Table 13: Factors associated with food insecurity among patients with tuberculosis in Southwest Ethiopia, 2017/18.

Variables		Model 1		Model 2		Model3		Full model	
		OR	95%CI	OR	95%CI	OR	95%CI	aOR	95%CI
Income	<14568 Eth Birr	1.0	1.0, 1.1	0.72	0.70, 0.73	0.91	0.89, 0.92	1.1	1.11, 1.12
	>14568 Eth Birr	Ref.							
Family size	Less than five	Ref.							
	Five and more	-0.21	-0.22, -.0.20	-0.24	-0.25, -0.23	1.10	1.08, 1.12	-0.35	-0.353, -0.340
Gender	Female	Ref.							
	Male			0.3	0.29,0.30	0.397	0.39, 0.40	0.407	0.40, 0.414
Age	18-24	Ref.							
	25-34			-0.12	-0.13, -0.10	0.02	0.003, .03	0.01	-0.002, 0.03
	35-44			-0.23	-0.25, -0.22	-0.11	-0.12, -0.09	-0.11	-0.122, -0.10
	45-54			0.11	0.10, 0.13	0.22	0.21, .24	0.22	0.20, 0.23
	≥55	Ref.		-0.06	-0.07, -0.04	0.01	-.01,0.02	0.004	-0.01, 0. 02
Marital status	Married	Ref.							
	Single			-0.11	-0.12, -0.09	-0.01	-0.02, 0.010	-0.01	-0.02, 0.01
	Widowed/divo			-0.01	-0.03, 0.01	0.09	0.07,	0.09	0.08,

	rced						0.11		0.11
Occupation	Merchant	Ref.							
	Farmer			-0.82	-0.83, -.80	-0.81	-0.82, -0.79	-0.82	-0.84, -0.81
	Government employee			-1.03	-1.04, -1.02	-0.99	-1.00, -0.98	-1.001	-1.01, -0.99
	Daily laborer			-1.81	-1.82, -1.20	-1.60	-1.61, -1.59	-1.60	-1.60, -1.58
Social support	Strong	Ref.							
	Moderate					-0.74	-0.75, -0.74	-0.74	-0.75, -0.73
	Poor					0.1	0.09, 0.11	0.10	0.095, 0.11
AUDS	no	Ref.							
	Yes					0.23	0.22, 0.24	0.23	0.22, 0.24
Khat use	No	Ref.							
	Yes							-0.05	-0.06
Mental distress	No	Ref.							
	Yes					-0.84	-0.85, -0.83	-0.84	-0.85, -0.83

*Ref=Reference

4. Discussions

This study is conducted among patients undergoing standardized treatment for tuberculosis in Southwest Ethiopia and revealed three important findings: 1) adherence to medication decreased over the course of treatment; 2) substance use disorders, particularly khat and alcohol contributed to this non-adherence, and 3) this association was independent of other factors such as education, social support, and occupation, 4, however, substance use disorders (khat and alcohol) did not affect the quality of life and mental distress. Food insecurity and being a government employee affected mental distress independent of substance use disorder and socio-demographic variables. The mean score of quality of life improved during the course of anti-TB treatment across all domains.

4.1 Alcohol use disorder and associated factors

The prevalence of alcohol use disorder at baseline (10.8%) and during both follow-up (16.0%) was lower than the findings of similar studies done in Thailand (24.4%) (88) and South India (31%) (157), Tomsk Russia (63.0%) (158), South Africa (21.2 -23.2%) (159, 160), Brazil (26·8%) (140). The discrepancy between these studies might be related to the socio-cultural difference. In the study conducted in Brazil, the minimum age of participants was 13 years while it was 18 years in our study. So, the difference between the two studies may be related to the age variation of age as substance use is higher among adolescents compared to adults (161). Also, there is a difference between the tools to assess substance use disorder (AUDIT vs CAGE). AUDIT includes CAGE questions plus more additional questions which allow exploring more about substance use disorder than CAGE. Also, AUDIT is developed and used by WHO to assess alcohol use disorder. AUDIT is also validated to be used among medical patients (162). Furthermore, according to WHO report, Russia, South Africa, and Brazil are among countries with a higher risk of alcohol use disorder and related risks compared to Ethiopia(163). Also, Russia is amongst the countries with the highest level of alcohol use (163, 164)

The prevalence of AUDs found in our study at baseline, first, and second follow-up was slightly in line with a mixed-method study conducted among patients with TB-HV co-infection in Lesotho (7.0%) (165), a community-based study conducted in Scotland (18.0%) (166), USA (15.1%) (122), and Karnataka, India (20.3%) (167). In our study, the prevalence of alcohol use disorder was increased over time from 10.8% at baseline to 16.0% at the first and second follow-up. This might be due to patients get relief from symptoms of tuberculosis within two to three weeks of initiating treatment so that they may increase their alcohol consumption. In our study

men were found to have higher AUD than women at baseline (11.8% vs 9.3%), first (17.4% vs 14.0%), and second (18.0% vs 13.1%) follow-up which is consistent with the finding of a study done in South Africa and Zambia (159, 168). The prevalence of AUD found in our study among male patients during the second follow-up was in agreement with a finding of a similar study done in the USA (20.6%) (122). This could be due to the fact that women are soberer than men as well as drink less so that they are less likely to develop alcohol use disorder (169). Likewise, the difference between males and females could be related to biological factors. In other words, males can easily metabolize alcohol because they have a high amount of water and less fat in their body, and as a result, males consume more alcohol than females (170). Moreover, gender differences could be modified by culture, because in many cultures, females are not accepted if they drink much alcohol as males (169, 171). Being male gender was associated with alcohol use disorder which was in agreement with a population-based retrospective cohort study done in Scotland, Pondicherry, India, and Lesotho (165, 166, 172, 173). In our study, we found that being Muslim was negatively associated with alcohol use disorder and this could be due to the fact that alcohol consumption is not acceptable by Islam religion (174). Likewise, we found that being educated (primary/secondary and tertiary) was associated with alcohol use disorder which is in line with a previous study (175).

The magnitude of mental distress at baseline (11.0%), first (18.6%), and second (13.6%) follow-ups among patients with AUD in our study is lower than the finding of a study conducted in Dire Dawa and Harar cities (87.5%) (38). Even though the study done in Dire Dawa and Harar had used AUDIT they did not report about AUD rather they report risky alcohol use. Likewise, the study conducted in Dire Dawa and Harar used a short form of AUDIT which is AUDIT-3.

4.2 Khat use and associated factors

In this study, the prevalence of khat use was slightly declined over time from 39.2% at baseline to 37.3% at the end of six months. The reason might be patients use more khat at baseline as a self-treatment for tuberculosis related symptoms and medication side effects. Because we identified that most patients believe khat can reduce symptoms of tuberculosis and medication side- effects. So, when they get improvement from the disease, they might reduce their khat use but further study is needed.

The prevalence of khat use observed in our study was far higher than another study conducted in South Ethiopia which found moderate and high khat use to be 14.3% and 1.7% respectively (139). The difference might be due to the fact that the setting for the present study is known

with a higher level of khat consumption, availability, and production than other regions and zones in Ethiopia except for the Dire Dawa town and Harari region (176). In these regions, khat is considered as part of the culture for the lubrication of social cohesion. Arguably, it is also seen as a help to stay alert during the praying time which patients would not like to miss (177-179). This is generally worrisome as khat use is associated with poor treatment outcomes among patients with tuberculosis (180).

The prevalence of khat use found in the current study is lower than the finding from a prospective nested case-control study done in Yemen (46.7%) (90). The difference might be due to the definition of current khat use which is 30 days in our study, while this was not specified in the Yemenite study. Likewise, socio-cultural differences might contribute to the discrepancy between the two studies. We found that the proportion of khat use among male participants (46.6%) was far higher than among female participants (28.0%), which is in line with the findings of previous studies (181, 182). This might be due to cultural restrictions on females regarding substance use including khat (181, 182). Even though khat consumption among women is substantially lower than men, they are at higher risk of mental and physical effects of substance use disorder than men which is associated with hormonal factors (181, 183). In this study, more than $2/5^{th}$ of khat users reported that they were suffering from mental distress. Previous studies found that substance use (khat, alcohol, and tobacco) is associated with mental distress (184, 185), and specifically, khat was reported to increase emotional disturbance (186). However, we could not show a clear association between mental distress and khat use in the adjusted models. Patients might be tempted to use khat as a self-treatment for their mental distress, but this observation needs to be supported by further investigations.

During the first follow-up, a majority (76.7%) of patients who were using khat reported that they have alcohol use disorder. This could be due to the fact that patients might resume drinking alcohol after they begin to feel better within two to three weeks because bacterial load then usually starts to decline (29). In addition, since alcohol counteracts the stimulant effect of khat such as sleep disturbance and restlessness, patients might be inclined to use both substances together (178, 187, 188). Likewise, in this study, khat use was associated with alcohol use which is in agreement with previous studies (178, 185). Combining alcohol and khat would affect patients' treatment outcomes and lead to physical and mental health problems. Because both khat and alcohol were found to have a potential impact on the immunity of the user and associated with mental distress so that patients may develop severe medical and mental health

complications or die earlier than non-users (189-191). Furthermore, these two substances have an association with treatment-resistant tuberculosis (111, 134, 192, 193).

This study found that the majority (77.1%) of khat users believe that using khat can reduce anti-TB medication side effects which is consistent with a cross-sectional study conducted in the Butajira, Ethiopia (179). This may be due to misinterpreting the euphoric mood from khat as a decrease in medication side effects. However, health professionals should create awareness regarding the effect of khat on mental and physical health so that patients may consider reducing their khat use. In this study, almost all khat users (96.2%) believe that khat use reduces TB symptoms, however, this is in clear contrast to the study indicating that patients with khat use had a higher bacterial load (192).

Moreover, we have found that merchants were using khat more than farmers, government employees, and daily laborers which is in line with studies conducted in the general population (176, 194, 195). This might be due to the fact that merchants use khat to be alert and energetic at the workplace (196). Also, some of the merchants may be khat sellers, and as a result, they chew khat to attract customers but further study assessing this situation is needed.

4.3 Tobacco and cannabis use disorder

Studies showed that TB patients also use tobacco in addition to other substances (197, 198). Also, in Ethiopia, the prevalence of toacco use was 4.1% in the general population in 2011 (199). Tobacco use goes hand in hand with alcohol use (200, 201). However, in our study we could not get data regarding tobacco use disorders. This might be due to health professionals might provide education for patients regarding the effects of tobacco use on lung. So, patients might either deny their tobacco use due to fear of health professionals or stop using tobacco. But further study is needed to identify the reasons.

Eventhough cannabis is illegal in Ethiopia, people use it in some parts of the country (202). There is no study done regarding cannabis use among patients with TB in Ethiopia. So, we tried to assess cannabis use in this study but there was no data regarding this substance. Due to the illegality of this substance, patients may deny their use. Also, due to the limited availability of cannabis, patients might not access it in the study area. However, further research with a large sample is important to identify the use of cannabis among TB patients in Southwest Ethiopia.

4.4 Effect of substance use disorder on adherence to anti-TB medication

It is alarming that adherence to TB medication decreased over the course of treatment, as already shown by studies done in South (51), Northwest (52), and Addis Ababa (53) Ethiopia. Possible reasons for non-compliance included distance from the health institution that dispenses medications (13, 51), lack of knowledge about tuberculosis (51, 52), psychological distress (53), being busy with work (52), and alcohol intake (52). To solve the problem related to adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs throughout the whole treatment and all over the country starting from initiation to completion of treatment (12).

In this study, the prevalence of non-adherence to anti-TB medication in the first month of treatment was 9·7 % which is in line with a systematic review that found 10·0% of non-adherence in the Amhara region (13, 54). The proportion of non-adherence to anti-TB medications during the first (26·1%) and second (27·6%) follow up was slightly higher than findings from South (24·5%) (51), Northwest (21·2%) (52), and Addis Ababa (19·5%) (53) Ethiopia. This might be explained by the high proportion of persons with a substance use disorder in our study, in which we deliberately oversampled persons with SUD to maximize power. The discrepancy may be due to patients in our study were using substances whereas in the systematic review there was no data regarding substance use.

In this study, the prevalence of non-adherence among patients with substance use disorder at baseline, first, and second follow-up was 16·4%, 41·7%, and 45·7% respectively. This is in line with a study from the US (39%) (52, 55, 56).

Moreover, this study provides evidence that substance use disorders have a significant negative effect on adherence to anti-TB medications among patients with tuberculosis, which supports earlier findings from previous studies that found alcohol use disorder, tobacco dependence, and illicit drug use have a negative impact on adherence in Uzbekistan, Spain, and Morocco (57-59). This is also, in line with retrospective studies conducted in Russia and New York which found that alcohol use disorder and drug addiction were significantly associated with non-adherence to anti-TB medications (8, 9). Likewise, the finding of this study is in line with studies conducted in different parts of Ethiopia which found khat, alcohol, and tobacco are the main factors for non-adherence to anti-TB medications (52, 56, 60). In our study, patients with substance use disorder were more than two times more likely not to follow their medication plan than patients without substance use disorders. This finding is consistent with the finding of a study from the US that

found the risk of missing a DOT appointment was 2.6 times higher among patients with substance use disorder than in patients without drug consumption (55).

In our study, khat use disorder turned out to be the most stringent factor that decreased adherence. This confirms earlier findings from Yemen (61) and Ethiopia (14, 60). A plausible explanation is that khat chewing disrupts night sleep (62) causing patients to oversleep which may lead to missing the DOT appointments at the health facility. Another reason may be that khat is omnipresent in Ethiopia, and therefore less attention is paid to the use of khat. Since little is known about the effect of khat on patients with tuberculosis (14), khat may be considered as part of a normal social interaction (61).

A higher level of education was associated with non-adherence to anti-TB medications in our study. This result confirms the findings from Yemen that found more educated patients were 19% times less likely to be adherent to their medication (61). Also, a study from Ethiopia showed that attending primary education was associated with non-adherence to anti-TB medications (60). Our findings are contrary to previous studies which have suggested that lower or no formal education decreases adherence to TB medication (13, 63). Our finding seems counterintuitive. However, our results are likely to be related to findings from a study indicating that persons with higher educational attainment might be reluctant to accept DOTS regimes (64). Daily visits to the health facility have been reported as too time-consuming and probably stigmatizing for patients with a job (65). In this study, being a merchant was associated with poor adherence to anti-TB medications. This might be due to patients miss their medications because of busy working time, but it needs further investigation.

4.5 Quality of life and associated factors

Measuring quality of life is crucial for the evaluation of TB treatment programs for better services. Because better treatment services reduce the morbidity and mortality related to TB. Considering its importance, this longitudinal study assessed the quality of life among tuberculosis patients in Ethiopia using SF-36. This longitudinal study is the first in Ethiopia that shading light on QoL and predicting factors among TB patients in Ethiopia. The mean score of social functioning, bodily pain, physical functioning was improved significantly, while there was no much improvement of the energy/fatigue dimension of QoL which is in line with a study conducted in South Africa (48). After completing DOTS, all components of QoL were improved which is consistent with a study conducted in Yemen (203). This could be due to the fact that DOTS improves QoL among patients with TB (51, 204, 205). At the beginning of treatment,

patients might feel very sick, but get improved from the TB related symptoms after completing treatment. Also, the finding of this study showed that being in the age group of 45-54 was associated with physical functioning dimensions of QoL which is consistent with previous studies that revealed older patients with TB (age greater than 45 years) had lower quality of life compared to younger patients at all phases of treatments (50, 51, 87, 205, 206). Likewise, the dimension of emotional wellbeing had a low mean score among patients in the age group of 55-64 years. This could be due to emotional well-being decline as age increases which is associated with the dysregulation of the hypothalamic-pituitary-adrenal axis (207). Physical functioning is the capability of a person to perform routine activities (208). In this study, at the baseline, role limitations due to physical health problems (RPF) score was the lowest of all QoL dimensions which are similar to previous studies done in the same population (50, 51, 209-212). This could be due to the fact that Tuberculosis related signs and symptoms affect the daily activities of the patients which were witnessed by the improvement of physical function during follow-up that reduce RPF. Also, role limitations due to personal or emotional problems score were the second-lowest which was similar with similar studies conducted in the United Kingdom and Yemen (48, 50, 86, 211). The lowest RE dimension of QoL among TB patients indicated that the emotional disturbance might be associated with the severity of TB symptoms at the beginning of the treatment. Also, the study indicated that the lowest score of RE has an association with depressed mood among TB patients (50). The mean score of energy/fatigue increased from 45.1 at baseline to 54.9 at the end of six months which is in line with a study conducted in Malaysia that revealed the mean score in energy/fatigue increased to more than 47 at the end of the continuation phase (213). This could be as a result of the effectiveness of treatment that also improved all dimensions of quality of life (51). On the other hand, the social functioning domain score was the highest of all, which is in agreement with a previous study indicating that TB has no significant impact on the social relationship of patients (49, 214).

In this study, mental distress was associated with role limitation due to physical functioning, energy/fatigue, physical functioning, and body pain dimensions of QoL which was similar to the study conducted in South Africa (48). Also, at the end of six months, social functioning and bodily pain score were the highest of all domains of QoL which was similar to the study conducted in Wuhan, China (51). This could be due to the fact that anti-TB medications improve quality of life, particularly, physical health dimensions (45). In this study, the mean score of energy/fatigue was the third lowest (45.1) dimension of QoL which is in line with the studies conducted in South Africa and Hamadan, Western Iran (128, 215). This could be due to the effect of anti-TB medication side effects (216). In this study, being farmers and government

employees had a better quality of life compared to Merchants. This might be related to financial security and more social interaction that helps patients to give less attention to their illness but focus on their job. Also, in this study as one unit increase in being single, the social functioning decreases by 6.4. This may be due to single individuals has lower social support compared to married ones (217).

Older patients whose age was more than 45 years had poor physical functioning which was in line with previous studies (49, 218). This may be due to physical activities decreases as age increases. In this study, mental distress was found to negatively predict all components of QoL except social functioning and general health. A similar study conducted in South Africa showed that mental distress was negatively associated with physical and mental components of quality of life (48). This could be related to the fear of social exclusion after being infected by the disease that could lead to stress which could exacerbate mental distress (219-221). Also, symptoms of the disease might overlap with the symptoms of mental distress, and as a result, there might be an association between mental distress and all dimensions of QoL but it needs further investigation.

Even though it is expected that khat use has an association with QoL, no association was seen between all components of QoL and khat use in our study. This finding is against a study conducted in Yemen that showed khat use is a predictor of QoL (86). Also, in this study alcohol use disorder was not associated with quality of life which is in agreement with a study conducted in South Africa that showed alcohol dependence was not associated with poorer physical and mental health components of QoL (65). However, evidence showed that heavy alcohol consumption has a significant effect on the immunity of patients which in turn could affect physical and mental health components of QoL (104).

4.6 Mental distress and associated factors

The prevalence of mental distress found in this study was decreasing over six months from 61.2% at baseline to 22.0% at the second follow-up. This is consistent with other studies done on similar populations in Ethiopia (222) and South Africa (223). This might be due to patients with tuberculosis experience severe symptoms of the disease in the first month of treatment initiation which may overlap with the symptoms of mental distress but as patients get improvement from TB, symptoms of mental distress may also decline. Also, since SRQ-20 contains several physical symptoms that overlap with the symptoms of TB, the improvement of TB symptoms such as fatigue, loss of appetite throughout anti-TB treatment may account for the reduction in the level of mental distress. However, the baseline prevalence of mental distress found in this study

(61.2%) was greater than the finding of a study conducted in Angola (44.4%) (224) and South Africa (34.1%) (223). The difference might be due to the tool used to assess mental distress (SRQ-20 vs. Hospital Anxiety and Depression Scale (HADS), and K-10). For example, K-10 has nine items of psychological symptoms and only one physical item, so little overlap with TB symptoms compared to SRQ-20. The prevalence of mental distress at the first (38.1%) and second (22.0%) follow-up found in this study was in line with the studies conducted in Huambo hospital, Angola (44.4%) (224) and South Africa (21.8%) (225) but lower than the finding of studies conducted in a similar population in Dire Dawa and Harar cities (63.3%) (226) and Addis Ababa Ethiopia (48.5%) (222).

In our study, the prevalence of mental distress was higher among men than females (i.e at baseline 64.6 vs 56.1, at first follow up 41.0 vs33.6, at second follow up 28.0vs13.1) which is consistent a study conducted in Liaoning Province, China which found high anxiety and depression among male TB patients (227). The prevalence of psychological distress among patients with TB looks controversial because there are researches that indicated the prevalence of mental distress is higher among female participants. A study conducted among TB patients in Ethiopia showed that the prevalence of mental distress among males and females is not significantly different at the second month of follow-up (67.5 vs 67.6) (222). In our study, the prevalence difference between the two genders may be related to substance use because many male patients were using alcohol and khat than females. This could be due to the fact that alcohol and khat use increase the risk of developing mental distress (228). But further study is needed to explore the reason why high mental distress is observed among male TB patients.

In this study, being a government employee is associated with mental distress which is in line with a study conducted in Tasmania (229). This could be due to the fact that low income has a negative effect on mental health (230). Severe food insecurity was also associated with mental distress which is similar to studies conducted among a similar population in Zambia and South Africa (231-233). Furthermore, it is similar to community-based studies conducted in four African countries (Ethiopia, Nigeria, Uganda, and Ghana) (234, 235). This might be related to the uncertainty to have adequate food could lead to chronic stress that affects the mental health of the patients (232).

4.7 The association between social support and adherence to anti-TB medications

This study is the first in Ethiopia to assess the association between social support and adherence to anti-TB medications among TB patients. The findings of this longitudinal study showed that

the prevalence of poor social support was increasing over time, while the lowest prevalence of strong social support was observed at the end of six months. In this longitudinal study, there was no association between social support and adherence to anti-TB medications after adjusting for covariates. However, factors such as khat use, alcohol use disorder, and being educated were associated with poor adherence to anti-TB medications. The prevalence of non-adherence to anti-TB medication was 9.7 % (n=26) at baseline, while it was 26.1% (n=70) and 27.6% (n=74) at the two and six months respectively. The adherence to anti-TB medications among patients with poor and moderate social support was decreased over time.

The overall prevalence of poor social support found in this study was almost two times that of strong social support (42.9% vs 23.5%). Also, the high prevalence of poor social support (42.9%) found in this study is in line with the study conducted in Addis Ababa (42.7%) and Wolaita Sodo, Ethiopia (45.0%) (236, 237). This could be due to the fact that patients are excluded from social activities in the first few weeks because of the fear that they can transmit the disease to other people. However, this trend has a major impact on treatment outcomes, because patients with poor social support refrain from disclosing their illness (238-241). Also, lack of social support can lead to mental health problems which are detrimental to adherence to anti-TB medications (184, 236, 242, 243). Similarly, poor social support has an association with decreased health-related quality of life (244).

In this study, about half of patients with poor social support (44.7%) were non-adherent to their medication and this could be due to the fact that low social support was found to affect anti-TB medication adherence (63, 245). Because, families and relatives play a great role in motivating and providing moral, emotional, and financial support for the patients which are crucial to reducing non-adherence and loss to follow-up (246, 247).

In this study, social support was not associated with anti-TB medication non-adherence which is in agreement with a study conducted in Metro Manila, the Philippines (248). This might be due to family engagement in the treatment during directly observed treatment is less, because patient take medication under the observation of a health professional, and as a result, social support from family or relative may not have a potential impact on adherence to the medication but further study is needed to investigate this issues. However, studies showed that social support plays a great role in reducing physical and mental distress which improves patients' ability to cope up with the disease condition (249). Also, the provision of informational support from family members improved adherence to anti-TB medications (250). Because, during intensive

phase treatment, patients need care and support from family and relatives, and this is important for adherence to medication. Social support is also important to engage patients in social activities so that social exclusion during the illness can be reduced (238).

On the other hand, 42.7% of patients with poor social support reported symptoms of mental distress which is in line with a previous study conducted in a similar population in Wolayita Sodo, Southcentral and Northern Ethiopia (184, 251). This may be related to low support from family members and TB related physical symptoms that can lead to mental distress (184, 252).

In this study, almost 3/4th of patients with few family members less than five reported having poor social support. This may be as the number of more family members increases; they can share the responsibility to provide the necessary support for the patients during the illness. The prevalence of poor social support among patients living in the urban area (66.8%) was two times that of those who were living in rural areas (33.2%). This could be due to because people who are living in urban are less connected than people living in the countryside. Also, those living in rural area have good bonds, a higher frequency of direct contact, and giving and receiving support (253, 254). About 2/3 of divorced/widowed patients reported having poor social support which is in line with a study conducted in Pakistan that showed widow receive less social support compared to single and married participants(255).

4.8 Food insecurity and associated factors

In this study, about half (49.3%) of the total patients were suffering from food insecurity at baseline and this could affect their treatment adherence and lead to poor treatment outcomes. However, having good nutrition is crucial for general health, good treatment outcomes, strong immunity, and halting disease progression (256). According to a systematic review done by *Balinda IG et al,* food insecurity is responsible for malnutrition which in turn leads to worsening anti-TB medications side effects especially hepatoxicity (257). Also, food insecurity exposes patients to delay their treatment which might pave ways for non-adherence and multidrug resistance tuberculosis (257).

The prevalence of household food insecurity found in our study at baseline (49.3%), first (45.9%), and second follow-up (39.6%) was higher than the finding of a study done in South Africa among patients with multidrug resistance tuberculosis (21.01%)(233). This difference might be due to the socio-cultural difference between Ethiopia and South Africa. Also, while our study was done among patients attending their treatment at the outpatient department, the study done in South Africa was done among patients admitted to the hospital and this might lead to

lower food insecurity due to patients may access food from the hospital. The prevalence of severe food insecurity found in our study at the end of six months (second follow-up) (23.5%) was in line with a similar study done in South India (23.1%) (258).

In this study, the male gender was less likely to have food insecurity which is in line with the studies done in South Africa (233) and a systematic review done by *Jung NM et al* in which females were 75% times more likely to be food insecure compared to male (259). Severe food insecurity was also found to be associated with mental distress in our study which is similar to a systematic review done by *Maynard M et al* (260). Also, a systematic review done by *Jone A.D* showed that food insecurity has a strong relationship with mental health problems (232, 260). Our finding is also in line with a community-based study done among adolescents in Southwest Ethiopia (261). This might be due to food insecurity could be a chronic stressor that may lead to mental distress but further study is needed.

4.9 Strengths

The strengths of this study are the prospective cohort design, longitudinal data collection, intensive training given for data collectors, multi-center data collection, and the use of standardized instruments to assess outcome variables and predicting factors.

4.10 Limitations

This study has some limitations. Due to social desirability bias, patients might minimize reporting of the amount and frequency of substance they were using. Also, measuring adherence based on pills count may not reflect the real adherence situation for the same reason as some patients might not bring all leftovers of medications during the follow-up. Likewise, follow-up and data collections have been carried out by health professionals working in the respective TB clinic, so their assessment of adherence might be biased. However, overestimating adherence may have biased our results towards a null effect and led to underestimating the effect of substance use disorders, so we are confident that our estimates are conservative. The participation of district tuberculosis focal persons and other health professionals in the supervision of data collection might also introduce bias.

The generalizability of this finding is only to new patients who were on treatment at outpatient health centers and the hospital found in Jimma because this study did not include health posts, patients on re-treatment, MDR-TB, and patients attending their treatment at inpatient department.

5. Conclusions

The prevalence of substance use disorder (alcohol and khat) was high among patients with TB in Southwest Ethiopia. Substance use disorders predict a greater likelihood of anti-TB medication non-adherence among TB patients. These findings imply the importance of integrating substance use disorder screening and treatment into the existing tuberculosis services to reduce the effect of substances on treatment outcomes including adherence.

There is a high prevalence of mental distress and food insecurity in this study, and this could affect treatment outcomes. Quality of life improved over the six months of follow-up. However, there was no association between substance use disorder and quality of life, and mental distress.

Furthermore, it is essential to integrate mental health services into TB treatment programs to prevent and treat mental distress which could affect TB treatment outcomes. Also, future research should focus on the relationship between mental distress and TB treatment outcomes as well as how to mitigate this problem. Likewise, it would be better to screen food insecurity among TB patients and provide food or cash assistance for those who need it. Food insecurity may lead to exacerbation of the disease and malnutrition so that early detection and intervention are mandatory.

References

1. Hayman J. Mycobacterium ulcerans: an infection from Jurassic time? Lancet. 1984;2(8410):1015-6.
2. Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. Journal of preventive medicine and hygiene. 2017;58(1):E9-e12.
3. WHO. Global Tuberculosis Report 2019. World Health Organization. 2019.
4. Gutierrez MC, Brisse S, Brosch R, Fabre M, Omaïs B, Marmiesse M, et al. Ancient origin and gene mosaicism of the progenitor of Mycobacterium tuberculosis. PLoS pathogens. 2005;1(1):e5.
5. Morse D, Brothwell DR, Ucko PJ. TUBERCULOSIS IN ANCIENT EGYPT. The American review of respiratory disease. 1964;90:524-41.
6. Zimmerman MR. Pulmonary and osseous tuberculosis in an Egyptian mummy. Bulletin of the New York Academy of Medicine. 1979;55(6):604-8.
7. D. Pedrazzoli RMH, N. Grede, S. de Pee, D. Boccia. Food assistance to tuberculosis patients: lessons from Afghanistan2016.
8. EM MD. Mac Donald EM, Izzo AA. Tuberculosis vaccine development. In: Ribbon W, editor. Tuberculosis-expanding knowledge. In Tech; 2015.
9. WHO. WHO. Global tuberculosis report 2013 Geneva Swizwerland.
10. WHO. World Health Organization. The End TB Strategy. Geneva, Switzerland: World Health Organization; 2015. 2015.
11. MacNeil A, Glaziou P, Sismanidis C, Date A, Maloney S, Floyd K. Global Epidemiology of Tuberculosis and Progress Toward Meeting Global Targets - Worldwide, 2018. MMWR Morbidity and mortality weekly report. 2020;69(11):281-5.
12. WHO. WHO calls for urgent action to end TB2018.
13. WHO. Global tuberculosis control: WHO report 2011. Who. 2011:258-.
14. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: The role of risk factors and social determinants. Social Science and Medicine. 2009;68(12):2240-6.
15. Lienhardt C, Fielding K, Sillah JS, Bah B, Gustafson P, Warndorff D, et al. Investigation of the risk factors for tuberculosis : a case – control study in three countries in West Africa. 2005(May):914-23.
16. UN. Sustainable development goals New York: United Nations; .
17. Institute) EEHaNR. First Ethiopian National Population Based Tuberculosis Prevalence Survey2011.
18. Related H, Page EFY. Federal Ministry of Health Health and Health Related Indicators 2005 E . C (2012 / 2013). 2014.
19. Global Tuberculosis Control (MPCBM 5VCFSDVMPTJT $ POUSPM. 2010.
20. Deribew A, Deribe K, Dejene T, Tessema GA, Melaku YA, Lakew Y, et al. Tuberculosis Burden in Ethiopia from 1990 to 2016: Evidence from the Global Burden of Diseases 2016 Study. Ethiopian journal of health sciences. 2018;28(5):519-28.
21. FMOH. Health Sector Transformation Plan 2015/16–2019/20. Federal Democratic Republic of Ethiopia; 20152015.
22. Biadglegne F, Sack U, Rodloff AC. Multidrug-resistant tuberculosis in Ethiopia: efforts to expand diagnostic services, treatment and care. Antimicrobial resistance and infection control. 2014;3(1):31-.
23. Mekonnen F, Tessema B, Moges F, Gelaw A, Eshetie S, Kumera G. Multidrug resistant tuberculosis: prevalence and risk factors in districts of metema and west armachiho, Northwest Ethiopia. BMC Infect Dis. 2015;15:461.

24. Seyoum B, Demissie M, Worku A, Bekele S, Aseffa A. Prevalence and Drug Resistance Patterns of Mycobacterium tuberculosis among New Smear Positive Pulmonary Tuberculosis Patients in Eastern Ethiopia. Tuberc Res Treat. 2014;2014:753492.
25. Biadglegne F, Sack U, Rodloff AC. Multidrug-resistant tuberculosis in Ethiopia: efforts to expand diagnostic services, treatment and care. Antimicrobial resistance and infection control. 2014;3(1):31.
26. Hirpa S, Medhin G, Girma B, Melese M, Mekonen A, Suarez P, et al. Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in Addis Ababa: a case control study. BMC Public Health. 2013;13:782.
27. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review. Iranian journal of public health. 2015;44(1):1-11.
28. Dick J, Lombard C. Shared vision--a health education project designed to enhance adherence to anti-tuberculosis treatment. Int J Tuberc Lung Dis. 1997;1(2):181-6.
29. FMoH. Federal Democratic Republic of Ethiopia, Ministry of Health. Guidelines for clinical and programmatic management of tb, leprosy and tb/hiv in ethiopia fifth edition: MoH; 2012.
30. Nezenega ZS, Perimal-Lewis L, Maeder AJ. Factors Influencing Patient Adherence to Tuberculosis Treatment in Ethiopia: A Literature Review. Int J Environ Res Public Health. 2020;17(15).
31. Doherty AM, Kelly J, McDonald C, O'Dywer AM, Keane J, Cooney J. A review of the interplay between tuberculosis and mental health. General Hospital Psychiatry. 2013;35(4):398-406.
32. De Araújo GS, Pereira SM, dos Santos DN, Marinho JM, Rodrigues LC, Barreto ML. Common mental disorders associated with tuberculosis: a matched case-control study. PLoS One. 2014 Jun 17;9(6):e99551. doi: 10.1371/journal.pone.0099551. PMID: 24937319; PMCID: PMC4061008..
33. Aline Drapeau AM, Dominic Beaulieu-Prévost. Epidemiology of Psychological Distress In Mental Illnesses – Understanding, Prediction and Control,: LAbate PL ed; 2012. 155–34 p.

34. Goldberg D. A bio-social model for common mental disorders. Acta psychiatrica Scandinavica Supplementum. 1994;385:66-70.
35. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-Adherence in Addis Ababa, Ethiopia. Ethiopian journal of health sciences. 2017;27(5):447-58.
36. Peltzer K, Naidoo P, Matseke G, Louw J, McHunu G, Tutshana B. Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. BMC psychiatry. 2012;12:89.
37. Cassidy DA, Ivers LC. Food Insecurity and Tuberculosis: Policy Urgently Needs To Play Catch-Up. Ir Med J. 2018;111(6):777.
38. Ayana TM, Roba KT, Mabalhin MO. Prevalence of psychological distress and associated factors among adult tuberculosis patients attending public health institutions in Dire Dawa and Harar cities, Eastern Ethiopia. BMC Public Health. 2019;19(1):1392.
39. Tola HH, Shojaeizadeh D, Garmaroudi G, Tol A, Yekaninejad MS, Ejeta LT, et al. Psychological distress and its effect on tuberculosis treatment outcomes in Ethiopia. Glob Health Action. 2015;8:29019.
40. Deribew A, Tesfaye M, Hailmichael Y, Apers L, Abebe G, Duchateau L, et al. Common mental disorders in TB / HIV co-infected patients in Ethiopia. BMC Infectious Diseases. 2010;10(201):1-8.

41. Deribew A, Deribe K, Reda AA, Tesfaye M, Hailmichael Y, Maja T. Do common mental disorders decline over time in TB/HIV co-infected and HIV patients without TB who are on antiretroviral treatment? BMC psychiatry. 2013;13(1):174-.
42. Tola HH, Shojaeizadeh D, Garmaroudi G, Tol A, Yekaninejad MS, Ejeta LT, et al. Psychological distress and its effect on tuberculosis treatment outcomes in Ethiopia. Global Health Action. 2015;8(1):1-11.
43. Peltzer K, Naidoo P, Matseke G, Louw J, McHunu G, Tutshana B. Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. BMC Psychiatry 2012;12(89).
44. World Health Organization. Division of Mental H, Prevention of Substance A. WHOQOL : measuring quality of life. Geneva: World Health Organization; 1997.
45. Guo N, Marra F, Marra CA. Measuring health-related quality of life in tuberculosis: a systematic review. Health and quality of life outcomes. 2009;7:14.
46. de Wit M, Hajos T. Health-Related Quality of Life. In: Gellman MD, Turner JR, editors. Encyclopedia of Behavioral Medicine. New York, NY: Springer New York; 2013. p. 929-31.
47. Bauer M, Ahmed S, Benedetti A, Greenaway C, Lalli M, Leavens A, et al. Health-related quality of life and tuberculosis: a longitudinal cohort study. Health and quality of life outcomes. 2015;13:65.
48. Louw J, Peltzer K, Naidoo P, Matseke G, McHunu G, Tutshana B. Quality of life among tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health care patients in three districts in South Africa. Health and quality of life outcomes. 2012;10:77.
49. Li CT, Chu KH, Reiher B, Kienene T, Chien LY. Evaluation of health-related quality of life in patients with tuberculosis who completed treatment in Kiribati. J Int Med Res. 2017;45(2):610-20.
50. Marra CA, Marra F, Colley L, Moadebi S, Elwood RK, Fitzgerald JM. Health-related quality of life trajectories among adults with tuberculosis: differences between latent and active infection. Chest. 2008;133(2):396-403.
51. Chamla D. The assessment of patients' health-related quality of life during tuberculosis treatment in Wuhan, China. Int J Tuberc Lung Dis. 2004;8(9):1100-6.
52. Othman G.Q, Ibrahim M.IM, Raja'a Y.A. Health related quality of life of pulmonary and extrapulmonary tuberculosis patients in Yemen: African Journal of Pharmacy and Pharmacology; 2011. 547-53 p.
53. Kisaka SM, Rutebemberwa E, Kasasa S, Ocen F, Nankya-Mutyoba J. Does health-related quality of life among adults with pulmonary tuberculosis improve across the treatment period? A hospital-based cross sectional study in Mbale Region, Eastern Uganda. BMC research notes. 2016;9(1):467.
54. Rajeswari R, Muniyandi M, Balasubramanian R, Narayanan PR. Perceptions of tuberculosis patients about their physical, mental and social well-being: a field report from south India. Soc Sci Med. 2005;60(8):1845-53.
55. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, et al. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review. PLoS One. 2016;11(1):e0147397.
56. Fuady A, Houweling TAJ, Mansyur M, Richardus JH. Catastrophic total costs in tuberculosis-affected households and their determinants since Indonesia's implementation of universal health coverage. Infect Dis Poverty. 2018;7(1):3.
57. Marra CA, Marra F, Cox VC, Palepu A, Fitzgerald JM. Factors influencing quality of life in patients with active tuberculosis. Health and quality of life outcomes. 2004;2:58.
58. Dujaili JA, Sulaiman SA, Hassali MA, Awaisu A, Blebil AQ, Bredle JM. Health-related quality of life as a predictor of tuberculosis treatment outcomes in Iraq. Int J Infect Dis. 2015;31:4-8.

59. Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health status and quality of life in tuberculosis. Int J Infect Dis. 2015;32:68-75.
60. Guo N, Marra F, Fitzgerald JM, Elwood RK, Marra CA. Impact of adverse drug reaction and predictivity of quality of life status in tuberculosis. Eur Respir J. 2010;36(1):206-8.
61. Zhou C, Long Q, Chen J, Xiang L, Li Q, Tang S, et al. Factors that determine catastrophic expenditure for tuberculosis care: a patient survey in China. Infect Dis Poverty. 2016;5:6.
62. Onazi O, Gidado M, Onazi M, Daniel O, Kuye J, Obasanya O, et al. Estimating the cost of TB and its social impact on TB patients and their households. Public Health Action. 2015;5(2):127-31.
63. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative study. J Health Popul Nutr. 2018;37(1):1.
64. Cremers AL, de Laat MM, Kapata N, Gerrets R, Klipstein-Grobusch K, Grobusch MP. Assessing the consequences of stigma for tuberculosis patients in urban Zambia. PLoS One. 2015;10(3):e0119861.
65. Peltzer K, Pengpid S. Alcohol use and health-related quality of life among hospital outpatients in South Africa. Alcohol Alcohol. 2012;47(3):291-5.
66. Srivastava S. BMS, Rajender G., Angad S. Quality of Life in Substance Use Disorders: DELHI PSYCHIATRY JOURNAL 2009.
67. Lynch JB. Multidrug-resistant Tuberculosis. Medical Clinics of North America. 2013;97(4):553-79.
68. Connell RO, Chishinga N, Kinyanda E, Patel V, Ayles H, Helen A. Prevalence and Correlates of Alcohol Dependence Disorder among TB and HIV Infected Patients in Zambia. 2013;8(9):1-9.
69. WHO. Global Tuberculosis Control Report 2009. 2009. p. 1-97.
70. Michael N. Bates AKMP, Lisa Chang FLKRS. Risk of Tuberculosis From Exposure to Tobacco Smoke. 2012;167:335-42.
71. Zetola NM, Modongo C, Kip EC, Gross R, Bisson GP, Collman RG. Alcohol use and abuse among patients with multidrug-resistant tuberculosis in Botswana. Int J Tuberc Lung Dis. 2012 Nov;16(11):1529-34. doi: 10.5588/ijtld.12.0026. Epub 2012 Sep 7. PMID: 22963934; PMCID: PMC3730124.
72. Slama K CC-Y, Enarson DA. Tobacco cessation intervations for tuberculosis patients. A guide for low income countries. Paris, France: International Union against Tuberculosis and Lung Disease2008.
73. Wang J, Shen H. Review of cigarette smoking and tuberculosis in China : intervention is needed for smoking cessation among tuberculosis patients. 2009;9:1-9.
74. Dalton T, Cegielski P, Akksilp S, Asencios L, Caoili JC, Cho S-n, et al. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries : a prospective cohort study. The Lancet. 2012;380(9851):1406-17.
75. Whiteford Ha, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. The Lancet. 2013;382(9904):1575-86.
76. Gebremedhin AT, Gesesew HA, Demissie TD, Kerie MW, Sudhakar M. Khat Chewing and Risky Sexual Behavior in Sub Saharan Africa : A systematic Review Protocol. JBI Database of Systematic Reviews & Implementation Reports, 2013;11(12) 59 - 67.
77. Turnip SS, Hauff E. Household roles, poverty and psychological distress in internally displaced persons affected by violent conflicts in Indonesia. Soc Psychiatry Psychiatr Epidemiol. 2007;42(12):997-1004.

78. WHO. Mortality attributed to tobacco. Geneva Switzerland, 2012
79. Alvi A, Rizwan M, Bin A, Jerah A. Does khat chewing increases the risk of Mycobacterium tuberculosis infection by macrophage immune modulation ? 2014.
80. Tilahun M, Ayele G. Factors associated with Khat use among youths visiting HIV testing and counseling centers in Gamo Gofa, Southern Ethiopia. BMC Public Health. 2013;12(1199).
81. WHO. ATLAS on substance use : resources for the prevention and treatment of substance use disorders, Geneva, , Switzerland.
82. Jack H, Masterson AR, Khoshnood K. Violent conflict and opiate use in low and middle-income countries: a systematic review. Int J Drug Policy. 2014 Mar;25(2):196-203.
83. Morina N, Akhtar A, Barth J, Schnyder U. Psychiatric Disorders in Refugees and Internally Displaced Persons After Forced Displacement: A Systematic Review. Front Psychiatry. 2018;9:433.
84. WHO. Waterpipe Tobacco Smoking: Health Effects, Research Needs, and Recommended Actions by Regulators. 2013:1-20.
85. Deribe K, Hailekiros F, Biadgilign S, Amberbir A, Beyene BK. Defaulters from antiretroviral treatment in Jimma University Specialized Hospital, Southwest Ethiopia. Tropical Medicine and International Health. 2008;13(3):328-33.
86. Jaber AA, Khan AH, Syed Sulaiman SA, Ahmad N, Anaam MS. Evaluation of Health-Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. PLoS One. 2016;11(6):e0156258.
87. Muniyandi M, Rajeswari R, Balasubramanian R, Nirupa C, Gopi PG, Jaggarajamma K, et al. Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. Int J Tuberc Lung Dis. 2007;11(8):887-92.
88. Laprawat S, Peltzer K, Pansila W, Tansakul C. Alcohol use disorder and tuberculosis treatment: A longitudinal mixed method study in Thailand. S Afr J Psychiatr. 2017;23:1074.
89. Mwiru RS, Nagu TJ, Kaduri P, Fawzi W, Mugusi F. Prevalence and factors associated with alcohol drinking among HIV and tuberculosis co-infected patients in Dar es Salaam, Tanzania. AIDS Care. 2018;30(2):173-7.
90. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to anti-tuberculosis treatment in Yemen: JPHSR; 2013.
91. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on tuberculosis treatment outcomes: a retrospective cohort study. Archives of public health = Archives belges de sante publique. 2018;76:45-.
92. Christensen AS, Roed C, Andersen PH, Andersen AB, Obel N. Long-term mortality in patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study. Clinical epidemiology. 2014;6:405-21.
93. CDC. Diseases and Death. Available at https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm#:~:text=Smoking%20is%20the%20leading%20cause,7%20million%20deaths%20per%20year.&text=If%20the%20pattern%20of%20smoking,to%20tobacco%20use%20by%202030. Accessed on 17/04/2020.
94. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual Healthcare Spending Attributable to Cigarette Smoking: An Updateexternal icon. American Journal of Preventive Medicine 2014;48(3):326–333.
95. Britton J, Edwards R. Tobacco smoking , harm reduction , and nicotine product regulation. 1962:441-5.
96. Wang M-G, Huang W-W, Wang Y, Zhang Y-X, Zhang M-M, Wu S-Q, et al. Association between tobacco smoking and drug-resistant tuberculosis. Infect Drug Resist. 2018;11:873-87.
97. Doherty AM, Kelly J, McDoanld c, Anne Marie O'Dywer, Joseph Keane, John Cooney. A review of the interplay between tuberculosis and mental health. 2013.

98. 2018 Gsroaah. Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.2018.

99. WHO. The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
100. Swift RM. Drug therapy for alcohol dependence. N Engl J Med. 1999;340(19):1482-90.
101. Thomas B, Suhadev M, Mani J, Ganapathy BG, Armugam A, Faizunnisha F, et al. Feasibility of an alcohol intervention programme for TB patients with alcohol use disorder (AUD)--a qualitative study from Chennai, South India. PloS one. 2011;6(11):e27752-e.
102. WHO. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5(12):987-1012.
103. Simou E, Britton J, Leonardi-Bee J. Alcohol consumption and risk of tuberculosis: a systematic review and meta-analysis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(11):1277-85.
104. Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC public health. 2008;8:289-.
105. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lonnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J. 2017;50(1).
106. Porretta E, Happel KI, Teng XS, Ramsay A, Mason CM. The impact of alcohol on BCG-induced immunity against Mycobacterium tuberculosis. Alcohol Clin Exp Res. 2012;36(2):310-7.
107. Barr T, Helms C, Grant K, Messaoudi I. Opposing effects of alcohol on the immune system. Prog Neuropsychopharmacol Biol Psychiatry. 2016;65:242-51.
108. Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lönnroth K, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC public health. 2009;9:450-.
109. Schoeman JH, Parry CD, Lombard CJ, Klopper HJ. Assessment of alcohol-screening instruments in tuberculosis patients. Tuber Lung Dis. 1994 Oct;75(5):371-6.
110. Ayano G, Yohannis K, Abraha M, Duko B. The epidemiology of alcohol consumption in Ethiopia: a systematic review and meta-analysis. Subst Abuse Treat Prev Policy. 2019;14(1):26.
111. Zetola NM, Modongo C, Kip EC, Gross R, Bisson GP, Collman RG. Alcohol use and abuse among patients with multidrug-resistant tuberculosis in Botswana. Int J Tuberc Lung Dis. 2012;16(11):1529-34.
112. Naidoo P, Peltzer K, Louw J, Matseke G, McHunu G, Tutshana B. Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: a cross sectional study. BMC public health. 2013;13:396-.
113. Rumende CM. Risk Factors for Multidrug-resistant Tuberculosis. Acta Med Indones. 2018;50(1):1-2.
114. Liu Q, Lu P, Martinez L, Yang H, Lu W, Ding X, et al. Factors affecting time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis in China. BMC infectious diseases. 2018;18(1):114-.
115. Lucenko I, Riekstina V, Perevoscikovs J, Mozgis D, Khogali M, Gadoev J, et al. Treatment outcomes among drug-susceptible tuberculosis patients in Latvia, 2006-2010. Public health action. 2014;4(Suppl 2):S54-S8.
116. Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lönnroth K, et al. The association between alcohol use , alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2004;12:1-12.

117. Duraisamy K, Mrithyunjayan S, Ghosh S, Nair SA, Balakrishnan S, Subramoniapillai J, et al. Does Alcohol consumption during multidrug-resistant tuberculosis treatment affect outcome?. A population-based study in Kerala, India. Annals of the American Thoracic Society. 2014;11(5):712-8.
118. Holden IK, Lillebaek T, Seersholm N, Andersen PH, Wejse C, Johansen IS. Predictors for Pulmonary Tuberculosis Treatment Outcome in Denmark 2009-2014. Sci Rep. 2019;9(1):12995.
119. Thomas BE, Thiruvengadam K, S R, Kadam D, Ovung S, Sivakumar S, et al. Smoking, alcohol use disorder and tuberculosis treatment outcomes: A dual co-morbidity burden that cannot be ignored. PLoS One. 2019;14(7):e0220507.
120. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on tuberculosis treatment outcomes: a retrospective cohort study. Arch Public Health. 2018;76:45.
121. Volkmann T, Moonan PK, Miramontes R, Oeltmann JE. Excess Alcohol Use and Death among Tuberculosis Patients in the United States, 1997-2012. Journal of tuberculosis research. 2016;4(1):18-22.
122. Volkmann T, Moonan PK, Miramontes R, Oeltmann JE. Tuberculosis and excess alcohol use in the United States, 1997-2012. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(1):111-9.
123. Pednekar MS, Sansone G, Gupta PC. Association of alcohol, alcohol and tobacco with mortality: findings from a prospective cohort study in Mumbai (Bombay), India. Alcohol. 2012;46(2):139-46.
124. Santha T, Garg R, Frieden TR, Chandrasekaran V, Subramani R, Gopi PG, et al. Risk factors associated with default , failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District , South India , 2000. INT J TUBERC LUNG DIS 2002;6(May):780-8.
125. Jaggarajamma K, Sudha G, Chandrasekaran V, Nirupa C, Thomas A, Santha T, Muniyandi M, Narayanan PR. Reasons for non-compliance among patients treated under Revised National Tuberculosis Control Programme (RNTCP), Tiruvallur district, south India. Indian J Tuberc. 2007 Jul;54(3):130-5.
126. Vijay S, Kumar P, Chauhan LS, Hanumanthappa B, Kizhakkethil UP, Rao SG. Risk Factors Associated with Default among New Smear Positive TB Patients Treated Under DOTS in India. PLoS ONE. 2010;5(4).
127. Theron G, Peter J, Zijenah L, Chanda D, Mangu C, Clowes P, et al. Psychological distress and its relationship with non-adherence to TB treatment: a multicentre study. BMC Infect Dis. 2015;15:253.
128. Louw JS, Mabaso M, Peltzer K. Change in Health-Related Quality of Life among Pulmonary Tuberculosis Patients at Primary Health Care Settings in South Africa: A Prospective Cohort Study. PLoS One. 2016;11(5):e0151892.
129. Wabe NT. Chemistry, pharmacology, and toxicology of khat (catha edulis forsk): a review. Addict Health. 2011;3(3-4):137-49.
130. http://healthbrk.com/health-problems/disease-symptoms/8532-khat-qat-or-chat-facts-and-information. Accessed on 25/01/2017. 2016:2016-.
131. El-Menyar A, Mekkodathil A, Al-Thani H, Al-Motarreb A. Khat use: history and heart failure. Oman Med J. 2015 Mar;30(2):77-82.
132. Dhadphale M, Omolo OE. Psychiatric morbidity among khat chewers. East Afr Med J. 1988 Jun;65(6):355-9.
133. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of Mycobacterium tuberculosis infection by macrophage immune modulation? Med Hypotheses. 2014;82(6):667-9.

134. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study. J Pharm Policy Pract. 2017;10:36.
135. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of Saudi Arabia. PloS one. 2015;10(10):e0140245-e.
136. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2004;148(1):11-5.
137. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bulletin of the World Health Organization. 2007;85(9):703-11.
138. Pablos-Mendez A, Knirsch CA, Barr RG, Lerner BH, Frieden TR. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. The American journal of medicine. 1997;102(2):164-70.
139. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and tuberculosis treatment outcomes, quality of life and disability, Ethiopia. Bulletin of the World Health Organization. 2018;96(4):243-55.
140. Silva MR, Pereira JC, Costa RR, Dias JA, Guimaraes MDC, Leite ICG. Drug addiction and alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort study. Epidemiol Infect. 2017;145(16):3516-24.
141. Saban A, Flisher AJ, Grimsrud A, Morojele N, London L, Williams DR, et al. The association between substance use and common mental disorders in young adults: results from the South African Stress and Health (SASH) Survey. The Pan African medical journal. 2014;17 Suppl 1(Suppl 1):11.
142. Janse Van Rensburg A, Dube A, Curran R, Ambaw F, Murdoch J, Bachmann M, Petersen I, Fairall L. Comorbidities between tuberculosis and common mental disorders: a scoping review of epidemiological patterns and person-centred care interventions from low-to-middle income and BRICS countries. Infect Dis Poverty. 2020 Jan 15;9(1):4.
143. Peltzer K, Naidoo P, Matseke G, Louw J, McHunu G, Tutshana B. Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. BMC psychiatry. 2012;12(1):89.
144. Tola HH, Shojaeizadeh D, Garmaroudi G, Tol A, Yekaninejad MS, Ejeta LT, et al. Psychological distress and its effect on tuberculosis treatment outcomes in Ethiopia. Global Health Action. 2015;8(1):29019.
145. Ruiz-Grosso P, Cachay R, de la Flor A, Schwalb A, Ugarte-Gil C. Association between tuberculosis and depression on negative outcomes of tuberculosis treatment: A systematic review and meta-analysis. PLoS One. 2020;15(1):e0227472.
146. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008 Feb;4(1):269-86.
147. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001:pp1-40.
148. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated factors among people living with HIV who are attending services in south west Ethiopia. BMC research notes. 2014;7(1):828-.
149. Mikami I, Akechi T, Kugaya A, Okuyama T, Nakano T, Okamura H, et al. Screening for nicotine dependence among smoking-related cancer patients. Japanese journal of cancer research : Gann. 1999;90(10):1071-5.

150. Ababa A. Guidelines for clinical and programmatic management of tb, leprosy and tb/hiv in ethiopia fifth edition. 2012.
151. Kebede D, Alem A, Shibre T, Negash A, Deyassa N, Beyero T. Health related quality of life (SF-36) survey in Butajira, rural Ethiopia: normative data and evaluation of reliability and validity. Ethiop Med J. 2004 Oct;42(4):289-97.
152. Ware JE. How to score and interpret single-item health status measures: a manual for users of the of the SF-8 health survey. 2001. p. 220-.
153. Robert Koch I. Instrument Manual: Oslo-3 Social Support Scale (OSS-3). 2006. 2006;2006(1).
154. Coates J, Swindale A, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for measurement of food access: indicator guide. Washington, DC: Food and Nutrition Technical …. 2007(August):Version 3-Version
155. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity, mental health and quality of life among people living with HIV commencing antiretroviral treatment in Ethiopia: a cross-sectional study. Health and quality of life outcomes. 2016;14:37-.
156. Maes KC, Hadley C, Tesfaye F, Shifferaw S, Tesfaye YA. Food insecurity among volunteer AIDS caregivers in Addis Ababa, Ethiopia was highly prevalent but buffered from the 2008 food crisis. The Journal of nutrition. 2009;139(9):1758-64.
157. Thomas B, Watson B, Senthil EK, Deepalakshmi A, Balaji G, Chandra S, et al. Alcohol intervention strategy among tuberculosis patients: a pilot study from South India. Int J Tuberc Lung Dis. 2017;21(8):947-52.
158. Shin S, Livchits V, Connery HS, Shields A, Yanov S, Yanova G, et al. Effectiveness of alcohol treatment interventions integrated into routine tuberculosis care in Tomsk, Russia. Addiction. 2013;108(8):1387-96.
159. Peltzer K, Louw J, McHunu G, Naidoo P, Matseke G, Tutshana B. Hazardous and harmful alcohol use and associated factors in tuberculosis public primary care patients in South Africa. Int J Environ Res Public Health. 2012;9(9):3245-57.
160. Peltzer K, Naidoo P, Louw J, Matseke G, Zuma K, McHunu G, et al. Screening and brief interventions for hazardous and harmful alcohol use among patients with active tuberculosis attending primary public care clinics in South Africa: results from a cluster randomized controlled trial. BMC Public Health. 2013;13:699.
161. Schramm-Sapyta NL, Walker QD, Caster JM, Levin ED, Kuhn CM. Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models. Psychopharmacology (Berl). 2009;206(1):1-21.
162. Bohn MJ, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. Journal of studies on alcohol. 1995;56(4):423-32.
163. WHO. Global status report on alcohol and health, 2011.
164. Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction. 2018;113(10):1905-26.
165. Hayes-Larson E, Hirsch-Moverman Y, Saito S, Frederix K, Pitt B, Maama-Maime L, et al. Depressive symptoms and hazardous/harmful alcohol use are prevalent and correlate with stigma among TB-HIV patients in Lesotho. Int J Tuberc Lung Dis. 2017;21(11):34-41.
166. De la Haye B, Wild SH, Stevenson J, Johnston F, Blatchford O, Laurenson IF. Tuberculosis and alcohol misuse in Scotland: a population-based study using enhanced surveillance data. Int J Tuberc Lung Dis. 2012;16(7):886-90.
167. Thapa P, Kamath R, Shetty BK, Monteiro A, Sekaran VC. Prevalence and Associated Factors of Alcoholism among Tuberculosis Patients in Udupi Taluk, Karnataka, India: A Cross Sectional Study. Journal of Nepal Health Research Council. 2014;12(28):177-81.

168. O'Connell R, Chishinga N, Kinyanda E, Patel V, Ayles H, Weiss HA, et al. Prevalence and correlates of alcohol dependence disorder among TB and HIV infected patients in Zambia. PLoS One. 2013;8(9):e74406.
169. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. Drug Alcohol Depend. 2015;156:1-13.
170. H Thomasson H.R. (2002) Gender Differences in Alcohol Metabolism. In: Galanter M. et al. (eds) Recent Developments in Alcoholism. Recent Developments in Alcoholism, vol 12. Springer, Boston, MA.
171. Wilsnack RW, Vogeltanz ND, Wilsnack SC, Harris TR, Ahlström S, Bondy S, et al. Gender differences in alcohol consumption and adverse drinking consequences: cross-cultural patterns. Addiction. 2000;95(2):251-65.
172. Veerakumar AM, Sahu SK, Sarkar S, Kattimani S, Govindarajan S. Alcohol use disorders among pulmonary tuberculosis patients under RNTCP in urban Pondicherry, India. The Indian journal of tuberculosis. 2015;62(3):171-7.
173. Hayes-Larson E, Hirsch-Moverman Y, Saito S, Frederix K, Pitt B, Maama-Maime L, et al. Depressive symptoms and hazardous/harmful alcohol use are prevalent and correlate with stigma among TB-HIV patients in Lesotho. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2017;21(11):34-41.
174. Khaderi SA. Introduction: Alcohol and Alcoholism. Clin Liver Dis. 2019;23(1):1-10.
175. Rosoff DB, Clarke TK, Adams MJ, McIntosh AM, Davey Smith G, Jung J, et al. Educational attainment impacts drinking behaviors and risk for alcohol dependence: results from a two-sample Mendelian randomization study with ~780,000 participants. Mol Psychiatry. 2019.
176. Haile D, Lakew Y. Khat Chewing Practice and Associated Factors among Adults in Ethiopia: Further Analysis Using the 2011 Demographic and Health Survey. PLoS One. 2015 Jun 19;10(6).

177. Stevenson M, Fitzgerald J, Banwell C. Chewing as a social act: cultural displacement and khat consumption in the East African communities of Melbourne. Drug Alcohol Rev. 1996;15(1):73-82.
178. Rampes GCH. Adverse effects of khat: a review: Advances in Psychiatric Treatment; 2003. 456–63 p.
179. Teferra S, Hanlon C, Alem A, Jacobsson L, Shibre T. Khat chewing in persons with severe mental illness in Ethiopia: a qualitative study exploring perspectives of patients and caregivers. Transcult Psychiatry. 2011 Sep;48(4):455-72.

180. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to anti-tuberculosis treatment in Yemen. Journal of Pharmaceutical Health Services Research. 2013;4(2):115-22.
181. National Institute on Drug Abuse. Substance Use in Women, 2019.
182. Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. Psychiatr Clin North Am. 2010;33(2):339-55.
183. Cormier RA, Dell CA, Poole N. Women and Substance Abuse Problems. BMC Womens Health. 2004;4 Suppl 1:S8.
184. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center, WolaitaSodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015;15:214.
185. Damena T, Mossie A, Tesfaye M. Khat chewing and mental distress: a community based study, in jimma city, southwestern ethiopia. Ethiopian journal of health sciences. 2011;21(1):37-45.

186. Hassan NA, Gunaid AA, El-Khally FM, Murray-Lyon IM. The effect of chewing Khat leaves on human mood. Saudi Med J. 2002;23(7):850-3.
187. Omolo OE, Dhadphale M. Alcohol use among khat (Catha) chewers in Kenya. Br J Addict. 1987;82(1):97-9.
188. Mihretu A, Teferra S, Fekadu A. Problematic khat use as a possible risk factor for harmful use of other psychoactive substances: a mixed method study in Ethiopia. Subst Abuse Treat Prev Policy. 2017;12(1):47.
189. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of Mycobacterium tuberculosis infection by macrophage immune modulation? Med Hypotheses. 2014;82(6):667-9.
190. Ranzani OT, Rodrigues LC, Bombarda S, Minto CM, Waldman EA, Carvalho CRR. Long-term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010-15: a population-based, longitudinal study. Lancet Infect Dis. 2020;20(1):123-32.
191. Corkery JM, Schifano F, Oyefeso A, Ghodse AH, Tonia T, Naidoo V, et al. Overview of literature and information on "khat-related" mortality: a call for recognition of the issue and further research. Ann Ist Super Sanita. 2011;47(4):445-64.
192. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of Saudi Arabia. PLoS One. 2015;10(10):e0140245.
193. Santha T, Garg R, Frieden TR, Chandrasekaran V, Subramani R, Gopi PG, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. Int J Tuberc Lung Dis. 2002;6(9):780-8.
194. Wondemagegn AT, Cheme MC, Kibret KT. Perceived Psychological, Economic, and Social Impact of Khat Chewing among Adolescents and Adults in Nekemte Town, East Welega Zone, West Ethiopia. Biomed Res Int. 2017;2017:7427892.
195. Abate A, Tareke M, Tirfie M, Semachew A, Amare D, Ayalew E. Chewing khat and risky sexual behavior among residents of Bahir Dar City administration, Northwest Ethiopia. Ann Gen Psychiatry. 2018;17:26.
196. Ageely HM. Health and socio-economic hazards associated with khat consumption. J Family Community Med. 2008;15(1):3-11.
197. Safa M, Tabarsi P, Sharifi H. Pattern of Tobacco Consumption among TB Patients in a Tuberculosis Referral Center. Tanaffos. 2011;10(2):50-5.
198. Ajema D, Shibru T, Endalew T, Gebeyehu S. Level of and associated factors for non-adherence to anti-tuberculosis treatment among tuberculosis patients in Gamo Gofa zone, southern Ethiopia: cross-sectional study. BMC Public Health. 2020;20(1):1705.
199. Lakew Y, Haile D. Tobacco use and associated factors among adults in Ethiopia: further analysis of the 2011 Ethiopian Demographic and Health Survey. BMC Public Health. 2015;15:487.
200. Leavens ELS, Morgan TL, Brett EI, Patzkowsky K, Son J, Molina N, et al. Concurrent Alcohol Use and Waterpipe Tobacco Smoking: Smoking Topography, Toxicant Exposure, and Abuse Liability. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2020;22(2):280-7.
201. Schmid B, Hohm E, Blomeyer D, Zimmermann US, Schmidt MH, Esser G, et al. Concurrent alcohol and tobacco use during early adolescence characterizes a group at risk. Alcohol and Alcoholism. 2007;42(3):219-25.
202. Tullu M, Azale T, Abebaw D, Solomon H, Habtamu Y. Prevalence of Cannabis Use Disorder and Associated Factors among Cannabis Young Adult Users at Shashemene Town, Oromia Region, Ethiopia, 2016. Psychiatry journal. 2018;2018:6731341.

203. Jaber AAS, Ibrahim B. Health-related quality of life of patients with multidrug-resistant tuberculosis in Yemen: prospective study. Health Qual Life Outcomes. 2019 Aug 16;17(1):142.
204. Maguire GP, Anstey NM, Ardian M, Waramori G, Tjitra E, Kenangalem E, et al. Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. Int J Tuberc Lung Dis. 2009;13(12):1500-6.
205. Kittikraisak W, Kingkaew P, Teerawattananon Y, Yothasamut J, Natesuwan S, Manosuthi W, et al. Health related quality of life among patients with tuberculosis and HIV in Thailand. PLoS One. 2012;7(1):e29775.
206. Miller TL, McNabb SJ, Hilsenrath P, Pasipanodya J, Weis SE. Personal and societal health quality lost to tuberculosis. PLoS One. 2009;4(4):e5080.
207. Weiss EL, Longhurst JG, Mazure CM. Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. The American journal of psychiatry. 1999;156(6):816-28.
208. Chang B, Wu AW, Hansel NN, Diette GB. Quality of life in tuberculosis: a review of the English language literature. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2004;13(10):1633-42.
209. Malik M, Nasir R, Hussain A. Health Related Quality of Life among TB Patients: Question Mark on Performance of TB DOTS in Pakistan. J Trop Med. 2018 Feb 12;2018:2538532.
210. Darvishpoor Kakhki A, Masjedi MR. Factors Associated with Health-Related Quality of Life in Tuberculosis Patients Referred to the National Research Institute of Tuberculosis and Lung Disease in Tehran. Tuberculosis and respiratory diseases. 2015;78(4):309-14.
211. Kruijshaar ME, Lipman M, Essink-Bot ML, Lozewicz S, Creer D, Dart S, et al. Health status of UK patients with active tuberculosis. Int J Tuberc Lung Dis. 2010;14(3):296-302.
212. Budweiser S, Hitzl AP, Jörres RA, Schmidbauer K, Heinemann F, Pfeifer M. Health-related quality of life and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. Respiratory research. 2007;8(1):92.
213. Atif M, Sulaiman SA, Shafie AA, Asif M, Sarfraz MK, Low HC, et al. Impact of tuberculosis treatment on health-related quality of life of pulmonary tuberculosis patients: a follow-up study. Health and quality of life outcomes. 2014;12:19.
214. Mohammed S, Nagla S, Morten S, Asma E, Arja A. Illness perceptions and quality of life among tuberculosis patients in Gezira, Sudan. Afr Health Sci. 2015;15(2):385-93.
215. Mamani M, Majzoobi MM, Ghahfarokhi SM, Esna-Ashari F, Keramat F. Assessment of Health-related Quality of Life among Patients with Tuberculosis in Hamadan, Western Iran. Oman Med J. 2014 Mar;29(2):102-5.
216. Pachi A, Bratis D, Moussas G, Tselebis A. Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients. Tuberc Res Treat. 2013;2013:489865.
217. Qadir F, Khalid A, Haqqani S, Zill e H, Medhin G. The association of marital relationship and perceived social support with mental health of women in Pakistan. BMC Public Health. 2013;13(1):1150.
218. Guo N, Marra CA, Marra F, Moadebi S, Elwood RK, Fitzgerald JM. Health state utilities in latent and active tuberculosis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2008;11(7):1154-61.
219. Kibrisli E, Bez Y, Yilmaz A, Aslanhan H, Taylan M, Kaya H, et al. High social anxiety and poor quality of life in patients with pulmonary tuberculosis. Medicine. 2015;94(3):e413.
220. Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J. 2014;43(2):554-65.

221. Kirenga BJ, Ssengooba W, Muwonge C, Nakiyingi L, Kyaligonza S, Kasozi S, et al. Tuberculosis risk factors among tuberculosis patients in Kampala, Uganda: implications for tuberculosis control. BMC Public Health. 2015;15:13.
222. Tola HH, Shojaeizadeh D, Garmaroudi G, Tol A, Yekaninejad MS, Ejeta LT, et al. Psychological distress and its effect on tuberculosis treatment outcomes in Ethiopia. Glob Health Action. 2015;8:29019 .
223. Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol. 1997;48:191-214.
224. Paulo BX, Peixoto B. Emotional distress patients with several types of tuberculosis. A pilot study with patients from the Sanatorium Hospital of Huambo. International journal of mycobacteriology. 2016;5 Suppl 1:S58.
225. Theron G, Peter J, Zijenah L, Chanda D, Mangu C, Clowes P, et al. Psychological distress and its relationship with non-adherence to TB treatment: a multicentre study. BMC Infect Dis. 2015;15:253.
226. Ayana TM, Roba KT, Mabalhin MO. Prevalence of psychological distress and associated factors among adult tuberculosis patients attending public health institutions in Dire Dawa and Harar cities, Eastern Ethiopia. BMC Public Health. 2019;19(1):1392.
227. Wang XB, Li XL, Zhang Q, Zhang J, Chen HY, Xu WY, Fu YH, Wang QY, Kang J, Hou G. A Survey of Anxiety and Depressive Symptoms in Pulmonary Tuberculosis Patients With and Without Tracheobronchial Tuberculosis. Front Psychiatry. 2018 Jul 19;9:308.
228. Dachew BA, Bifftu BB, Tiruneh BT, Anlay DZ, Wassie MA. Prevalence of mental distress and associated factors among university students in Ethiopia: a meta-analysis. J Ment Health. 2019 Jun 28:1-8.
229. Parslow, R.A., Jorm, A.F., Christensen, H. et al. The impact of employee level and work stress on mental health and GP service use: an analysis of a sample of Australian government employees. BMC Public Health 4, 41 (2004).
230. Sareen J, Afifi TO, McMillan KA, Asmundson GJ. Relationship between household income and mental disorders: findings from a population-based longitudinal study. Archives of general psychiatry. 2011;68(4):419-27.
231. Steven M. Cole GT. The effect of food insecurity on mental health: Panel evidence from rural Zambia: Social Science & Medicine; 2011. 1071e9 p.
232. Jones AD. Food Insecurity and Mental Health Status: A Global Analysis of 149 Countries. Am J Prev Med. 2017;53(2):264-73.
233. Tomita A, Ramlall S, Naidu T, Mthembu SS, Padayatchi N, Burns JK. Major depression and household food insecurity among individuals with multidrug-resistant tuberculosis (MDR-TB) in South Africa. Soc Psychiatry Psychiatr Epidemiol. 2019;54(3):387-93.
234. Birhanu TT, Tadesse AW. Food Insecurity and Mental Distress among Mothers in Rural Tigray and SNNP Regions, Ethiopia. Psychiatry journal. 2019;2019:7458341.
235. Sweetland AC, Norcini Pala A, Mootz J, Kao JC, Carlson C, Oquendo MA, et al. Food insecurity, mental distress and suicidal ideation in rural Africa: Evidence from Nigeria, Uganda and Ghana. Int J Soc Psychiatry. 2019;65(1):20-7.
236. Molla A, Mekuriaw B, Kerebih H. Depression and associated factors among patients with tuberculosis in Ethiopia: a cross-sectional study. Neuropsychiatr Dis Treat. 2019;15:1887-93.
237. Duko B, Bedaso A, Ayano G, Yohannis Z. Perceived Stigma and Associated Factors among Patient with Tuberculosis, Wolaita Sodo, Ethiopia: Cross-Sectional Study. Tuberc Res Treat. 2019;2019:5917537.
238. Da Silva RD, de Luna FDT, de Araújo AJ, Camêlo ELS, Bertolozzi MR, Hino P, et al. Patients' perception regarding the influence of individual and social vulnerabilities on the adherence to tuberculosis treatment: a qualitative study. BMC Public Health. 2017;17(1):725.

239. Long NH, Johansson E, Diwan VK, Winkvist A. Fear and social isolation as consequences of tuberculosis in VietNam: a gender analysis. Health policy (Amsterdam, Netherlands). 2001;58(1):69-81.
240. Tadesse S. Stigma against Tuberculosis Patients in Addis Ababa, Ethiopia. PLoS One. 2016;11(4):e0152900.
241. Chen B, Peng Y, Zhou L, Chai C, Yeh HC, Chen S, et al. Social support received by multidrug-resistant tuberculosis patients and related factors: a cross-sectional study in Zhejiang Province, People's Republic of China. Patient preference and adherence. 2016;10:1063-70.
242. WHO. WHO Guidelines Approved by the Guidelines Review Committee. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization Copyright © World Health Organization 2014.; 2014.

243. Duko B, Geja E, Zewude M, Mekonen S. Prevalence and associated factors of depression among patients with HIV/AIDS in Hawassa, Ethiopia, cross-sectional study. Ann Gen Psychiatry. 2018;17:45.
244. Zarova C, Chiwaridzo M, Tadyanemhandu C, Machando D, Dambi JM. The impact of social support on the health-related quality of life of adult patients with tuberculosis in Harare, Zimbabwe: a cross-sectional survey. BMC research notes. 2018;11(1):795.
245. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review. Iranian journal of public health. 2015;44(1):1-11.
246. Samal J, Dehury R. Role of families in tuberculosis care: A case study. Muller Journal of Medical Sciences and Research. 2016;7:150.
247. Charyeva Z, Curtis S, Mullen S, Senik T, Zaliznyak O. What works best for ensuring treatment adherence. Lessons from a social support program for people treated for tuberculosis in Ukraine. PLoS One. 2019;14(8):e0221688.
248. Baniqued MG, Ballecer BAP, Ballesteros BDC, Balmonte JRR, Bancud EMF, Rebueno M, et al. Social support from nurses and non-adherence with directly observed therapy (DOTS) maintenance phase among patients with tuberculosis in Metro Manila, Philippines. Public Health Nurs. 2020;37(3):339-46.
249. Marquez B, Anderson A, Wing RR, West DS, Newton RL, Meacham M, et al. The relationship of social support with treatment adherence and weight loss in Latinos with type 2 diabetes. Obesity (Silver Spring). 2016;24(3):568-75.
250. Arifin VN, Nur JA, and Uzair FM. The Relationship of Social Support with Medication Adherence Pulmonary Tuberculosis Patients Through DOTS Strategy in Pidie Aceh Indonesia: IOP Conference Series: Materials Science and Engineering; 2019.
251. Ambaw F, Mayston R, Hanlon C, Alem A. Incidence of depression in people with newly diagnosed tuberculosis in Ethiopia: a cohort study. Global mental health (Cambridge, England). 2020;7:e1.
252. Naidoo P, Mwaba K. Helplessness, Depression, and Social Support Among People Being Treated for Tuberculosis in South Africa. Social Behavior and Personality: an international journal. 2010;38:1323-33.
253. Adjaye-Gbewonyo D, Rebok GW, Gross AL, Gallo JJ, Underwood CR. Assessing urban-rural differences in the relationship between social capital and depression among Ghanaian and South African older adults. PLoS One. 2019;14(6):e0218620.
254. Chruściel P, Kulik T, Jakubowska K, Nalepa D. Differences in the Perception of Social Support Among Rural Area Seniors-A Cross-Sectional Survey of Polish Population. Int J Environ Res Public Health. 2018;15(6).

255. Saqib SE, Ahmad MM, Panezai S. Care and social support from family and community in patients with pulmonary tuberculosis in Pakistan. Family medicine and community health. 2019;7(4):e000121.
256. Bloem MW, Saadeh R. Foreword: The role of nutrition and food insecurity in HIV and tuberculosis infections and the implications for interventions in resource-limited settings. Food Nutr Bull. 2010 Dec;31(4 Suppl):S289-91.

257. Balinda IG, Sugrue DD, Ivers LC. More Than Malnutrition: A Review of the Relationship Between Food Insecurity and Tuberculosis. Open Forum Infect Dis. 2019;6(4):ofz102.
258. Ayiraveetil R, Sarkar S, Chinnakali P, Jeyashree K, Vijayageetha M, Thekkur P, et al. Household food insecurity among patients with pulmonary tuberculosis and its associated factors in South India: a cross-sectional analysis. BMJ Open. 2020;10(2):e033798.
259. Jung NM, de Bairros FS, Pattussi MP, Pauli S, Neutzling MB. Gender differences in the prevalence of household food insecurity: a systematic review and meta-analysis. Public Health Nutr. 2017 Apr;20(5):902-916.
260. Maynard M, Andrade L, Packull-McCormick S, Perlman CM, Leos-Toro C, Kirkpatrick SI. Food Insecurity and Mental Health among Females in High-Income Countries. Int J Environ Res Public Health. 2018;15(7).
261. Jebena MG, Lindstrom D, Belachew T, Hadley C, Lachat C, Verstraeten R, et al. Food Insecurity and Common Mental Disorders among Ethiopian Youth: Structural Equation Modeling. PloS one. 2016;11(11):e0165931-e.

Appendix

Published munuscript

a. Publishded

PLOS ONE

RESEARCH ARTICLE

Magnitude and predictors of khat use among patients with tuberculosis in Southwest Ethiopia: A longitudinal study

Matiwos Soboka[1,2]*, Omega Tolessa[3], Markos Tesfaye[2,4], Kristina Adorjan[2,5,6], Wolfgang Krahl[2,7], Elias Tesfaye[1], Yimenu Yitayih[1], Ralf Strobl[8], Eva Grill[2,8]

1 Department of Psychiatry, Jimma University, Jimma, Ethiopia, 2 Center for International Health, Ludwig Maximilian University, Munich, Germany, 3 Department of Nursing, Wolkite University, Wolkite, Ethiopia, 4 Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 5 Department of Psychiatry and Psychotherapy, LMU, Munich, Germany, 6 Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany, 7 Department of Forensic Psychiatry, IsarAmper Klinikum, Munich, Germany, 8 Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

Abstract

Introduction: Tuberculosis (TB) is a leading cause of morbidity and mortality in low and middle-income countries. Substance use negatively affects TB treatment outcomes. Our recent study has found that khat use predicted poorer adherence to anti-TB medications. However, there is scarce longitudinal study on predictors of khat use among outpatients with TB, and this study aimed at addressing this research gap.

Methods: From October 2017 to October 2018, 268 outpatients with tuberculosis on DOTs were enrolled in a longitudinal study from 26 health institutions in Southwest Ethiopia. Structured questionnaires translated into local languages (Afaan Oromoo and Amharic) were used to assess khat use. Patients were followed for six months, and data were collected on three occasions during the follow-up. A generalized linear mixed model was used to identify the relation between khat use and predictors. Model fitness was checked using the Bayesian Information Criterion (BIC). Odds ratio (OR) and 95% CI were used to describe the strength of association between the outcome variable and predictors.

Results: The overall prevalence of khat use at baseline and first follow up was 39.2% while it was 37.3% at second follow up. Of this, 77.1% and 96.2% of them believed that khat use reduces the side effects of anti-TB medications and symptoms of tuberculosis respectively. In the final model, being male (aOR=7.0, p-value=0.001), being government employee (aOR=0.03, p-

value≤0.001) and presence of alcohol use disorders (AUD) (aOR=2.0, p-value≤0.001) predicted khat use among outpatients with tuberculosis.

Conclusion: A considerable proportion of patients with TB used khat throughout DOTs and wrongly perceived that it had health benefits. The finding implies that all patients diagnosed with TB should be screened for khat use, and a particular emphasis should be given to males and individuals with a history of alcohol use. Moreover, further studies are needed to assess patients' beliefs regarding the benefits of khat use so that interventions can be developed.

Keywords: Khat use, alcohol use disorder, tuberculosis, anti-TB adherence, Ethiopia, sub-Saharan Africa.

Introduction

Globally, despite the availability of effective anti-TB drugs, tuberculosis (TB) remains a major public health problem and one of the top ten causes of death from a single agent (1). According to the 2018 World Health Organization (WHO) report, 10 million people were infected by TB across the world, while an estimated 1.6 million of people died because of the disease in 2017 (1). The burden of TB is exceptionally high in middle and low-income countries because of poverty, malnutrition, overcrowded living condition, poor ventilation, HIV, and other chronic diseases. Similarly, substance use disorders, remain the major contributing factors for TB in these countries (1-5). Almost 90% of all patients with TB living in these countries face elevated TB-related mortality rates (1, 4). Out of the total deaths attributed to TB in 2017, over 80% of the deaths were from Africa and Southeast Asia (1). Ethiopia is one of the 22 countries with the highest burden of tuberculosis with an incidence rate of 164 and a mortality rate of 24 per 100,000 (1, 4). Moreover, TB was the second most frequent cause of death in Ethiopia next to Malaria (4). Non-adherence to the medication has been earmarked as one of the major issues contributing to excess mortality in Ethiopia (6-8). Besides, non-adherence increases the risk of multi-resistant TB strains. While any substance use disorder among patients with TB might decrease adherence, it has been shown that excessive use of khat and alcohol may be one major reason for non-adherence to treatment regimens in Ethiopia (9-11).

Khat is an amphetamine-like natural stimulant that has legally been used for many years in East Africa and the Southern Arabian Peninsula (12-14). Khat use belongs to stimulant use disorder (15). Fresh leaves of khat contain more than 40 types of compounds, among these, cathinone and cathine are known stimulants (12-14, 16, 17).

Studies showed that people use khat to be alert while praying, to reduce the feeling of hunger, to enhance productivity at work, and to elevate their mood and to be physically strong (18-22). Also, factors such as common mental disorder, being male, and other sociodemographic characteristics were found to determine khat use in the general population (21, 23). However, using khat for a long period leads to khat use disorder which could have a potential impact on the mental and physical health of the users (24, 25). Likewise, cathinone which is found in khat has been linked to a decreased immune response that might increase the risk of developing TB (26). Besides, TB seems to be more frequently underdiagnosed in khat users (27-29). Khat users with TB were found to have higher bacillary load and were more likely to develop drug resistance (30). Also, they were more likely to be stigmatized (31), had longer treatment regimens (32),

poor adherence (7, 19), poor appetite (33), and increased levels of anxiety (10). Even though khat use is known to affect treatment outcomes and mental health of patients with tuberculosis, there is only limited longitudinal study on the magnitude and predictors of khat use among patients with TB in Ethiopia and other African countries. Knowing the predictors and magnitude of khat use would help to tailor interventions and to intensify the efforts to improve treatment outcomes of TB. Moreover, early identification of predictors of khat use is important to take preventive measures to mitigate complications such as comorbid mental illness and MDR-TB. Therefore, our study aimed at assessing longitudinally the magnitude and predictors of khat use among patients with TB in Southwest Ethiopia.

Methods

Study area and design

A longitudinal study was conducted among patients with tuberculosis in Jimma Zone, Southwest Ethiopia. Jimma Zone has more than three million inhabitants; about 3% of the total population of Ethiopia. In Ethiopia, TB care is mainly provided by local decentralized health centers to increase take-up of therapy and to monitor Directly Observed Treatment (DOT). There were 112 health centers in Jimma Zone. Out of these, 91 were providing services for patients with TB at the time of data collection.. Likewise, there were dedicated TB treatment services at all hospitals. Patients were recruited from four hospitals and 22 randomly selected health centers of Jimma Zone. Twenty health centers and three hospitals were situated in rural areas whereas one hospital and two health centers are found in Jimma town. The study was conducted over a year from October 2017 to October 2018.

Study population and sampling procedure

This study included all patients who had recently been diagnosed with TB and started DOT in the selected health centers and hospitals. Patients who had started TB treatment within less than four weeks and not planning to transfer to other health institutions were included in the study. There are two reasons for including new patients who started treatment within four weeks. The first one is to see if there will be any change over time and the second is to see whether the patients increase or decrease their Khat use. Patients whose age is less than 18 years, patients infected with multidrug-resistant TB strains, polysubstance users (using three or more substances), and patients who were hospitalized during data collection were excluded from the study. The data for this study was drawn from a cohort registered as ጤ/ኢ/ም/ድ/ም/ዳ/476/2011

(Institute of health, research, and postgraduate director 476/2011) which aimed to assess substance use disorder, quality of life, mental health and adherence to anti-TB medication. The sample was calculated considering power=80%, 95% confidence interval, 62.4% prevalence of non-adherence to anti-TB medications among khat users, 43.6% prevalence of non-adherence among non-khat user TB patients, and 20% of drop out. The total sample size was 268, and patients who fulfilled the inclusion criteria and consented to participate in the study during the data collection period were consecutively recruited then baseline data were collected. Patients were followed on two occasions: at the end of two and six months.

Patients who were using khat (105) and free of khat use (163) were followed for six months. Detail information regarding the study was given by trained data collectors to each patient before the written informed consent was obtained.

Data collection procedure

Before data collection, the questionnaires were pretested on a sample (5% of the total sample) of patients with TB outpatients who had been on treatment at one health center in Agaro (a town found in Jimma zone at a distance of about 45 kilometers from Jimma city) to check whether the questions work as intended or understood by patients. Fourteen patients from the pretest were not included in the final analysis of the data. Patients were interviewed on three occasions, namely, baseline (starting treatment), first follow up (after 2 months), and second follow up (at the end of six months). The follow up was made at the end of two and six months of treatment because it is the end of intensive as well as the continuous phase of the treatment. Also, at the end of the six-month, patients received another test for tuberculosis so that the status of the patients would be known. Recruitment of patients and data collection were carried out by health professionals who were working in the tuberculosis clinic and specifically trained on the questionnaires, supervised by trained district focal persons. Interviews were conducted within the respective health institutions when the participants came for their TB clinic visits. All questionnaires including the pretest were translated into Afaan Oromoo and Amharic languages because the participants speak either of the two languages.

Data collection tools

Outcome variable: A questionnaire used to assess khat use was developed after reviewing different kinds of literature because there is no specific standard tool to assess khat use in any population. In this study, khat use was defined as using khat in the past 30 days before the

interview (34). The questionnaire includes ever use of khat, current khat use, frequency, amount, and patients' beliefs regarding khat use.

Explanatory variables

Socio-demographic characteristics: Structured questionnaires were used to assess the socio-demographic characteristics (age, sex, marital status, level of education, religion, ethnicity, annual income, household size, occupation, place of residence) of the participants. Income was categorized considering the minimum monthly wage for employees of a governmental organization in Ethiopia which is 1,214 Ethiopian birr (36.67 Euros) (35). Then, the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian birr (439.98 Euros).

Alcohol use disorders (AUDs): Alcohol use disorder identification test (AUDIT) was used to assess alcohol use disorders. The AUDIT has been evaluated over two decades and provides an accurate measure of the risk of AUDs across gender, age, and cultures. A multi-country validation of AUDIT among people attending primary health care in Norway, Australia, Kenya, Bulgaria, Mexico and the United States of America showed that at a cut-off score of eight or more, the sensitivity and specificity of AUDIT for AUDs were 0.90 and 0.80, respectively (36). The AUDIT has been translated and adapted for studies in the Ethiopian setting (37).

Disease-related factors: Type of TB diagnoses (smear-positive, smear-negative, and extrapulmonary TB) were collected from the patients' charts.

Comorbidities: Any comorbidity such as HIV, previous mental illness, hypertension, and diabetes mellitus were collected from patients' charts.

Mental distress: Self-reporting questionnaire-20 (SRQ-20) which was developed by WHO was used to assess mental distress. This questionnaire assesses depressive, anxiety, and somatic symptoms that patients have experienced in the past four weeks. SRQ-20 has been adapted and validated in the Ethiopian setting, but the cut-off point varies from study to study (38, 39). In this study, a total score of below 7 indicates the absence of mental distress whereas values of 7 and above indicate mental distress. At a cut-off point 7/8 the sensitivity and specificity was 89.7% and 95.2% respectively (40, 41).

Data analysis

Participants' characteristics and study variables were described using descriptive statistics. A generalized linear mixed model was used to examine the predictors of khat use over six months. The model was built based on the theoretical importance and the adequate number of participants in each cell for each category. The missing value was excluded from the analysis. The findings have been adjusted for potential confounders. An intercept only model was used to investigate khat use over time (model 0) without adding other variables; model 1 investigated the longitudinal association of khat use and socio-demographic characteristics variables. Model 2 investigated the association between socio-demographic variables, mental distress, and the outcome variable (khat use). Model 3 was adjusted for the full set of predictors and examined covariates related to the khat use. Model fit was examined with the Bayesian Information Criterion (BIC). Lower BIC indicates a better model fit. Data were analyzed using R studio (1.2.1335). The study findings are reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Ethical considerations

Ethical clearance was obtained from Jimma University and LMU Ethical Review Boards. After the participants were given detail information about the importance of the study, written informed consent was obtained from each patient. The anonymity of the study participants was kept in all stages of data processing and write-up of the manuscript. Patients who were using khat more than once weekly were advised to contact a mental health professional.

Results

Socio-demographic and clinical characteristic

In this longitudinal study, a total of 268 patients (age range of 18 to 80 years, mean age 32.4, SD =14.4, 60.1% male) were recruited. The majority of the study participants were married (58.6%) and Muslim (61.6%). Two-third (63.1%, n=169) of all participants did not attend formal education (see table 1). A total of 40.3% (n=108), 32.5% (n=87), and 27.2% (n=73) were diagnosed as smear-positive, smear-negative and extrapulmonary TB, respectively. At baseline, 3.7% (n=10) patients were diagnosed with HIV, and 7.1% (n=19) with other comorbidities (see table 1). There were 22 missing data of annual income which we excluded from the analysis.

Table1: Characteristics of patients with tuberculosis in Southwest Ethiopia 2017/18 (n=268).

Variables		Frequency N (%)	Khat use		
			Baseline	First follow-up (end 2nd month)	Second follow-up (end of six months)
			N (%)	N (%)	N (%)
Gender	Male	161(60.1)	75(46.6)	75(46.6)	67(41.6)
	Female	107(39.9)	30(28.0)	30(28.0)	33(30.8)
Age	18-24	93(34.7)	33(35.5)	30(32.3)	28(30.1)
	25-34	87(32.5)	32(36.8)	30(34.5)	32(36.8)
	35-44	36(13.4)	18(50.0)	20(55.6)	15(41.7)
	45-54	27(10.1)	13(48.1)	13(48.1)	13(48.1)
	55-64	25(9.3)	9(36.0)	12(48.0)	12(48.0)
Annual income in Eth Birr	<14,568	206(76.9)	86(41.7)	85(41.3)	83(40.3)
	≥14,568	40(14.9)	11(27.5)	15(37.5)	13(32.5)
Marital status	Single	97(36.2)	33(34.0)	30(30.9)	26(26.8)
	Married	157(58.6)	66(42.0)	70(44.6)	68(43.3)
	Divorced/widow	14(5.2)	6(42.9)	5(35.7)	6(42.9)
Religion	Orthodox	82(30.6)	21(25.6)	19(23.2)	20(24.4)
	Muslim	165(61.6)	83(50.3)	84(50.9)	78(47.3)
	Protestant and others	21(7.8)	1(4.8%)	2(9.5)	2(9.5)
Ethnicity	Amhara	59(22.0)	13(22.0)	12(20.3)	12(20.3)
	Oromo	165(61.6)	79(47.9)	79(47.9)	74(44.8)
	Tigre/Gurage	44(16.4)	13(29.5)	14(31.8)	14(31.8)
Occupation	Merchant	29(10.8)	21(72.4)	7(58.6)	17(58.6)

	Farmer	92(34.3)	47(51.1)	47(51.1)	49(53.3)
	Government Employee	105(39.2)	24(22.9)	26(24.8)	21(20.0)
	Daily laborer	42(15.7)	13(31.0)	15(35.7)	13(31.0)
Education	No formal education	169(63.1)	15(32.5)	56(33.1)	46(27.2)
	Primary/secondary	71(26.5)	35(49.3)	34(47.9)	36(50.7)
	Tertiary	28(10.4)	15(53.6)	15(53.6)	18(64.3)
Family size	Less than 5	181(67.5)	70(38.7)	37(42.5)	66(36.5)
	5 and more	87(32.5)	35(40.2)	8(37.6)	34(39.1)
Residence	Rural	127(47.4)	59(46.5)	57(44.9)	55(43.3)
	Urban	141(52.6)	46(32.6)	48(34.0)	45(31.9)
HIV	Positive	10(3.7)	6(60.0%)	7(58.3)	8(42.1)
	Negative	258(96.3)	99(38.4)	98(38.3)	92(36.9)
Mental distress	No		36(34.6)	55(33.1)	77(36.8)
	Yes		69(42.1)	50(49.0)	23(39.0)

*There were 22 missing data of annual income.

Prevalence of khat use

The prevalence of khat use was 39.2% (n=105) at baseline and after two months, and 37.3% (n=100) at the end of six months. Of the total khat users, 24.8% (n=26), 46.7% (n=49), and 37.0% (n=37) chewed khat daily at baseline, first follow up and second follow up respectively, while 55.2% (n=58), 46.7% (n=49) and 32.0% (n=32) chewed it 2-3 times per week.

Those patients who were using khat were compared against patients free of khat use during the follow-up. Males were found to use khat more than women at baseline (46.6% versus 28.0%, $p<0.05$), at second month (46.6% versus 28.0%, $p<0.001$), and sixth month (41.6% versus 30.8%). The majority of khat users were merchants (72.4%, n=21), followed by farmers (51.1%, n=47), and being educated till the tertiary level (53.6%, n=15) at baseline (see table 1). The

majority of khat users (77.1%, n=81) believed that khat can reduce medication side effects or reduce symptoms of tuberculosis (96.2%, n=101).

The prevalence of mental distress among patients with khat users was 42.1% (n=69), 49.0% (n=50) and 39.0% (n=23) at baseline (T0), first (T1) and second (T2) follow up respectively. At the end of the second month, the majority (76.7%, n=33), of khat users were found to have alcohol use disorder).

Predictors of khat use

The results of multivariable modeling are shown in Table 2. The prevalence of khat use did not change significantly over time (p=0.48 in the final fully adjusted model). The strength of association was improved over time as witnessed by further improvement of model fit (BIC=815.7). Being male and having AUDs were indicators for khat use after multivariable adjustment. Merchants still had a higher probability of khat use than government employees or day laborers. The odds of khat use among government employees was 97% lower when compared to that of merchants (aOR=0.03, p-value= 0.001). Age, income, and mental distress were not associated with khat use.

Table 2: Predictors of khat use among patients with tuberculosis in Southwest Ethiopia (n=268) in 2017/18).

Variables		Intercept only (empty model)			Model1 (Socio-demography)			Model2 (Model 1 including mental distress)			Model3 (Full model)		
		OR	P-Value	95%CI(upper, lower)	aOR	P-Value	95%CI(upper, lower)	aOR	P-Value	95%CI(upper, lower)	aOR	P-Value	95%CI(upper, lower)
Gender	Female	Reference											
	Male	-	-		5.9	0.01	2.0,17.7	5.9	0.01	2.0,17.7	7.0	0.001	2.2,22.2
Age	18-24	Reference											
	25-34	-	-		0.9	0.83	0.2,3.2	0.9	0.83	0.2,3.2	0.9	0.83	0.2.3.4
	35-44	-	-		1.8	0.50	0.3,10.1	1.8	0.49	0.3,10.1	2.0	0.47	0.3,12
	45-54	-	-		1.1	0.91	0.2,7.4	1.1	0.92	0.2,7.4	1.3	0.82	0.2,9.2
	55-64	-	-		0.5	0.41	0.1,3.0	0.5	0.42	0.1,3.0	0.5	0.47	0.1.3.5
Annual Income in Ethiopian birr	<14,568	Reference											
	>14,568	-	-		0.4	0.19	0.1,1.6	0.4	0.19	0.1,1.6	0.3	0.16	0.8,1.5
Occupation	Merchant	Reference											
	Farmer	-	-		0.2	0.08	0.04,1.2	0.2	0.08	0.04,1.2	0.2	0.05	0.02,1.0
	Government Employee	-	-		0.04	0.001	0.01,0.3	0.04	0.001	0.01,0.3	0.03	0.001	0.01,0.2
	Day laborer	-	-		0.1	0.03	0.01,0.8	0.1	0.02	0.02,0.8	0.1	0.01	0.01,0.6
Religion	Orthodox	Reference											

	Muslim		-		3.3	0.04	1.0,10.6	3.3	0.04	1.0,10.6	2.6	0.3	0.8,8.6
	Protestant		-		0.03	0.01	0.01,0.5	0.03	0.01	0.01,0.5	0.01	0.01	0.01,0.3
AUD	No	Reference											
	Yes		-								2.0	0.001	6.0,38.1
Mental distress	No	Reference											
	Yes				-	-	-	1.0	0.96	0.5,2.0	1.0	0.94	0.7,5.2
Time		0.9	0.48	0.7,1.2	0.8	0.2	0.6,1.1	0.8	0.25	0.6,1.2	0.9	0.47	0.6,1.3
BIC		819.0			815.2			821.9			815.7		

Discussion

To our knowledge, this study is the first longitudinal study investigating predictors of khat use among patients with tuberculosis in Africa. Alarmingly, TB-patients believed that the use of khat is beneficial during treatment. Alcohol use disorder and male gender were predictors of continued khat use among TB patients in Southwest Ethiopia.

In this study, the prevalence of khat use was slightly declined over time from 39.2% at baseline to 37.3% at the end of six months. The reason might be patients use more khat at baseline as a self-treatment for tuberculosis related symptoms and medication side effects. Because we identified that most patients believe khat can reduce symptoms of tuberculosis and medication side- effects. So, when they get improvement from the disease, they might reduce their khat use but further study is needed.

The prevalence of khat use observed in this study at baseline (39.2%), during the first (39.2%) and second follow up (37.3%) was far higher than another study conducted in South Ethiopia which found moderate and high khat use to be 14.3% and 1.7% respectively (9). The difference might be due to the fact that the setting for the present study is known with a higher level of khat consumption than other regions and zones in Ethiopia except for the Diredawa town and Harari region (42). In these regions, khat is considered as part of the culture for the lubrication of social cohesion. Arguably, it is also seen as a help to stay alert during the praying time which patients would not like to miss (18, 22, 43). This is generally worrisome as khat use has been shown to be associated with poor treatment outcomes among patients with tuberculosis (44).

The prevalence of khat use found in the current study is lower than the finding from a prospective nest case-control study done in Yemen (46.7%)(19). The difference might be due to the definition of current khat use which is 30 days in our study, while this was not specified in the Yemenite study. Likewise, socio-cultural differences might contribute to the discrepancy between the two studies. We found that the proportion of khat use among male participants (46.6%) was far higher than among female participants (28.0%), which is consistent with the findings of previous studies (45, 46). This might be due to cultural restriction on females regarding substance use including khat (45, 46). Even though khat consumption among women is substantially lower than men, they are at higher risk of mental and physical effects of substance use disorder than men which is associated with hormonal factors (45, 47). In this study, more than 2/5th of khat users reported that they were suffering from mental distress. Previous studies found that substance use (khat, alcohol, and tobacco) is associated with mental

distress (10, 48), and specifically, khat was reported to increase emotional disturbance (49). However, we could not show a clear association of mental distress and khat use in the adjusted models. Patients might be tempted to use khat as a self-treatment for their mental distress, but this observation needs to be supported by further investigations.

During the first follow up, a majority (76.7%) of patients who were using khat reported that they have alcohol use disorder. This could be due to the fact that patients might resume drinking alcohol after they begin to feel better within two to three weeks because bacterial load then usually starts to decline (4). In addition, since alcohol counteracts the stimulant effect of khat such as sleep disturbance and restlessness, patients might be inclined to use both substances together (43, 50, 51). Likewise, in this study, khat use was associated with alcohol use which is in agreement with previous studies (43, 48). Combining alcohol and khat would affect patients' treatment outcomes and lead to physical and mental health problems. Because, both khat and alcohol were found to have a potential impact on the immunity of the user and associated with mental distress so that patients may develop severe medical and mental health complications or die earlier than non-users (26, 52, 53). Furthermore, these two substances have an association with treatment-resistant tuberculosis (30, 32, 54, 55).

This study found that the majority (77.1%) of khat users believe that using khat can reduce anti-TB medication side effects which is consistent with a cross-sectional study conducted in the Butajira, Ethiopian (18). This may be due to misinterpreting the euphoric mood from khat as a decrease in medication side effects. However, health professionals should create awareness regarding the effect of khat on mental and physical health so that patients may consider reducing their khat use. In this study, almost all khat users (96.2%) believe that khat use reduces TB symptoms, however, this is in clear contrast to the study indicating that patients with khat use had a higher bacterial load (30).

Moreover, we have found that merchants were using khat more than a farmers, government employees, and daily laborers which is in line with studies conducted in the general population (42, 56, 57). This might be due to the fact that merchants use khat to be alert and energetic at the workplace (58). Also, some of the merchants may be khat sellers and, as a result, they chew khat to attract customers but further study assessing this situation is needed.

To our knowledge, our study was unique in exploring predictors of continued khat use among patients with tuberculosis using a longitudinal study with multiple assessments and with no attrition. However, the following limitations need to be acknowledged. Because of social

desirability, patients might minimize or deny their khat use and this could underestimate the magnitude of khat use. It could also affect the association of predictors with the outcome variables. Also, health professionals who were working in a TB clinic collected the data that might contribute to this bias; because patients may be inclined to not report about their khat use or minimize its amount. However, the prevalence of khat use was still higher than in other studies so our estimates might be rather conservative. There is no standardized instrument for the assessment of khat use. However, we are confident that we were able to capture khat use with sufficient precision. Moreover, patients with MDR-TB and who were attending their treatment at health posts, i.e. in more remote areas, were excluded from the study; hence the findings of the study may not be generalized to all patients with TB in Southwest Ethiopia. The findings of this study cannot be generalized to those patients who are getting treatment at the inpatient department who have limited access to psychoactive substances including khat. Moreover, since our sample size is not adequate, it might be difficult to draw a strong conclusion, but we can make an estimation based on the sample size without having a critical problem that could affect our findings. Also, we did not cover all possible predictors, and as a result, we recommend a qualitative study to explore other predictors of khat use among TB patients.

Conclusions

In conclusion, a significant proportion of patients on anti-TB continue to use khat throughout their course of treatment. Predictors of khat use were being male and concomitant alcohol use disorder. These findings underscore the need to integrate the screening and treatment for substance use, specifically for khat, into the tuberculosis services. All patients diagnosed with TB should be screened for khat use and a particular emphasis should be given to males and individuals with a history of alcohol use. Furthermore, patients' beliefs about the beneficial effects of khat on tuberculosis outcomes need to be investigated so that these beliefs can be counteracted effectively.

Competing interest

All authors declare that they have no competing interests.

Authors' contributions

Conceptualization: MS

Data Curation: MS

Formal Analysis: MS, OT, MT, KA, WK, RS, EG

Funding Acquisition: MS, MT, KA, WK, ET, YY, RS, EG

Investigation: MS, OT, MT, KA, WK, ET, YY, RS, EG

Methodology: MS, OT, MT, KA, WK, ET, YY, RS, EG

Project Administration: MS

Resources: MS, OT, MT, KA, WK, ET, YY, RS, EG

Software: MS, OT, MT, KA, WK, ET, YY, RS, EG

Supervision: MS, OT, MT, KA, WK, ET, YY, RS, EG

Validation: MS, OT, MT, KA, WK, ET, YY, RS, EG

Visualization: MS

Writing – Original Draft Preparation: MS

Writing – Review & Editing: MS, OT, MT, KA, WK, ET, YY, RS, EG

Acknowledgment

We are thankful for the study participants to compromising their time to participate in the study.

References

1. World Health Organization. (2018). Global tuberculosis report 2018. World Health Organization. Available at https://apps.who.int/iris/handle/10665/274453. Accessed on 20/07/2019.

2. Millet JP, Moreno A, Fina L, del Baño L, Orcau A, de Olalla PG, et al. Factors that influence current tuberculosis epidemiology. Eur Spine J. 2013;22 Suppl 4(Suppl 4):539-48.

3. Federal Democratic Republic of Ethiopia Ministry of Health. Health and Health Related Indicators2011/12. Available at https://www.dktethiopia.org/sites/default/files/PublicationFiles/Health%20and%20Health%20Related%20Indicators%202004%20E.C.pdf. Accessed on 20/07/2019.

4. Federal Democratic Republic of Ethiopia, Ministry of Health. Guidelines for clinical and programmatic management of tb, leprosy and tb/hiv in ethiopia fifth edition: MoH; 2012.

Available at file:///C:/Users/GOD/Downloads/guidelines-for-the-clinical-and-programmatic-management-of-tbl-tb-hiv%20(5).pdf. Accessed on 12/02/2020.

5. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med. 2009;68(12):2240-6.

6. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and meta-analysis. PLoS One. 2019;14(1):e0210422.

7. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. BMC research notes. 2015;8:503.

8. Eshetie S, Gizachew M, Alebel A, van Soolingen D. Tuberculosis treatment outcomes in Ethiopia from 2003 to 2016, and impact of HIV co-infection and prior drug exposure: A systematic review and meta-analysis. PLoS One. 2018;13(3):e0194675.

9. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and tuberculosis treatment outcomes, quality of life and disability, Ethiopia. Bulletin of the World Health Organization. 2018;96(4):243-55.

10. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center, WolaitaSodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015;15:214.

11. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and associated factors among TB patients attending at Gondar town health centers, Northwest Ethiopia. BMC research notes. 2018;11(1):691.

12. Luqman W, Danowski TS. The use of khat (Catha edulis) in Yemen. Social and medical observations. Ann Intern Med. 1976;85(2):246-9.

13. Gebissa E. Khat in the Horn of Africa: historical perspectives and current trends. J Ethnopharmacol. 2010;132(3):607-14.

14. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2004;148(1):11-5.

15. Duresso SW, Matthews AJ, Ferguson SG, Bruno R. Is khat use disorder a valid diagnostic entity? Addiction. 2016;111(9):1666-76.

16. Adam F, Hasselot N. Khat: from traditional usage to risk of drug addiction. Med Trop (Mars). 1994;54(2):141-4.

17. Ali WM, Zubaid M, Al-Motarreb A, Singh R, Al-Shereiqi SZ, Shehab A, et al. Association of khat chewing with increased risk of stroke and death in patients presenting with acute coronary syndrome. Mayo Clin Proc. 2010;85(11):974-80.

18. Teferra S, Hanlon C, Alem A, Jacobsson L, Shibre T. Khat chewing in persons with severe mental illness in Ethiopia: A qualitative study exploring perspectives of patients and caregivers: Transcultural Psychiatry; 2011. 455–72.

19. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to anti-tuberculosis treatment in Yemen: JPHSR; 2013.

20. Eckersley W, Salmon R, Gebru M. Khat, driver impairment and road traffic injuries: a view from Ethiopia. Bulletin of the World Health Organization. 2010;88(3):235-6.

21. Abdelwahab SI, Alsanosy RM, Rahim BE, Mohan S, Taha S, Mohamed Elhassan M, et al. Khat (Catha edulis Forsk.) Dependence Potential and Pattern of Use in Saudi Arabia. Biomed Res Int. 2015.

22. Stevenson M, Fitzgerald J, Banwell C. Chewing as a social act: cultural displacement and khat consumption in the East African communities of Melbourne. Drug Alcohol Rev. 1996;15(1):73-82.

23. Akalu TY, Baraki AG, Wolde HF, Lakew AM, Gonete KA. Factors affecting current khat chewing among male adults 15-59 years in Ethiopia, 2016: a multi-level analysis from Ethiopian Demographic Health Survey. BMC psychiatry. 2020;20(1):21

24. Odenwald M, al'Absi M. Khat use and related addiction, mental health and physical disorders: the need to address a growing risk. Eastern Mediterranean Health Journal. 2017;23(3).

25. El-Setouhy M, Alsanosy RM, Alsharqi A, Ismail AA. Khat Dependency and Psychophysical Symptoms among Chewers in Jazan Region, Kingdom of Saudi Arabia. Biomed Res Int. 2016.

26. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of Mycobacterium tuberculosis infection by macrophage immune modulation? Med Hypotheses. 2014;82(6):667-9.

27. Adane K, Spigt M, Ferede S, Asmelash T, Abebe M, Dinant GJ. Half of Pulmonary Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia: Implications for Tuberculosis Control. PLoS One. 2016;11(2):e0149453.

28. Wolde D, Tadesse M, Abdella K, Abebe G, Ali S. Tuberculosis among Jimma University Undergraduate Students: First Insight about the Burden of Tuberculosis in Ethiopia Universities-Cross-Sectional Study. Int J Bacteriol. 2017.

29. Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case-control study. BMJ Open. 2016;6(4):e009058.

30. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of Saudi Arabia. PLoS One. 2015;10(10):e0140245.

31. Duko B, Bedaso A, Ayano G, Yohannis Z. Perceived Stigma and Associated Factors among Patient with Tuberculosis, Wolaita Sodo, Ethiopia: Cross-Sectional Study. Tuberc Res Treat. 2019.

32. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study. J Pharm Policy Pract. 2017;10:36.

33. Sahile Z, Yared A, Kaba M. Patients' experiences and perceptions on associates of TB treatment adherence: a qualitative study on DOTS service in public health centers in Addis Ababa, Ethiopia. BMC Public Health. 2018;18(1):462.

34. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Khat use in people living with HIV: a facility-based cross-sectional survey from South West Ethiopia. BMC psychiatry. 2015;15:69.

35. Average Salary in Ethiopia 2019. Available at http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1 accessed on 09/07/2019

36. Thomas F. Babor JCH-B, John B. Saunders, Maristela G. Monteiro. The Alcohol Use Disorders Identification TestGuidelines for Use in Primary Care. World Health Organization. 2nd ed ed. Geneva: World Health Organization; 2001.

37. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disoders and associated factors among people living with HIV who are attending services in Southwest Ethiopia. BMC Research Notes. 2014; 7:828

38. Youngmann R, Zilber N, Workneh F, Giel R. Adapting the SRQ for Ethiopian populations: a culturally-sensitive psychiatric screening instrument. Transcult Psychiatry. 2008;45(4):566-89.

39. Hanlon C, Medhin G, Alem A, Araya M, Abdulahi A, Hughes M, et al. Detecting perinatal common mental disorders in Ethiopia: validation of the self-reporting questionnaire and Edinburgh Postnatal Depression Scale. J Affect Disord. 2008;108(3):251-62.

40. Dhadphale M, Ellison RH, Griffin L. Frequency of mental disorders among outpatients at a rural district hospital in Kenya. Cent Afr J Med. 1982;28(4):85-9.

41. Beusenberg M, Orley JH, World Health Organization. Division of Mental Healh. (1994). A User's guide to the self reporting questionnaire (SRQ / compiled by M. Beusenberg and J. Orley. Geneva: World Health Organization; 1994. https://apps.who.int/iris/handle/10665/61113

42. Haile1D, Lakew Y. Khat Chewing Practice and Associated Factors among Adults in Ethiopia: Further Analysis Using the 2011 Demographic and Health Survey: PLoS ONE; 2015.

43. Rampes GCH. Adverse effects of khat: a review: Advances in Psychiatric Treatment; 2003;9(6): 456–63.

44. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to anti-tuberculosis treatment in Yemen. Journal of Pharmaceutical Health Services Research. 2013;4(2):115-22.

45. National Institute on Drug Abuse. Substance Use in Women. Availale at https://www.drugabuse.gov/publications/drugfacts/substance-use-in-women. Accessed on 13/07/2019

46. Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. Psychiatr Clin North Am. 2010;33(2):339-55.

47. Cormier RA, Dell CA, Poole N. Women and Substance Abuse Problems. BMC Womens Health. 2004;4(1):S8.

48. Damena T, Mossie A, Tesfaye M. Khat chewing and mental distress: a community based study, in jimma city, southwestern ethiopia. Ethiopian journal of health sciences. 2011;21(1):37-45.

49. Hassan NA, Gunaid AA, El-Khally FM, Murray-Lyon IM. The effect of chewing Khat leaves on human mood. Saudi Med J. 2002;23(7):850-3.

50. Omolo OE, Dhadphale M. Alcohol use among khat (Catha) chewers in Kenya. Br J Addict. 1987;82(1):97-9.

51. Mihretu A, Teferra S, Fekadu A. Problematic khat use as a possible risk factor for harmful use of other psychoactive substances: a mixed method study in Ethiopia. Subst Abuse Treat Prev Policy. 2017;12(1):47.

52. Ranzani OT, Rodrigues LC, Bombarda S, Minto CM, Waldman EA, Carvalho CRR. Long-term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010-15: a population-based, longitudinal study. Lancet Infect Dis. 2020;20(1):123-32.

53. Corkery JM, Schifano F, Oyefeso A, Ghodse AH, Tonia T, Naidoo V, et al. Overview of literature and information on "khat-related" mortality: a call for recognition of the issue and further research. Ann Ist Super Sanita. 2011;47(4):445-64.

54. Zetola NM, Modongo C, Kip EC, Gross R, Bisson GP, Collman RG. Alcohol use and abuse among patients with multidrug-resistant tuberculosis in Botswana. Int J Tuberc Lung Dis. 2012;16(11):1529-34.

55. Santha T, Garg R, Frieden TR, Chandrasekaran V, Subramani R, Gopi PG, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. Int J Tuberc Lung Dis. 2002;6(9):780-8.

56. Wondemagegn AT, Cheme MC, Kibret KT. Perceived Psychological, Economic, and Social Impact of Khat Chewing among Adolescents and Adults in Nekemte Town, East Welega Zone, West Ethiopia. Biomed Res Int. 2017.

57. Abate A, Tareke M, Tirfie M, Semachew A, Amare D, Ayalew E. Chewing khat and risky sexual behavior among residents of Bahir Dar City administration, Northwest Ethiopia. Ann Gen Psychiatry. 2018;17:26.

58. Ageely HM. Health and socio-economic hazards associated with khat consumption. J Family Community Med. 2008;15(1):3-11.

b.

Open access Original research

BMJ Open

Substance use disorders and adherence to antituberculosis medications in Southwest Ethiopia: a prospective cohort study

Matiwos Soboka [1,2] Markos Tesfaye,[2,3] Kristina Adorjan,[2,4,5] Wolfgang Krahl,[2,6] Elias Tesfaye,[1] Yimenu Yitayih [1] Ralf Strobl,[7,8] Eva Grill[2,7,8]

* **Corresponding author**: Matiwos Soboka, Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia, Center for International Health, Ludwig Maxmillians University, Munich, Germany

Email: matiwos2004@yahoo.com

Author affiliations

[1]Department of Psychiatry, Medical Faculty, Jimma University, Jimma, Ethiopia
[2]Center for International Health, Ludwig Maxmilians University, Munich, Germany
[3]Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
[4]Department of Psychiatry and Psychotherapy, LMU Munich, Munich, Germany
[5]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany
[6]Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
[7]Institute for Medical Information Processing, Biometry and Epidemiology,Ludwig Maximilians University Muenchen, Munich, Germany
[8]German Center for Vertigo and Balance Disorders, University Hospital LMU Muenchen, Munich, Germany

Abstract

Objectives: In Ethiopia, little is known about the association between substance use disorders and adherence to anti-TB medications. Therefore, the objective of this study was to assess the effect of substance use disorders on adherence to anti-TB medications in Southwest Ethiopia.

Design: Prospective cohort study.

Settings: Patients were recruited from 22 health centers and four hospitals in Southwest Ethiopia.

Participants: This study was conducted among 268 patients with tuberculosis, aged 18-80 in Southwest Ethiopia between October 2017 and October 2018. At baseline, patients who were exposed substance use disorders (134 patients) and unexposed to substance use disorders (134 patients) were recruited. Patients were followed for six months, and data were collected on three occasions.

Main outcome measure: Adherence to anti-TB medications.

Results: Patients with substance use disorders had consistently higher prevalence of non-adherence than those without, 16.4% vs. 3.0% at baseline, 41.7% vs 14.4% at two month follow up, and 45.7% vs 10.8% at six month follow up assessments. Patients with khat use disorder were 3.8 times more likely to be non-adherent to anti-TB medications than patients without khat use disorder (aOR 3.8, 95%CI=1.8-8.0). Patients who had alcohol use disorder were also 3.2 times likely to have poor adherence compared to their counterparts (aOR=3.2, 95%CI=1.6-6.6). In addition, being educated (aOR =4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI=1.2-3.0) were associated with non-adherence to anti-TB medications.

Conclusion: Khat and alcohol use disorders predict greater likelihood of non-adherence to anti-TB medication. This implies the need to integrate the management for substance use disorders into the existing tuberculosis treatment services.

Keywords: Substance use disorders, alcohol, khat, anti-TB adherence, non-adherence, Ethiopia.

Strengths and limitations

- The strengths of this study are the prospective cohort design, longitudinal data collection, including patients from urban and rural health institutions, intensive training for data collectors, multi-center data collection, and use of standardized instruments.
- Due to social desirability, patients might minimize reporting of the amount and frequency of the substances they were using.
- Measuring adherence based on pills count may not reflect the real adherence situation, since patients may not bring all leftover medications during the follow up.
- Follow up and data collections have been carried out by health professionals working in the respective TB clinic. As a result, their assessment of adherence might be biased.
- Hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, and this may limit the generalizability of the result for these patients.

Introduction

Tuberculosis (TB) is a preventable and treatable disease but it remains one of the major diseases leading to death worldwide (1, 2). World Health Organization (WHO) estimates that 1.6 million persons died of TB in 2017 (1); almost 20% of them were HIV positive (1). The number of TB patients is estimated at about 10 million with an annual incidence of 6·4%. TB remains the main reason for premature mortality among HIV positive patients (1).

TB is most prevalent in middle and low-income countries. This exerts enormous pressure on societies as TB mainly affects mostly adults in the economically productive age groups (1, 3, 4). In fact, 87% of cases worldwide are from Asia, Africa, and the Russian Federation (1, 5). Tuberculosis related morbidity and mortality also remain high in low and middle-income countries. Because these countries have poor nutrition, unfavorable housing conditions, and unstable health care (1). Notably, 117,705 new cases were registered in 2017 in Ethiopia, corresponding to an annual incidence of 164 per 100,000 habitants (1). Ethiopia remains one of the top 22 countries having the highest TB mortality with an estimated mortality rate of 24 per 100, 000 inhabitants in 2017 (1).

Long-term adherence to standardized medication is the key to successful treatment of TB as non-adherence may lead to the emergence of multidrug-resistant TB (MDR-TB), an increasing global health threat (1, 6, 7). Non-adherence to anti-TB medication could also lead to a lower treatment success rate (8, 9), default, and death (10, 11). Thus, Ethiopia has developed a national TB treatment guideline to ensure adherence through regular appointments and supervised drug administration, and to reduce poor treatment outcomes (12).

In Ethiopia, the prevalence of non-adherence among TB patients has been estimated to range from 10% in Amhara region to 24% in Southern Nations and Nationalities of Ethiopia (13). To counteract this, the Ethiopian has implemented Direct Observed Treatment (DOT) services in

almost all health institutions (12), but its impact on medication adherence is unclear and the reasons for non-adherence are still poorly understood.

Among the reasons for non-adherence, substance use disorders have been found to play a dominant role (8, 14-16). Substances such as alcohol, tobacco, khat, and illicit drugs are commonly used among patients with TB (17-19). Patients with TB are also at risk of increased morbidity, and premature mortality due to substance use disorders (20). Because, substance use disorders such as alcohol and tobacco are associated with MDR-TB (21, 22).

Khat is a natural stimulant with over 40 active compounds. Among these, psychoactive alkaloids, cathinone, and cathine cause the stimulating effect, and lead to craving and dependency (23-26). There is evidence that khat use increases susceptibility to tuberculosis (27-31), and maybe associated with poor TB treatment outcomes (14, 32), prolonged duration of treatment (33), and high load of bacteria in TB patients (34). In Yemen, khat use has been shown to be associated with non-adherence to anti-tuberculosis medications (35), probably because khat disrupts patients' sleep patterns and causes them to miss their appointments (35, 36). Ethiopia, like Yemen, counts among the few countries where khat use is legal. Khat use disorder may be an important but unrecognized threat to anti-TB medication adherence. Filling the information gaps about the effect of substance use disorders will help to improve TB treatment outcomes and inform decision makers about the need for an integration of substance use disorder treatment in TB control programs in the future. Therefore, the objective of this study is to assess the effect of substance use disorders (including khat and alcohol) on adherence to anti-TB medications in Southwest Ethiopia. Specifically, we examined the association of the most frequently used substances, namely khat and/or alcohol, on adherence to guideline compatible TB treatment.

Methods

Study area, period, and patients

We conducted a prospective cohort study in Jimma zone and Jimma city special zone. Jimma city special zone is the capital city of Jimma zone and located in the Southwestern part of Ethiopia, 352 km from Addis Ababa, the capital of the country. The city has a tertiary hospital and a zonal hospital, as well as four functional health centers those currently providing services. Similarly, Jimma Zone has 18 districts and located in the Southwest of Ethiopia. Overall, the zone has more than three million inhabitants. During the period of this study, Jimma Zone had 112 health centers and three hospitals. Out of these government's public health facilities, 91 health centers and all hospitals were providing services to TB patients. In this study, data was collected from a total of 26 health institutions (22 health centers and four hospitals). From Jimma city, we randomly selected 2 health centers and one hospital. We also randomly selected 20 health centers and three hospitals from the Jimma Zone. Patients were included if they had initiated anti-TB treatment within a month of start of the study at the selected health centers and hospitals between October 2017 and October 2018. Patients were recruited over the first six months. Follow-ups were done at the end of two and six months of treatment.

Study design

This study is a multicenter prospective cohort study. We did not pair exposed and non-exposed patients by a certain character. Patients recruited to the cohort were interviewed on three occasions, namely, baseline (starting treatment), first follow up (after 2 months), and second follow up (at the end of six months).

Sample size assumption and sampling procedure

In Ethiopia and other African countries, we could not find a study done regarding substance use disorders (alcohol, tobacco, cannabis, amphetamine and others) and adherence to anti-TB. So, we were forced to calculate the sample based on the proportion of adherence to anti-TB among khat users TB patients. The prevalence of non-adherence among TB patients who also used khat from previous studies was 62·4% (35). The prevalence of non-adherence among non khat user TB patients was 43·6% (35). We have included 111 exposed (with substance use) and 111 unexposed (without substance use) individuals to detect a difference of non-adherence to anti-TB medication at an alpha level of 0·05 and with a power of 80% using the corrected Fleiss sample size calculation [EPInfo^{TM}] (37). The total sample size was calculated considering a 20% of drop out rate and the final sample size was 134 in each group which totals 268 TB patients. New TB patients who were 18 years or older were recruited to participate in the study. Patients who had been on treatment for more than one month, patients on re-treatment, and MDR-TB cases were not included in the study.

Instruments

Exposure variables

In this study, the exposure variable is substance use disorder which includes khat and/or alcohol use disorder.

Substance use disorder: In this study substance use disorder was defined as having khat and/or alcohol use disorder. Data on tobacco, shisha, and cannabis use were collected for explorative data analysis.

Alcohol use disorders (AUDs):-Alcohol use disorder identification test (AUDIT) was used to collect data on AUDs (38). The AUDIT was evaluated over a period of two decades, and

provides an accurate measure of risk of AUDs across gender, age, and cultures. With a cut-off score of eight or more, the sensitivity, and specificity of AUDIT for AUDs was 0·90 and 0·80, respectively (39). AUDIT was used in Ethiopian context and questions number two and three regarding standard drinks were adapted to a more locally appropriate question (40).

Nicotine dependence: The Fagerstrom test for nicotine dependence (FTND) was used to assess tobacco dependence. A total score of FTND $\geq$ 5 was considered as tobacco dependence (41). At a cut-off score $\geq$5, the FTND has good sensitivity (0·75), and specificity (0·80). The FTND has six items, with a total score ranging from 0-10 to measure nicotine dependence. A total FTND score of five indicates moderate nicotine dependence, a score of 6-7 indicates high nicotine dependence, and a score of 8-10 indicates very high nicotine dependence. Patients were also asked about their reasons for smoking tobacco (41).

Cannabis and shisha use: Use of both substances and their frequency were assessed.

Khat use: - Khat use was assessed by self-reported questionnaire. Since there is no standardized questionnaire for khat use, patterns, and reasons of khat use were assessed by using a structured questionnaire which was developed in the context of a literature review. Any consumption of khat in the last one month was considered as current khat use.

In this study, frequent khat use (using khat daily and 2-3 times per week) and using more than one bundle of khat per day was considered as khat use disorder. The term 'khat use disorder' is also supported by previous study (42).

Outcome variable

Adherence: Adherence status of tuberculosis patients was assessed by Direct Observed Treatment (DOT) (based on missing appointments) and pills counts. In this study, adherence is defined as taking medication regularly and attending follow-up according to appointments and

national guideline for tuberculosis in Ethiopia (12). In this study, non-adherence is defined as missing at least one follow-up appointment during DOT. Non-adherence during intensive phase is defined as missing at least one dose of the prescribed anti-TB medication and noted separately. Adherence was assessed at baseline (beginning of intensive phase), at second month (end of intensive phase), and at end of 6 month (end of continuation phase).

Explanatory variables

Socio-demographic variables: Age, sex, marital status, level of education, religion, ethnicity, income, household size, occupation, place of residence, and living conditions were assessed using a structured questionnaire. Income was categorized considering that the minimum monthly wage for employees of governmental organization in Ethiopia of 1,214 Ethiopian birr (36·67 Euros) (43). Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian birr (439·98 Euros).

Disease related factors: Types of TB diagnosis (smear positive, smear negative, extrapulmonary TB, and MDR-TB) were collected from patients' charts.

Comorbidities: All confirmed diagnoses of HIV, previous mental illness, hypertension, and diabetes mellitus were collected from patients' charts.

Social support: Oslo Social Support Scale (The Oslo 3-items) was used to collect data on the strength of social support. The Oslo-3 total score 3-8 indicate poor social support, 9-11 indicate moderate social support, and 12-14 indicate strong social support (44). The scale had been validated in Ethiopia among patients with tuberculosis (45). Social support was assessed at baseline, second month (at first follow up), and six month (at the completion of anti-TB treatment or second follow up).

Food insecurity: It was assessed using the Household Food Insecurity Access Scale (HFIAS) to determine whether the respondent has experienced any of the indicators of food insecurity in the previous month. Food secure if none of the items were endorsed on HFIAS, mild food insecurity if the respondent endorsed any of the items 1, 2, 3, and/or 4 but not the items 5 to 9, 'moderate food insecurity' if the respondent has endorsed items 5, and/or 6 but not the items 7 to 9, and 'severe food insecurity' if the respondent has endorsed items 7, 8, and/or 9 (46). This tool had been validated in Ethiopia among people living with HIV (47, 48). Food insecurity assessed at baseline, second month (at first follow up), and six month (at the completion of anti-TB treatment or second follow up).

Data collection procedures

Before starting data collection, the questionnaires were pretested on a sample (5% of the total sample) of patients with TB who were on treatment at Agaro health center. Those patients who participated in the pretest were not included in the main cohort study. Data were collected by trained health professionals working in the respective TB clinics. Data collectors were not blind to exposure status of the patients. Also, district tuberculosis focal persons and other health professionals specifically trained for this purpose participated in the supervision of data collection.

Data analysis

Data were entered to Epi Data (version 3·1) and analyzed using R studio (1.2.1335). Missing values of income were excluded from the analysis. Participants' characteristics and study variables were presented using descriptive statistics. Generalized linear model was used to examine the longitudinal effect of khat and alcohol use disorders on medication adherence (binary outcome). We used an intercept only model to investigate the trajectory of adherence over time (model 0). Model 1 investigated the longitudinal effect of presence or absence of khat

and alcohol use disorders on adherence without adjusting for covariates, model 2 investigated the longitudinal effect of khat and alcohol on adherence while adjusting for the full set of covariates. Model fit was examined with the Bayesian Information Criterion (BIC).

The covariate selection was based on a directed acyclic graph (DAG). DAGs are analytical method for visualizing hypotheses about causal relationships between exposure (substance use disorders) and outcome (adherence) (49, 50). This approach has been shown to yield valid adjustment sets of variables and to avoid bias (51).

Ethical considerations

Ethical clearance was obtained from the Ethical Review Board of Jimma University (IHRPGC1095/2017) and LMU (Nr: 18-017). The study was discussed in detail and written informed consent was obtained from each participant. The anonymity of the study participants was kept at all stages of data processing and write-up of the manuscript. Patients who had alcohol and khat use disorder were advised to contact a mental health professional for further evaluation and treatment.

Patient and public involvement

Patients were not involved in development of the research questions, study design, interpretation of results or writing of the manuscript.

Results

Socio-demographic characteristics

A total of 268 newly diagnosed patients (50% with substance use disorders, mean age 32.4, SD 14.4, 60.1% male) with tuberculosis were recruited. There was no loss to follow up.

Of all patients, 10.8% (n=29), and 39.2% (n= 105) had alcohol and khat use disorders, respectively. No participant had tobacco, shisha, or cannabis use disorders. Age range was 18-80 years with 35% under 25 years (Refer to table 1). There were 22 missing data of annual income which we excluded from the analysis.

Table1: Socio-demographic characteristics and substance use disorder among a cohort of patients on anti-tuberculosis treatment in Southwest Ethiopia, 2017/18 (n=268).

Variables		**Total (%)**	**Substance use disorder**		
			Baseline N (%)	**First follow-up N (%)**	**2nd follow up N (%)**
Gender	Female	39·9	40(37·4)	35(32·7)	45(42·1)
	Male	60·1	94(58·4)	80(49·7)	84(52·2)
Age	18-24	34·7	42(45·2)	31(33·3)	38(40·9)
	25-34	32·5	35(40·2)	34(39·1)	35(40·2)
	35-44	13·4	23(63·9)	20(55·6)	22(61·1)
	45-54	10·1	17(63·0)	16(59·3)	18(66·7)
	55-64	9·3	17(68·0)	14(56·0)	16(64·0)
Occupation	Merchant	10·8	23(79·3)	19(65·5)	20(69·0)
	Farmer	34·3	57(62·0)	51(55·4)	57(62·0)
	Government employee	39·2	37(35·2)	29(27·6)	33(31·4)
	Daily laborer	15·7	17(40·5)	16(38·1)	19(45·2)
Education	No formal education	63·1	68(40·2)	59(34·9)	62(36·7)
	Literate	36·9	66(66·7)	56(56·6)	67(67·7)
Annual income in Birr	<14568	76·9	108(52·4)	92(44·7)	104(50·5)
	≥14568	14·9	16(40·0)	17(42·5)	18(45·0)
Marital	Single	36·2	85(54·1)	76(48·4)	87(55·4)
	Married	58·6	39(40·2)	32(33·0)	34(35·1)

	Divorced/widowed	5·2	10(71·4)	7(50·0)	8(57·1)
Religion	Orthodox	30·6	43(52·4)	27(32·9)	43(52·4)
	Muslim	61·6	89(53·9)	86(52·1)	82(49·7)
	Protestant/others	7·8	2(9·5)	2(9·5)	4(19·0)
Ethnicity	Amhara	22·0	27(45·8)	17(28·8)	29(49·2)
	Oromo	61·6	83(50·3)	82(49·7)	79(47·9)
	Tigre/Gurage	16·4	24(54·5)	16(36·4)	21(47·7)
Family size	Less than five	67·5	89(49·2)	76(42·0)	89(49·2)
	Five or greater	32·5	45(51·7)	39(44·8)	40(46·0)
Residence	Rural	47·4	72(56·7)	59(46·5)	68(53·5)
	Urban	52·6	62(44·0)	56(39·7)	61(43·3)
Type of tuberculosis	Smear positive,	40·3	54(50·0)	43(39·8)	46(42·6)
	Smear negative	32·5	43(49·4)	39(44·8)	46(52·9)
	Extra pulmonary	27·2	37(50·7)	33(45·2)	37(50·7)

Clinical characteristics and non-adherence

Out of all patients, 40.3 % (n=108), 32.5 % (n=87), and 27.2 % (n=73) were diagnosed with smear positive, smear negative, and extra pulmonary TB respectively. At baseline, 3.7% (n=10) patients were diagnosed with HIV, and 7.1% (n=19) with other comorbidities. At baseline 9.7 % (n=26) were non-adherent to TB medication. At two and six months of assessment, 26.1% (n=70) and 27.6% (n=74) missed at least one dose of their medications respectively. .

The prevalence of non-adherence among patients with substance use disorder was 16.4% (n=22), 41.7 % (n=48), and 45.7% (n=59) at baseline, first, and second follow up respectively (See table 2).

Table 2: Various characteristics by adherence to anti-TB medications at the three time point assessments among patients with tuberculosis in Southwest Ethiopia 2017/18 (n=268)

Variables		Adherence to anti-TB at baseline		Adherence to anti-TB at first follow-up		Adherence to anti-TB at second follow-up	
		Adherent N (%)	Non-adherent N (%)	Adherent N (%)	Non-adherent N (%)	Adherent N (%)	Non-adherent N (%)
Substance use disorder	No	130(97·0)	4(3·0)	131(85·6)	22(14·4)	124(89·2)	15(10·8)
	Yes	112(83·6)	22(16·4)	67(58·.3)	48(41·7)	70(54·3)	59(45·7)
Gender	Male	143(88·8)	18(11·.2)	112(69·6)	49(30·4)	83(77·6)	24(22·4)
	Female	99(92·5)	8(7·5)	86(80·4)	21(19·6)	111(68·9)	50(31·.1)
Age	18-24	88(94·6)	5(5·4)	72(77·3)	21(22·7)	69(74·2)	24(25·.8)
	25-34	79(90·.8)	8(9·.2)	64(73·.7)	23(26·3)	67(77·0)	20(23·0)
	35-44	28(77·.8)	8(22·.2)	24(66·7)	12(33·.3)	23(63·9)	13(36·1)
	45-54	24(88·.9)	3(11·1)	21(77·8)	6(22·2)	19(70·4)	8(29·6)
	55-64	23(92·0)	2(8·0)	17(68·.0)	8(32·0)	16(64·0)	9(36·0)
Occupation	Merchant	22(75·9)	7(24·1)	17(58·6)	12(41·4)	14(48·3)	15(51·7)
	Farmer	79(85·9)	23(14·1)	66(71·7)	26(28·3)	64(69·6)	28(30·4)
	Government Employee	21(95·.5)	1(4·5)	79(75·2)	26(24·8)	82(78·1)	23(21·.9)
	Daily laborer	41(97·6)	1(2·4)	36(85·0)	6(14·3)	34(81·0)	8(19·.0)
Education	No formal education	165(97·6)	4(2·4)	145(85·8)	24(14·2)	139(82·2)	30(17·8)
	Literate	77(77·.8)	22(22·2)	53(53·5)	46(46·5)	55(55·6)	44(44·4)
	Tertiary	20(71·4)	8(28·6)	8(28·6)	20(71·.4)	10(35·.7)	18(64·.3)
Annual income in Birr	<14568	185(89·.8)	21(10·.2)	154(74·.8)	52(25·.2)	149(72·.3)	57(27·7)
	≥14568	37(92·5)	3(7·.5)	30(75·.0)	10(25·0)	31(77·5)	9(22·.5)

Food insecurity	No	129(94.9)	7(5·1)	105(72·.4)	40(27·6)	118(72·.8)	44(27·2)
	Middle/moderate	46(80·7)	11(19·.3)	29(70·0)	12(29·.3)	26(60·5)	17(39·5)
	Severe	67(89·.3)	8(10·.7)	64(78·0)	18(22·0)	50(79·4)	13(20·6)
Marital status	Single	92(94·8)	5(5·2)	109(69·.4	48(30·6)	80(82·5)	17(17·5)
	Married	140(89·2)	17(10·8)	80(85·8)	17(17·2)	104(66·2)	53(33·8)
	Divorced/widowed	10(71·4)	4(28·6)	9(64·6)	5(37·4)	10(71·4)	4(28·6)
Religion	Orthodox	74(90·2)	8(9·8)	63(76·8)	19(23·2)	61(74·4)	21(25·6)
	Muslim	147(89·7)	18(10·3)	118(71·5)	47(28·5)	114(69·1)	51(39·9)
	Protestant and others	20(95·2)	1(4·.8)	17(81·0)	4(19·0)	19(90·5)	2(9·5)
Ethnicity	Amhara	53(89·8)	6(10·2)	49(83·1)	10(16·9)	48(81·4)	11(18·6)
	Oromo	160(90·9)	16(9·1)	119(72·1)	46(27·9)	119(72·1)	46(27·9)
	Tigre/Gurage	29(87·9)	4(12·1)	30(68·2)	14(31·8)	27(61·4)	17(38·6)
Family size	Less than five	165(91·2)	16(8·8)	132(72·9)	49(27·1)	137(75·7)	44(24·3)
	Five or greater	77(88·5)	10(11·5)	66(75·9)	21(24·1)	57(64·5)	30(34·5)
Residence	Rural	113(89·0)	14(11·0)	94(74·0)	33(26·0)	93(73·2)	34(26·8)
	Urban	129(91·5)	12(8·5)	104(73·0)	37(26·2)	101(71·6)	40(28·4)
Type of TB	Smear positive	95(91.9)	13(8.1)	80(74.1)	28(25.9)	78(72.2)	30(27.8)
	Smear negative	81(9·1)	6(6·9)	66(75·9)	21(24·1)	64(73·6)	23(26·4)
	Extra pulmonary	66(90·4)	7(9·6)	52(71·2)	21(28·8)	52(71·2)	21(28·8)
HIV	Seronegative	233(90·3)	25(9·7)	190(74·2)	66(25·8)	183(73·5)	66(26·5)
	Seropositive	9(90·0)	1(10·0)	8(66·7)	4(33·3)	11(57·9)	8(42·1)
Social support	Poor	83(89·2)	10(10·.8)	83(74·8)	28(25·2)	96(68·6)	44(34·1)
	Moderate	101(89·4)	12(10·6)	68(80·0)	17(20·0)	58(78·4)	16(21·6)
	Good	58(93·5)	4(6·5)	47(65·3)	25(34·7)	40(74·1)	14(25·9)

Effect of substance use disorder on the adherence to anti-TB medications

The intercept only model (model 0) showed a significant decrease in the percentage of adherence over time (BIC= 642.5). Adding alcohol and khat use disorders (model 1) improved model fit (BIC=627.6): Patients with khat use disorder had a significantly higher probability of non-adherence over time (OR= 4.2, 95%CI=2.1-8.6). The odds of non-adherence among patients with alcohol use disorder (AUDs) was 3.3 times that of patients free of AUDs (OR=3.3, 95%CI=1.6-6.6). Adding covariates did not substantially change this association (OR= 2.8, 95%CI=2.0-3.8) and further improved model fit (BIC= 642.2). In the final model, khat use disorder (aOR= 3.8, 95%CI=1.8-8.0), or alcohol use disorder (aOR= 3.2, 95%CI=1.6-6.6), being educated (aOR=4.4, 95%CI=1.7-11.3), and being merchant (aOR=6.1, 95%CI= 1.2-30.8) were associated with decreasing adherence (See table 3). Patients with khat use disorder were 3.8 times more likely to be non-adherent to anti-TB medications than patients without khat use disorder. Also, participants whose occupation was merchant were 6.1 times more likely to be non-adherent to anti-TB medications compared to daily laborers.

Table 3: Predictors of non-adherence to anti TB medications among patients with tuberculosis in Southwest Ethiopia 2017/2018 (n=268).

Variables		**Model 0(Intercept only)**		**Model 1(khat and alcohol including age and gender)**		**Full model**	
		OR	**95%CI**	**OR**	**95%CI**	**aOR**	**95%CI**
Khat UD	No	Reference					
	Yes	-	-	4·2	2·1-8·6	3·8	1·8-8·0
AUDs	No	Reference					
	Yes	-	-	3·.3	1·6-6·6	3·2	1·6-6·6
Age	18-24	Reference					
	25-34	-	-	1·.2	0·4-3·2	-	-
	35-44	-	-	1·8	0·5-6·4	-	-

	45-54	-	-	0·9	0·2-4·0	-	-
	≥55	-	-	1·2	0·3-5·1	-	-
Gender	Female	Reference					
	Male	-	-	1·6	0·7-3·6	-	-
Education	No formal education	Reference					
	Read and write/literate	-	-	-	-	4·4	1·7-11·3
Social support	Good	Reference					
	moderate	-	-	-	-	0·5	0·2-1·2
	Poor	-	-	-	-	0·8	0·3-1·9
Occupation	Daily laborer	Reference					
	Farmer	-	-	-	-	2·1	0·5-8·0
	Government employee	-	-	-	-	2·1	0·6-8·0
	Merchant	-	-	-	-	6·1	1·2-30·8
Time T2		2·7	2·0-3·6	2·7	2·0-3·6	2·8	2·0-3·8
BIC		642·5		672·6		642·2	

Discussion

This study conducted in patients undergoing standardized treatment for tuberculosis in Southwest Ethiopia revealed three important findings: 1) adherence to medication decreased over the course of treatment; 2) substance use disorders, particularly khat and alcohol contributed to this non-adherence; and 3) this association was independent of other factors such as education, social support, and occupation.

It is alarming that adherence to TB medication decreased over the course of treatment, as already shown by studies done in South Ethiopia (52), Northwest Ethiopia (53), and Addis Ababa (54) Ethiopia. Possible reasons for non-compliance are distance from the health institution that dispenses medications (13, 52), lack of knowledge about tuberculosis (52, 53), psychological distress (54), being busy with work (53), and alcohol intake (51). To solve the problem related to

adherence, Ethiopian health authorities have reinforced their efforts to implement DOT programs throughout the whole treatment and all over the country starting from initiation to completion of treatment (12).

In this study, the prevalence of non-adherence to anti-TB medication in the first month of treatment was 9·7 % which is in line with a systematic review that found 10.0% of non-adherence in the Amhara region (13, 55). The proportion of non-adherence to anti-TB medications during the first (26.1%) and second (27.6%) follow up was slightly higher than findings from South Ethiopia (24.5%) (52), Northwest Ethiopia (21.2%) (53), and Addis Ababa (19.5%) (54). This might be explained by the high proportion of persons with a substance use disorder in our study, in which we deliberately oversampled persons with SUD to maximize power. The discrepancy may be also due to patients in our study were using substances whereas in the systematic review there was no data regarding substance use.

In this study, the prevalence of non-adherence among patients with substance use disorder at baseline, first, and second follow up was 16·4%, 41.7%, and 45.7% respectively. This is in line with a study from the US (39%) (53, 56, 57).

Moreover, this study provides the evidence that substance use disorders have a significant negative effect on adherence to anti-TB medications among patients with tuberculosis, which supports earlier findings from previous studies that found alcohol use disorder, tobacco dependence, and illicit drug use have a negative impact on adherence in Uzbekistan, Spain, and Morocco (58-60). This is also comparable with retrospective studies conducted in Russia and New York which found that alcohol use disorder and drug addiction were significantly associated with non-adherence to anti-TB medications (8, 9). Likewise, the finding of this study is in line with studies conducted in different parts of Ethiopia which found khat, alcohol, and tobacco are the main factors for non-adherence to anti-TB medications (53, 57, 61). In our study,

patients with substance use disorder were more than two times more likely not to follow their medication plan than patients without substance use disorders. This finding is in line with the finding of a study conducted in US that found the risk of missing a DOT appointment was 2.6 times higher among patients with substance use disorder than in patients without drug consumption (56).

In our study, khat use disorder turned out to be the most stringent factor that decreased adherence. This confirms earlier findings from Yemen (62) and Ethiopia (14, 61). A plausible explanation is that khat chewing disrupts night sleep (63) causing patients to oversleep which may lead to missing of the DOT appointments at the health facility. Another reason may be that khat is common substance in Ethiopia, and therefore less attention is paid to its use. Since little is known about the effect of khat on patients with tuberculosis (14), it may be considered as part of a normal social interaction (62).

A higher level of education was associated with non-adherence to anti-TB medications in our study. This result confirms the findings from Yemen that found more educated patients were 19% times less likely to be adherent to their medication (62). Also, a study from Ethiopia showed that attending primary education was associated with non-adherence to anti-TB medications (61). Our findings are contrary to previous studies which have suggested that lower or no formal education decreases adherence to TB medication (13, 64). Our finding seems counterintuitive. However, our results are likely to be related to findings from a study indicating that persons with higher educational attainment might be reluctant to accept DOTS regimes (65). Daily visits to the health facility have been reported as time consuming and probably stigmatizing for patients with a job (66). In this study, being merchant was associated with poor adherence to anti-TB medications. This might be due to patients miss their medications because of busy working schedule, but this needs further investigation.

Limitations

This study has some limitations. Due to social desirability, patients might minimize reporting of the amount and frequency of substance they were using. The tools used for alcohol and khat use disorder are not gold-standard diagnostic for the respective disorders. Also, measuring adherence based on pills count may not reflect the real adherence situation since some patients might not bring all leftover medications during the follow up. Likewise, follow up and data collections have been carried out by health professionals working in the respective TB clinics which might have biased their assessment of adherence. However, overestimating adherence may have biased our results towards a null effect and led to underestimating the effect of substance use disorders, so we are confident that our estimates are conservative. The participation of district tuberculosis focal persons and other health professionals in the supervision of data collection might have also introduced bias.

Furthermore, hospitalized patients, patients on re-treatment, and patients with MDR-TB were not included in this study, so that the results cannot be generalized for these patients. However, MDR-TB patients are under special treatment and surveillance so that including this group of patients might have biased the results. Finally, we did not assess the reasons for non-adherence. This should be part of a separate study going more into the details of the situation of persons with khat and alcohol problems.

Strengths

The specific strengths of this study are the prospective cohort design, longitudinal data collection, including patients from urban and rural health institutions, intensive training given for data collectors, multi-center data collection, and the use of standardized instruments to assess exposure, outcomes, and explanatory variables.

Conclusions

Substance use disorders predict greater likelihood of anti-TB medication non-adherence among TB patients. Also, khat and alcohol use disorders were the main risk factors for anti-TB medication adherence. This finding implies the importance of integrating substance use disorders screening and treatment into the existing tuberculosis services to reduce the effect of substances on treatment outcomes including adherence.

Ethics approval and consent to participate

Ethical clearance was obtained from the ethical review committee of Jimma University, Institute of Health. Written informed consent was obtained from each participant before participation. Information obtained in due course was kept confidentially

Consent for publication

Not applicable.

Competing of interest

All authors declare that they have no conflict of interests.

Funding

The study was funded by Jimma University Institute of Health with the grant number of IHRPGC 1095/2017, Institute of Psychiatric Phenomics and Genomics (IPPG) with the grant number of 15106202/2018, and individual throughout data collection. The funders had no role in this study including interpretation and preparation of the manuscript.

Authors' contribution

MS contributed to the conceptualization, design, statistical analysis, and manuscript preparation. MT, KA, WK, ET, YY, RS, and EG contributed to the design, analysis, and review of the manuscript.

Author affiliations

[1] Department of Psychiatry, Medical Faculty, Jimma University, Jimma Ethiopia.

[2] Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

[3] Department of Psychiatry and Psychotherapy, LMU Munich, Germany

[4] Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany

[5]Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany

[6] Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

[7] Institute for Medical Information Processing, Biometrics and Epidemiology, LMU Munich, Munich, Germany

[8]Center for International Health, Ludwig Maxmillians University, Munich, Germany

Acknowledgment

We are grateful to the study participants for sacrificing their time to participate in the study. Our gratitude is extended to Jimma University for funding the project. We are also grateful to IPPG for funding part of the project. Our gratitude also extends to Dr. Michael Odenwald, who contributed money from his pocket to support the project.

Availability of data

It will be available upon official request from interested individuals or organizations.

References

1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/tb/publications/global_report/en/ accessed on 24/07/2019

2. Grobusch MP, Kapata N. Global burden of tuberculosis: where we are and what to do. Lancet Infect Dis. 2018; 18(12):1291-3.

3. Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME. Mental, Neurological, and Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). Washington (DC): The International Bank for Reconstruction and Development / The World Bank, 2016.

4. Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the end TB era. Lancet Respir Med. 2018; 6(4):299-314.

5. Global tuberculosis report 2016, Geneva, World Health Organization; 2016.

https://apps.who.int/medicinedocs/en/d/Js23098en/ accessed on 24/07/2019.

6. Dodor EA. Tuberculosis treatment default at the communicable diseases unit of Effia-Nkwanta Regional Hospital: a 2-year experience. Int J Tuberc Lung Dis. 2004; 8(11):1337-41.

7. Global tuberculosis report 2013. Geneva, World Health Organization; 2013. http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/ accessed on 25/07/2019

8. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bulletin of the World Health Organization. 2007; 85(9):703-11.

9. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and associated factors among TB patients attending at Gondar town health centers, Northwest Ethiopia. BMC Res Notes. 2018; 11: 691.

10.Mohd Shariff N, Shah SA, Kamaludin F. Predictors of death among drug-resistant tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to 2013. J Glob Antimicrob Resist. 2016; 6:102-7.

11. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis. 2011; 15(7):871-85.

12. Federal Democratic Republic of Ethiopia MoH. Guidelines for clinical and programmatic management of Tb, leprosy and Tb/HIV in Ethiopia fifth edition: MoH; 2012.

13. Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and meta-analysis. PLoS One. 2019; 14(1):e0210422.

14. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and tuberculosis treatment outcomes, quality of life and disability, Ethiopia. Bulletin of the World Health Organization. 2018; 96(4):243-55.

15. Pelissari DM, Diaz-Quijano FA. Impact of alcohol disorder and the use of illicit drugs on tuberculosis treatment outcomes: a retrospective cohort study. Arch Public Health. 2018; 76:45.

16. Silva MR, Pereira JC, Costa RR, Dias JA, Guimaraes MDC, Leite ICG. Drug addiction and alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort study. Epidemiol Infect. 2017; 145(16):3516-24.

17. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009 ;48(1):72-82.

18. Oeltmann JE, Kammerer JS, Pevzner ES, Moonan PK. Tuberculosis and substance abuse in the United States, 1997-2006. Arch Intern Med. 2009. 26;169(2):189-97

19. O'Connell R, Chishinga N, Kinyanda E, Patel V, Ayles H, Weiss HA, et al. Prevalence and correlates of alcohol dependence disorder among TB and HIV infected patients in Zambia. PloS one. 2013; 8(9):e74406.

20. Christensen AS, Roed C, Andersen PH, Andersen AB, Obel N. Long-term mortality in patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study. Clinical epidemiology. 2014; 6:405-21.

21. Fleming MF, Krupitsky E, Tsoy M, Zvartau E, Brazhenko N, Jakubowiak W, et al. Alcohol and drug use disorders, HIV status and drug resistance in a sample of Russian TB patients. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2006; 10(5):565-70.

22. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Hoffner S, et al. Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors. Bulletin of the World Health Organization. 2013; 91(1):36-45.

23. Luqman W, Danowski TS. The use of khat (Catha edulis) in Yemen. Social and medical observations. Ann Intern Med. 1976;85(2):246-9.

24. Gebissa E. Khat in the Horn of Africa: historical perspectives and current trends. J Ethnopharmacol. 2010; 132(3):607-14.

25. Dhaifalah I, Santavy J. Khat habit and its health effect. A natural amphetamine. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2004; 148(1):11-5.

26. Alfaifi H, Abdelwahab SI, Mohan S, Elhassan Taha MM, Syame SM, Shaala LA, et al. Catha edulis Forsk. (Khat): Evaluation of its Antidepressant-like Activity. Pharmacognosy magazine. 2017; 13(Suppl 2):S354-s8.

27. Wolde D, Tadesse M, Abdella K, Abebe G, Ali S. Tuberculosis among Jimma University Undergraduate Students: First Insight about the Burden of Tuberculosis in Ethiopia Universities-Cross-Sectional Study. Int J Bacteriol. 2017;9840670.

28. Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case-control study. BMJ Open. 2016; 6(4):e009058.

29. Jaber AA, Khan AH, Sulaiman SA, Ahmad N. Role of socio-demographical factors on tuberculosis outcome in Yemen. International journal of mycobacteriology. 2016; 5(1):S20.

30. Legesse M, Ameni G, Mamo G, Medhin G, Shawel D, Bjune G, et al. Knowledge and perception of pulmonary tuberculosis in pastoral communities in the middle and Lower Awash Valley of Afar region, Ethiopia. BMC Public Health. 2010; 10:187.

31. Alvi A, Rizwan M, Sunosi RA, Bin Ali Jerah A. Does khat chewing increases the risk of Mycobacterium tuberculosis infection by macrophage immune modulation? Med Hypotheses. 2014; 82(6):667-9.

32. Jaber AA, Khan AH, Syed Sulaiman SA, Ahmad N, Anaam MS. Evaluation of Health-Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. PLoS One. 2016; 11(6):e0156258.

33. Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study. J Pharm Policy Pract. 2017; 10:36.

34. Alvi A, Fatima N, Jerah AA, Rizwan M, Hobani YH, Sunosi RA, et al. Correlation between Resistin, Tuberculosis and Khat Addiction: A Study from South Western Province of Saudi Arabia. PLoS One. 2015; 10(10):e0140245.

35. Anaam MS I, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to anti-tuberculosis treatment in Yemen: JPHSR; 2013.

36. Cox G, Rampes H. Adverse effects of khat: a review. Advances in Psychiatric Treatment. 2018; 9(6):456-63.

37. EPInfoTM. http://apps.who.int/medicinedocs/en/m/abstract/Js21534en/ accessed on 19/08/2019

38. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=B5D5F8F1F1B82FE622D04E8F02635F05?sequence=1 accessed on 20/07/2019.

39. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001.

40. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated factors among people living with HIV who are attending services in south west Ethiopia. BMC research notes. 2014; 7:828.

41. Mikami I, Akechi T, Kugaya A, Okuyama T, Nakano T, Okamura H, et al. Screening for nicotine dependence among smoking-related cancer patients. Japanese journal of cancer research : Gann. 1999; 90(10):1071-5.

42. Duresso SW, Matthews AJ, Ferguson SG, Bruno R. Is khat use disorder a valid diagnostic entity? Addiction. 2016; 111(9):1666-76.

43. Average Salary in Ethiopia. http://www.salaryexplorer.com/salary-survey.php?loc=69&loctype=1 accessed on 09/07/2019.

44. Instrument Manual: Oslo-3 Social Support Scale (OSS-3)2006. https://circabc.europa.eu/webdav/CircaBC/ESTAT/healthtf/Library/ehis_wave_2/methodology_ehis/development/instruments/Manual_OSS_3.pdf , Accessed on 08/06/2019

45. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center, WolaitaSodo, South Ethiopia, Cross sectional study. BMC psychiatry. 2015; 15:214.

46. Coates J SA, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for measurement of food access: Indicator guide (V.3): Washington, D.C.: FHI 360/FANTA; 2007.

http://www.fao.org/fileadmin/user_upload/eufao-fsi4dm/doc-training/hfias.pdf accessed on 10/01/2017

47. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity, mental health and quality of life among people living with HIV commencing antiretroviral treatment in Ethiopia: a cross-sectional study. Health and quality of life outcomes. 2016; 14:37.

48. Maes KC, Hadley C, Tesfaye F, Shifferaw S, Tesfaye YA. Food insecurity among volunteer AIDS caregivers in Addis Ababa, Ethiopia was highly prevalent but buffered from the 2008 food crisis. The Journal of nutrition. 2009; 139(9):1758-64.

49. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999; 10(1):37-48.

50. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011; 22(5):745.

51. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008; 8:70.

52. Woimo TT, Yimer WK, Bati T, Gesesew HA. The prevalence and factors associated for anti-tuberculosis treatment non-adherence among pulmonary tuberculosis patients in public health care facilities in South Ethiopia: a cross-sectional study. BMC Public Health. 2017; 17(1):269.

53. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and associated factors among TB patients attending at Gondar town health centers, Northwest Ethiopia. BMC research notes. 2018; 11(1):691.

54. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-Adherence in Addis Ababa, Ethiopia. Ethiopian journal of health sciences. 2017; 27(5):447-58.

55. Adane AA, Alene KA, Koye DN, Zeleke BM. Non-adherence to anti-tuberculosis treatment and determinant factors among patients with tuberculosis in northwest Ethiopia. PLoS One. 2013; 8(11):e78791.

56. Ricks PM, Hershow RC, Rahimian A, Huo D, Johnson W, Prachand N, et al. A randomized trial comparing standard outcomes in two treatment models for substance users with tuberculosis. Int J Tuberc Lung Dis. 2015; 19(3):326-32.

57. Sahile Z, Yared A, Kaba M. Patients' experiences and perceptions on associates of TB treatment adherence: a qualitative study on DOTS service in public health centers in Addis Ababa, Ethiopia. BMC Public Health. 2018; 18(1):462.

58. Hasker E, Khodjikhanov M, Usarova S, Asamidinov U, Yuldashova U, van der Werf MJ, et al. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and why do they default? BMC Infect Dis. 2008; 8:97.

59. Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of treatment completion and fatality among tuberculosis patients in Spain. Int J Tuberc Lung Dis. 2004; 8(4):458-64.

60. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaoui I, et al. Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. BMC Public Health. 2011; 11:140.

61. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. BMC research notes. 2015; 8:503.

62. Anaam MS, Mohamed Ibrahim MI, Al Serouri AW, Aldobhani A. Factors affecting patients' compliance to anti-tuberculosis treatment in Yemen. Journal of Pharmaceutical Health Services Research. 2013; 4(2):115-22.

63. Adane K, Spigt M, Ferede S, Asmelash T, Abebe M, Dinant GJ. Half of Pulmonary Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia: Implications for Tuberculosis Control. PLoS One. 2016; 11(2):e0149453.

64. Fang XH, Dan YL, Liu J, Jun L, Zhang ZP, Kan XH, et al. Factors influencing completion of treatment among pulmonary tuberculosis patients. Patient Prefer Adherence. 2019; 13:491-6.

65. Kawatsu L, Uchimura K, Ohkado A, Kato S. A combination of quantitative and qualitative methods in investigating risk factors for lost to follow-up for tuberculosis treatment in Japan - Are physicians and nurses at a particular risk? PLoS One. 2018; 13(6):e0198075.

66. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative study. J Health Popul Nutr. 2018; 37(1):1.

c.

Open access Original research

BMJ Open

Effect of food insecurity on mental health of patients with tuberculosis in Southwest Ethiopia: a prospective cohort study

Matiwos Soboka ,[1,2] Markos Tesfaye,[1,3] Kristina Adorjan,[1,4,5] Wolfgang Krahl,[1,6] Elias Tesfaye,[2] Yimenu Yitayih ,[2] Ralf Strobl,[7,8] Eva Grill[1,7,8]

[1]Center for International Health, Ludwig Maximilian University, Munich, Germany
[2]Department of Psychiatry, Medical Faculty, Jimma University, Jimma, Ethiopia
[3]Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
[4]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU, Munich, Germany
[5]Department of Psychiatry and Psychotherapy, LMU Munich, Munich, Germany
[6]Department of Forensic Psychiatry, Isar Amper Klinikum, Munich, Germany
[7]German Center for Vertigo and Balance Disorders, University Hospital LMU Muenchen, Munich, Germany
[8]Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig Maximilians University Muenchen, Munich, Germany

Abstract

Background: Studies have consistently reported the association between food insecurity and poorer mental health in different populations. However, there is scarce information in the direction of the association from low-income countries. Therefore, we aimed to investigate the effect of food insecurity on the mental health of patients with tuberculosis (TB) in Ethiopia.

Method: In this longitudinal study, a total of 268 TB patients from 26 health institutions located in Southwest Ethiopia were included starting from October 2017 to October 2018. Structured questionnaires translated into the local language (Afaan Oromoo and Amharic) were used to assess food insecurity, mental distress, and substance use. Patients were followed for six months and data were collected at recruitment and two follow-up visit. A generalized linear mixed model was used to identify the effect of food insecurity on mental distress. Model fitness was checked using the Bayesian Information Criterion (BIC). Odds ratio (OR) and 95% CI were used to describe the strength of association between mental distress and food insecurity.

Result: The prevalence of food insecurity at baseline, first and second follow-up was 49.3 %, 45.9 %, and 39.6 % respectively. Of these, 28.0% of them reported severe food insecurity at baseline which declined to 23.5% at the end of the sixth month. Also, the prevalence of mental distress at baseline was 61.2% but it declined to 38.1% and 22.0% at the first and second follow-ups respectively. Out of patients with mental distress, 77.3% and 46.0% of them reported food insecurity at baseline and second follow-up respectively.

In the final model severe food insecurity (OR=4.7, 95%CI=2.4, 9.4), and being a government employee (aOR=0.3, 95%CI=0.1, 0.9) predicted mental distress.

Interpretation: In this study, food insecurity predicted mental distress over the course of follow-up. Also, there is a high prevalence of food insecurity and mental distress among TB patients on treatment. Therefore, early assessment and interventions for food insecurity may improve the mental health of TB patients on treatment.

Funding: Jimma University and IPPG

Keywords: Food insecurity, mental distress, khat use, alcohol use, tuberculosis, Ethiopia.

Introduction

Food insecurity is “a state of limited or uncertain availability of nutritionally adequate and safe foods, or lack of access to food of sufficient quality and quantity or limited or uncertain ability to acquire acceptable foods in socially acceptable ways” (1, 2). Across the world, nearly 2 billion people were suffering from moderate or severe food insecurity in 2019 (1). This magnitude is a great challenge for the second sustainable development goal which aims for zero hunger by 2030 (1). In Africa, food insecurity is increasing with about one-fifth of the population experiencing malnutrition (1). Approximately 25% of the Ethiopian population experienced food insecurity in 2016 (2) mainly because of drought (3). Studies have also shown that food insecurity is associated with increased risk for infectious disease burden, namely the occurrence of tuberculosis (TB) and worse TB treatment outcomes (4-6) as well as with poorer mental health among patients with TB (7).

Mental distress is a type of mental health problem that includes symptoms of depression, anxiety, and somatic complaints which may not fall into standard diagnostic criteria (8, 9). In Ethiopia, up to 67.6% of TB patients had symptoms of mental distress (10, 11). Food insecurity increases mental distress by generating uncertainty over the ability to maintain food supplies, or to acquire sufficient food in the future, so it provokes a stress response that may contribute to anxiety and depression (12, 13). Mental distress is associated with poorer adherence to anti-TB medications (14), and TB treatment outcomes (5). Also, food insecurity has a huge impact on treatment outcomes because those who have food insecurity at high risk of malnutrition and medication side effects (4).

Even though food insecurity may potentially contribute to the occurrence of mental distress and affect treatment outcomes among patients with TB in Ethiopia, the link between food insecurity and mental distress is under investigated. So, it is poorly understood how food insecurity affects

mental health of TB patients. Furthermore, most of the studies done in this region were cross-sectional design and thus did not investigate the direction of the association between food insecurity and mental distress in a longitudinal study. This information is important for planning intervention strategies to improve the mental health of TB patients and its complications. Therefore, this study aimed to fill the existing information gap by assessing longitudinally the effect of food insecurity on mental distress among TB patients in Southwest Ethiopia.

Methods

Study area, and design

A longitudinal study was conducted among patients with tuberculosis in Jimma Zone, Southwest Ethiopia. Jimma Zone has more than three million inhabitants, about 3% of the total population of Ethiopia. Typically, in Ethiopia TB care is mainly provided by local decentralized health centers to increase take-up of therapy and to monitor Directly Observed Treatment (DOT). At the time of data collection, 91 out of 112 health centers of Jimma Zone were providing services for patients with tuberculosis. Likewise, there were dedicated TB treatment services at all (four) hospitals. Patients were recruited from four hospitals and 22 randomly selected health centers of Jimma Zone. Twenty health centers and three hospitals were situated in rural areas, one hospital and two health centers in Jimma town. The study was conducted over a year from October 2017 to October 2018.

Sample size assumption and sampling procedure

We included all patients who had recently been diagnosed with TB who had started DOT in the selected health centers and hospitals. Patients were included only if they had started TB treatment within less than four weeks before inclusion and were not planning to transfer to other health institutions. Patients younger than 18 years, patients infected with multidrug-resistant TB

strains, polysubstance users (using two or more substances), and patients who were hospitalized during data collection were excluded from the study. The sample for this study was drawn from a cohort registered as ጤ/ኢ/ም/ድ/ም/ዳ/476/2011 (Institute of health, research, and postgraduate director 476/2011). Patients who consented to participate in the study were consecutively recruited. One hundred thirty-two food insecure and 136 food secure TB patients were followed-up for six months. Detailed information regarding the study was given by trained data collectors to each patient before written informed consent was obtained.

Data collection procedure

Before data collection, the questionnaires were pretested on a sample (5% of the total sample) of patients with TB patients who had been on treatment at one health center in Agaro to check whether the questions work as intended or understood by patients. 14 patients from the pretest were not included in the final analysis of the data. Patients were interviewed on three occasions namely: baseline (starting treatment), first follow up (after 2 months), and second follow up (at the end of the sixth month). Recruitment of patients and data collection was carried out by health professionals who were working in the TB clinic and specifically trained on the questionnaires, supervised by trained district focal persons (nurses).

Measures

Outcome variable

Mental distress: The Self-reporting questionnaire-20 (SRQ-20) was used to assess mental distress. Examples of the items are sleeplessness, tiredness, irritability, suicidal ideation, poor memory, difficulty in concentrating, and somatic complaints. SRQ-20 has been adapted and validated in the Ethiopian setting. This is a 20 item questionnaire with a maximum total score of

20 where a total score of below 7 indicates the absence of mental distress, while values of 7 and above indicate mental distress (15).

Independent variables

Food insecurity was assessed by using the Household Food Insecurity Access Scale (HFIAS) to determine whether the respondent has experienced any of the indicators of food insecurity in the previous month. No food insecurity is present if none of the items apply, mild food insecurity is defined as if the respondent endorsed any of the questions 1, 2, 3, and/or 4 but not the questions 5 to 9, 'moderate food insecurity' if the respondent has endorsed questions 5 and/or 6 but not the items 7 to 9, and 'severe food insecurity' if the respondent has endorsed questions 7, 8 and/or 9(16). The tool has been widely used among people living with human immunodeficiency virus (PLHIV) in Ethiopia(17).

Alcohol use disorders (AUDs):-The Alcohol use disorder identification test (AUDIT) was used to collect data on AUDs (18). The AUDIT was evaluated over two decades and provides an accurate measure of the risk of AUDs across gender, age, and cultures. With a cut-off score of eight or more, the sensitivity and specificity of AUDIT for AUDs were 0.90 and 0.80, respectively (19). AUDIT was used in the Ethiopian context and questions number two and three regarding standard drinks were adapted to a more locally appropriate question. Local alcohol drinks, for example, arake, tela and teji were first converted from local measurements to milliliters. Then the measured alcohol was converted into a standard drink by calculating the mass and volume of the alcohol. Similarly, local beer (bottles and glasses), draft, and wine were converted to standard drinks based on their alcohol content (20).

Khat use: - Khat use was assessed by a self-reported questionnaire. Since there is no standardized questionnaire for khat use, patterns and reasons for khat use were assessed by using

a structured questionnaire that was developed after reviewing the literature. Any consumption of khat during the last month was considered as current khat use.

Socio-demographic variables: Age, sex, marital status, level of education, religion, ethnicity, income, household size, occupation, place of residence, and living conditions were assessed using a structured questionnaire. Income was categorized considering that the minimum monthly wage for employees of a governmental organization in Ethiopia of 1,214 Ethiopian Birr (36.67 Euros) (21). Then the monthly income of each patient was multiplied by 12 months to obtain the annual income, and we used a cutoff 14,568 Ethiopian Birr (439.98 Euros).

Social support: The Oslo Social Support Scale (The Oslo 3-items) was used to collect data on the strength of social support. The Oslo-3 total score 3-8 indicates poor social support, 9-11 indicates moderate social support and 12-14 indicate strong social support (22). The scale has been widely used among patients with tuberculosis in Ethiopia (23, 24). Social support was assessed at baseline, second month (at first follow up), and six months (at the completion of anti-TB treatment or second follow up).

Data analysis

Participants' characteristics and study variables were described using descriptive statistics. A generalized linear mixed model was used to examine the effect of food insecurity over six months. An intercept only model was used to investigate mental distress over time (model 0) without adding other variables; model 1 investigated the longitudinal effect of food insecurity on mental distress without including other variables. Model 2 investigated the effect of food insecurity on mental distress after controlling for substance use. Model 3 (full model) investigated the longitudinal effect of food insecurity on mental distress after adjusting for the full set of a covariate. Model fitness was examined with the Bayesian Information Criterion (BIC). Data were analyzed using R studio (1.2.1335).

Ethical considerations

Ethical clearance was obtained from the Ethical Review Board of Jimma University (ጤ/ኢ/ም/ድ/ም/ዳ/476/2011) and LMU (Nr: 18-017). The study was explained in detail and written informed consent was obtained from each participant. The anonymity of the study participants was kept at all stages of data processing and write-up of the manuscript.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Socio-demographic characteristic

In this longitudinal study, a total of 268 patients (mean age= 32.4, SD =14.4, range=18-80 years, and 60.1% male) were recruited and followed over six months. Out of the total patients, 132 (49.3%) TB patients had food insecurity while 136 (50.7%) of them were food secure at baseline (See table 1).

Table1: Socio-demographic characteristics and food insecurity of tuberculosis patients in Southwest Ethiopia, 2017/18 (n=268).

Variables		Total %	Food insecurity					
			Baseline N (%)		First follow-up N (%)		2nd follow up N (%)	
			Mild/moderate	Severe	Mild/moderate	Severe	Mild/moderate	Severe
Gender	Female	39.9	24(22.4)	34(31.8)	19(17.8)	37(34.6)	16(15.0)	24(22.4)

	Male	60.1	33(20.5)	41(25.5)	22(13.7)	45(28.0)	27(16.8)	39(24.2)
Age	18-24	34.7	23(24.7)	21(22.6)	12(12.9)	24(25.8)	15(16.1)	18(19.4)
	25-34	32.5	17(19.5)	23(26.4)	16(18.4)	27(31.0)	14(16.1)	17(19.5)
	35-44	13.4	10(27.8)	11(30.6)	7(19.4)	11(30.6)	9(50.0)	9(50.0)
	45-54	10.1	4(14.8)	11(40.7)	3(11.1)	11(40.7)	2(7.4)	10(37.0)
	55-64	9.3	3(12.0)	9(36.0)	3(12.0)	9(36.0)	3(12.0)	9(36.0)
Occupation	merchant	10.8	8(27.6)	9(31.0)	6(20.7)	9(31.0)	7(24.1)	8(27.6)
	farmer	34.3	24(26.1)	28(30.4)	16(17.4)	30(32.6)	15(16.3)	23(25.0)
	governmen t employee	39.2	19(18.1)	13(12.4)	12(11.4)	19(18.1)	16(15.2)	11(10.5)
	daily laborer	15.7	6(14.3)	25(59.5)	7(16.7)	24(57.1)	5(11.9)	21(50.0)
Education	No formal education	63.1	16(16.7)	28(29.2)	17(17.7)	29(30.2)	16(16.7)	21(21.9)
	literate	36.9	41(23.8)	47(27.3)	24(14.0)	53(30.8)	27(15.7)	42(24.4)
Annual income in Birr	<14568	76.9	45(21.8)	60(29.1)	34(16.5)	62(30.1)	36(17.5)	47(22.8)
	≥14568	14.9	7(17.5)	14(35.0)	5(12.5)	17(42.5)	4(10.0)	14(35.0)
Marital	Single	36.2	18(18.6)	24(24.7)	11(11.3)	28(28.9)	14(14.4)	22(22.7)
	Married	58.6	36(22.9)	44(28.0)	27(17.2)	49(31.2)	27(17.2)	38(24.2)

	Divorced/ widowed	5.2	3(21.4)	7(50.0)	3(21.4)	5(35.7)	2(14.3)	3(21.4)
Family size	Less than five	67.5	33(18.2)	51(28.2)	25(13.8)	57(31.5)	23(12.7)	46(25.4)
	Five or larger	32.5	24(27.6)	24(27.6)	16(18.4)	25(28.7)	20(23.0)	17(19.5)
Residence	Rural	47.4	35(27.6)	32(25.2)	24(18.9)	33(26.0)	23(18.1)	27(21.3)
	urban	52.6	22(15.6)	43(30.5)	17(12.1)	49(34.8)	20(14.2)	36(25.5)
Type of tuberculosis	smear positive,	40.3	24(22.2)	26(24.1)	13(12.0)	34(31.5)	18(16.7)	23(21.3)
	smear negative	32.5	15(17.2)	34(39.1)	13(14.9)	33(37.9)	10(11.5)	28(32.2)
	extra pulmonary	27.2	18(24.7)	15(20.5)	15(20.5)	15(20.5)	15(20.5)	12(16.4)

The magnitude of food insecurity

The prevalence of food insecurity at baseline, second month and sixth month was 49.3 % (n=132), 45.9 % (n=123), and 39.6 % (n=106) respectively. Out of patients with food insecurity, 21.3% (n=57), and 28.0% (n=75) of them had mild to moderate and severe food insecurity respectively at baseline. The prevalence of severe food insecurity among female participants was 31.8%, 34.6%, and 22.4% at baseline, first and second follow-up respectively. Also, the proportion of food insecurity at the end of the sixth month was higher among patients within the age group of 44-55 years compared to patients within the age group of 18-24 years (37.0% vs 19.4%, P=0.03) (See table 1).

The magnitude of mental distress

The prevalence of mental distress at baseline, the second month and end of the sixth month was 61.2 % (n=164), 38.1 % (n=10.2), 22.0% (n=59) respectively. Out of patients with mental distress, the majority of them were in the age group of 55-64 years at baseline (76.0%) and first follow-up (56.0) while it was 32.0% in the second follow-up. Also, about 3/4th (77.3%) of patients with mental distress were suffering from severe food insecurity at baseline but it dropped to 64.6% and 46.0% in the second and sixth months respectively. Of patients with mental distress, 71.4% of them were either divorced or widowed. The prevalence of alcohol use disorder among patients with mental distress was 62.1%, 44.2% and 18.6% at baseline, first follow up and second follow up respectively, while 65.7%, 47.6, 23.0% of them were using khat at baseline, first, and second follow-up respectively (See table 2).

Table2: Mental distress at the three-time points among patients with tuberculosis in Southwest Ethiopia, 2017/18(n=268).

Variables		Mental distress					
		Baseline		First follow-up		Second follow-up	
		Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)
Gender	Male	104(64.6)	57(35.4)	66(41.0)	95(59.0)	45(28.0)	116(72.0)
	Female	60(56.1)	47(43.9)	36(33.6)	71(66.4)	14(13.1)	93(86.9)
Age	18-24	47(50.5)	46(49.5)	26(28.0)	67(72.0)	18(19.4)	75(80.6)
	25-34	52(59.8)	35(40.2)	33(37.9)	54(62.1)	17(19.5)	70(80.5)
	35-44	26(72.2)	10(27.8)	16(44.4)	20(55.6)	10(27.8)	26(72.2)
	45-54	20(74.1)	7(25.9)	13(48.1)	14(51.9)	6(22.2)	21(77.8)

	55-64	19(76.0)	6(24.0)	14(56.0)	11(44.0)	8(32.0)	17(68.0)
Occupation	Merchant	24(82.8)	5(17.2)	12(41.4)	17(58.6)	7(24.1)	22(75.9)
	Farmer	68(73.9)	24(26.1)	45(48.9)	47(51.1)	23(25.0)	69(75.0)
	Government Employee	43(41.0)	62(59.0)	23(21.9)	82(78.1)	14(13.3)	91(86.7)
	Daily laborer	29(69.0)	13(31.0)	22(52.4)	20(47.6)	15(35.7)	27(64.3)
Education	No formal education	55(57.3)	41(42.7)	35(36.5)	61(63.5)	21(21.9)	75(78.1)
	Educated	109(63.4)	63(36.6)	67(39.0)	105(61.0)	38(22.1)	134(77.9)
Marital status	Single	48(49.5)	49(50.5)	26(26.8)	71(73.2)	20(20.6)	77(79.4)
	Married	106(67.5)	51(32.5)	71(45.2)	86(54.8)	35(22.3)	122(77.7)
	Divorced/widow	10(71.4)	4(28.6)	5(35.7)	9(64.3)	4(28.6)	10(71.4)
Family size	Less than 5	103(56.9)	78(43.1)	74(40.9)	107(59.1)	44(24.3)	137(75.7)
	5 and more	61(70.1)	26(29.9)	28(32.2)	59(67.8)	15(17.2)	72(82.8)
Residence	Rural	93(73.2)	34(26.8)	48(37.8)	79(62.2)	24(18.9)	103(81.1)
	Urban	71(50.4)	70(49.6)	54(38.3)	87(61.7)	35(24.8)	106(75.2)
Type of tuberculosis	Smear positive	63(58.3)	45(41.7)	37(34.3)	71(65.7)	18(16.7)	90(83.3)
	Smear negative	62(71.3)	25(28.7)	41(47.1)	46(52.9)	27(31.0)	60(69.0)
	Extra pulmonary	39(53.4)	34(46.6)	24(32.9)	49(67.1)	14(19.2)	59(80.8)

Social support	poor	49(52.7)	44(47.3)	37(43.5)	48(56.5)	37(26.4)	103(73.6)
	moderate	77(68.1)	36(31.9)	45(40.5)	66(59.5)	19(25.7)	55(74.3)
	Good	38(61.3)	24(38.7)	20(27.8)	52(72.2)	3(5.6)	51(94.4)
Food insecurity	No	69(50.7)	67(49.3)	36(24.8)	109(75.2)	18(11.1)	144(88.9)
	Mild/moderate	37(64.9)	20(35.1)	13(31.7)	28(68.3)	12(27.9)	31(72.1)
	Severe	58(77.3)	17(22.7)	53(64.6)	29(35.4)	29(46.0)	34(54.0)
AUD	No	146(61.1)	93(38.9)	83(36.9)	142(63.1)	51(22.7)	174(77.3)
	Yes	18(62.1)	11(37.9)	19(44.2)	24(55.8)	8(18.6)	35(81.4)
Khat use	No	95(58.3)	68(41.7)	52(31.9)	111(68.1)	36(21.4)	132(78.6)
	Yes	69(65.7)	36(34.3)	50(47.6)	55(52.4)	23(23.0)	77(77.0)

*AUD=Alcohol use disorder

Effect of food insecurity on mental distress

The odds of having mental distress among patients with severe food insecurity was 7 times higher than that of patients who had no food insecurity (OR=7.3, 95%CI=3.7,14.2). After adding alcohol and khat use disorder into model 2 there was no change in the association between severe food insecurity and mental distress (aOR=7.0, 95%CI=3.6, 13.7).

After adjusting for potential confounder using generalized linear mixed model, severe food insecurity (OR=4.7, 95%CI=2.4, 9.4) predicted greater likelihood of mental distress and being government employee (aOR=0.3, 95%CI=0.1, 0.9) predicted a lower likelihood of mental distress. Government employees had a 70% lower likelihood of having mental distress compared to local trader (See table 3).

Table 3: Factors affecting mental distress among patients with tuberculosis in Southwest Ethiopia 2017/2018 (n=268).

Variables		Intercept only (Model0)			Model 1			Model 2			Full model		
		cOR	95%CI		aOR	95%CI		aOR	95%CI		aOR		
			Upper	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Food insecurity	No	Ref			Ref								
	Mild/Moderate	-	-	-	2.0	1.0	3.9	2.0	1.0	3.8	1.7	0.9	3.3
	Severe	-	-	-	7.3	3.7	14.2	7.0	3.6	13.7	**4.7**	**2.4**	**9.4**
Gender	Female	Re			Ref			Ref			Ref		
	Male	-	-	-	-	-	-	-	-	-	1.8	0.9	3.3
Age	18-24	Ref			Ref			Ref			Ref		
	25-34	-	-	-	-	-	-	-	-	-	0.9	0.5	2.1
	35-44	-	-	-	-	-	-	-	-	-	1.5	0.5	4.4
	45-54	-	-	-	-	-	-	-	-	-	1.2	0.4	3.9
	55-64	-	-	-	-	-	-	-	-	-	1.8	0.5	6.3

Occupation	Merchant	Ref			Ref			Ref			Ref		
	Farmer	-	-	-	-	-	-	-	-	-	0.9	0.3	2.6
	Government Employee	-	-	-	-	-	-	-	-	-	**0.3**	**0.1**	**0.9**
	Daily laborer	-	-	-	-	-	-	-	-	-	0.8	0.3	2.8
Annual income	<14568 Eth Birr	Ref			Ref			Ref			Ref		
	≥14568	-	-	-	-	-	-	-	-	-	1.9	0.8	4.3
Marital status	Married	Ref						Ref			Ref		
	Single	-	-	-	-	-	-	-	-	-	0.8	0.4	1.7
	Widowed/divorced	-	-	-	-	-	-	-	-	-	0.9	0.2	3.5
Type of TB	Smear positive	Ref			Ref								
	Smear negative	-	-	-	-	-	-	-	-	-	1.8	0.9	3.6
	Extra pulmonary	-	-	-	-	-	-	-	-	-	0.9	0.4	1.9
AUD	No	Ref			Ref			Ref			Ref		
	Yes	-	-	-	-	-	-	1.2	0.7	2.2	1.0	0.6	2.0
Khat use	No	Ref			Ref			Ref					

	Yes	-	-	-	-	-	-	1.5	0.9	2.6	1.1	0.6	1.9
Social support	Good	Ref			Ref			Ref			Ref		
	moderate	-	-	-	-	-	-	-	-	-	1.3	0.7	2.4
	poor	-	-	-	-	-	-	-	-	-	1.2	0.6	2.2
BIC		912.3			886.6			896.4			955.3		

*Ref=Reference

*BIC=Bayesian information criterion

Discussion

To our knowledge, this is the first longitudinal study that assessed the relationship between food insecurity and mental distress among TB patients. In this study we found: 1) a high prevalence of mental distress among patients with food insecurity, 2) severe food insecurity, independent of socio-demographic factors, substance use, social support and type of TB diagnosis, predicted mental distress.

The baseline prevalence of food insecurity found in this study (49.3%) was lower than the finding of a study done in Surabaya, Indonesia (64%) (25). The difference between the two studies may be due to the method of data collection (primary data vs. secondary data from a clinic). Because secondary data is less accurate and may be exaggerated due to personal bias compared to primary data. The baseline prevalence of food insecurity found in this study falls within the range of prevalence reported from two studies done among people living with HIV in Southwest Ethiopia (38.7% and 63.0%) (17, 26). This may be due to TB is a chronic disease which might negatively affect productivity and reduce income. This will affect individuals' ability to acquire sufficient food for themselves and their families. As adequate nutrition is important for recovery, TB programs need to address macronutrient requirements of patients to help recovery.

In this study, higher proportions of female patients were found to have food insecurity at baseline (54.2%) and first follow up (52.3%). This might be due to women's limited economic, educational, and employment opportunities and because they are more involved in unpaid work such as childcare and domestic activities than men particularly in a low-income country like Ethiopia (27-29). So, further study is needed to address the gender disparity in terms of food insecurity and treatment outcomes among TB patients in Ethiopia and other low income countries.

In this study, the prevalence of mental distress was decreasing over six months from 61.2% at baseline to 22.0% at the second follow-up. This is consistent with other studies done similar populations in Ethiopia (11) and South Africa (30). This might be due to patients with tuberculosis experience severe symptoms of the disease in the first month of treatment initiation which may overlap with the symptoms of mental distress but as patients get improvement from TB, symptoms of mental distress may also decline. Also, since SRQ-20 contains several physical symptoms that overlap with the symptoms of TB, the improvement of TB symptoms such as fatigue, loss of appetite throughout anti-TB treatment may account for the reduction in the level of mental distress. However, the baseline prevalence of mental distress found in this study (61.2%) was greater than the finding of a study done in Angola (44.4%) (31) and South Africa (34.1%) (30). The difference might be due to the tool used to assess mental distress (SRQ-20 vs. Hospital Anxiety and Depression Scale (HADS), and K-10). For example, K-10 has nine items of psychological symptoms and only one physical item, so little overlap with TB symptoms compared to SRQ-20. The prevalence of mental distress at the first (38.1%) and second (22.0%) follow-up found in this study was in line with the studies conducted in Huambo hospital, Angola (44.4%) (32) and South Africa (21.8%) (30, 33) but lower than the finding of studies conducted in a similar population in Dire Dawa and Harar cities (63.3%) (10) and Addis Ababa Ethiopia (48.5%) (11).

In this study, severe food insecurity predicted mental distress independent of other covariates which are in line with previous studies done in similar populations in Zambia and South Africa (7, 34, 35). Also, it is in line with a community-based study conducted in four African countries (Ethiopia, Nigeria, Uganda, and Ghana) (36, 37). This may be due to uncertainty to have adequate food could lead to chronic stress that affects the mental health of the patients(7).

The limitation of this study is that it did not include hospitalized patients, patients on re-treatment, and patients with MDR-TB, therefore, the results cannot be generalized for these patients. Patients with MDR-TB and hospitalized TB patients may have higher depression and anxiety and their exclusion might have led to underestimated prevalence of mental distress.

Patients with MDR-TB are under special treatment and surveillance so that including this group of patients might have biased the results. Moreover, SRQ-20 is not a gold-standard to measure mental disorders. So, TB related physical symptoms might overlap with SRQ-20 and led to the overestimate of mental distress.

Nonetheless, the longitudinal design, recruitment of participants from primary care facilities in rural and urban settings, and the consideration of several known confounding variables in the data analysis make our results robust. The good surveillance system and presence of follow-up make the data collection highly reliable.

Conclusions

In this longitudinal study, we have found a high prevalence of food insecurity and mental distress among TB patients. Also, food insecurity predicted mental distress independent of other covariates. This implies that many TB patients in Southwest Ethiopia are suffering from both mental health problems and lack of adequate food both of which might adversely affect treatment outcomes. Therefore, this finding would be an input for TB programs so that effective interventions for mental distress and food insecurity are integrated into the care of TB patients. Future studies need to evaluate the effectiveness of interventions for food insecurity in reducing mental distress in TB patients.

Declaration of interest

All authors declare that they have no conflict of interests.

Authors' contribution

MS contributed to the conceptualization, design, statistical analysis and manuscript preparation.

MT, KA, WK, ET, YY, RS and EG contributed to the design, analysis and the review of the manuscript.

Acknowledgement

We are grateful to the study participants for compromising their time to participate in the study.

Our gratitude is extended for Jimma University for funding the project. We are also grateful to IPPG for funding part of the project. Our gratitude extended to Dr. Michael Odenwald, who contributed money from his pocket to support the project.

References

1. FAO I, UNICEF, WFP and WHO. 2019. . The State of Food Security and Nutrition in the World 2019. Safeguarding against economic slowdowns and downturns. Rome, FAO. Licence: CC BY-NC-SA 3.0 IGO.2019.

2. Comprehensive Food Security and Vulnerability Analysis (CFSVA) 2019.

3. Abegaz KH. Determinants of food security: evidence from Ethiopian Rural Household Survey (ERHS) using pooled cross-sectional study. Agriculture & Food Security. 2017;6(1):70.

4. Balinda IG, Sugrue DD, Ivers LC. More Than Malnutrition: A Review of the Relationship Between Food Insecurity and Tuberculosis. Open Forum Infect Dis. 2019;6(4):ofz102.

5. Cassidy DA, Ivers LC. Food Insecurity and Tuberculosis: Policy Urgently Needs To Play Catch-Up. Ir Med J. 2018;111(6):777.

6. Claros JM, de Pee S, Bloem MW. Adherence to HIV and TB care and treatment, the role of food security and nutrition. AIDS Behav. 2014;18 Suppl 5:S459-S64.

7. Jones AD. Food Insecurity and Mental Health Status: A Global Analysis of 149 Countries. Am J Prev Med. 2017;53(2):264-73.

8. Aline Drapeau AM, Dominic Beaulieu-Prévost. Epidemiology of Psychological Distress In Mental Illnesses – Understanding, Prediction and

Control,: LAbate PL ed; 2012. 155–34 p.

9. Goldberg D. A bio-social model for common mental disorders. Acta psychiatrica Scandinavica Supplementum. 1994;385:66-70.

10. Ayana TM, Roba KT, Mabalhin MO. Prevalence of psychological distress and associated factors among adult tuberculosis patients attending public health institutions in Dire Dawa and Harar cities, Eastern Ethiopia. BMC Public Health. 2019;19(1):1392.

11. Tola HH, Shojaeizadeh D, Garmaroudi G, Tol A, Yekaninejad MS, Ejeta LT, et al. Psychological distress and its effect on tuberculosis treatment outcomes in Ethiopia. Glob Health Action. 2015;8:29019.

12. Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol. 1997;48:191-214.

13. Whitaker RC, Phillips SM, Orzol SM. Food insecurity and the risks of depression and anxiety in mothers and behavior problems in their preschool-aged children. Pediatrics. 2006;118(3):e859-68.

14. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The Effect of Psychosocial Factors and Patients' Perception of Tuberculosis Treatment Non-Adherence in Addis Ababa, Ethiopia. Ethiopian journal of health sciences. 2017;27(5):447-58.

15. Hanlon C, Medhin G, Alem A, Araya M, Abdulahi A, Hughes M, et al. Detecting perinatal common mental disorders in Ethiopia: validation of the self-reporting questionnaire and Edinburgh Postnatal Depression Scale. J Affect Disord. 2008;108(3):251-62.

16. Coates J SA, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for measurement of food access: Indicator guide(V.3): Washington, D.C.: FHI 360/FANTA; 2007.

17. Tesfaye M, Kaestel P, Olsen MF, Girma T, Yilma D, Abdissa A, et al. Food insecurity, mental health and quality of life among people living with HIV commencing antiretroviral treatment in Ethiopia: a cross-sectional study. Health and quality of life outcomes. 2016;14:37.

18. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care. World Health Organization. 2001:pp1-40.

19. Monteiro TFBCH-BBSG. The Alcohol Use Disorders Identification TestGuidelines for Use in Primary Care. Second Edition: World Health Organization; 2001.

20. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated factors among people living with HIV who are attending services in south west Ethiopia. BMC research notes. 2014;7:828.

21. Average Salary in Ethiopia 20192019 accessed on 09/07/2019.

22. I RK. Instrument Manual: Oslo-3 Social Support Scale (OSS-3)2006.

23. Molla A, Mekuriaw B, Kerebih H. Depression and associated factors among patients with tuberculosis in Ethiopia: a cross-sectional study. Neuropsychiatr Dis Treat. 2019;15:1887-93.

24. Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and tuberculosis treatment outcomes, quality of life and disability, Ethiopia. Bulletin of the World Health Organization. 2018;96(4):243-55.

25. D Susilaningrum BSSU, R Lathifah. Mapping the Factors Affecting Household Food Security of Tuberculosis Patients in Coastal Region of Surabaya2018.

26. Tiyou A, Belachew T, Alemseged F, Biadgilign S. Food insecurity and associated factors among HIV-infected individuals receiving highly active antiretroviral therapy in Jimma zone Southwest Ethiopia. Nutrition journal. 2012;11:51.

27. Thim GFaA. Measuring Women's Economic Empowerment: Time Use Data and Gender Inequality: OECD Development Policy Papers; 2019.

28. Fund IM. WOMEN AND THE ECONOMY IN ETHIOPIA2018.

29. Ivers LC, Cullen KA. Food insecurity: special considerations for women. Am J Clin Nutr. 2011;94(6):1740s-4s.

30. Peltzer K. Decline of common mental disorders over time in public primary care tuberculosis patients in South Africa. Int J Psychiatry Med. 2016;51(3):236-45.

31. Xavier PB, Peixoto B. Emotional distress in Angolan patients with several types of tuberculosis. Afr Health Sci. 2015;15(2):378-84.

32. Benvinda Xavier Paulo BP. Emotional distress patients with several types of tuberculosis. A pilot study with patients from the Sanatorium Hospital of Huambo: I n t e r n a t i o n a l J o u r n a l o f M y c o b a c t e r i o l o g y 2016. S 5 8 p.

33. Theron G, Peter J, Zijenah L, Chanda D, Mangu C, Clowes P, et al. Psychological distress and its relationship with non-adherence to TB treatment: a multicentre study. BMC Infect Dis. 2015;15:253.

34. Steven M. Cole GT. The effect of food insecurity on mental health: Panel evidence from rural Zambia: Social Science & Medicine; 2011. 1071e9 p.

35. Tomita A, Ramlall S, Naidu T, Mthembu SS, Padayatchi N, Burns JK. Major depression and household food insecurity among individuals with multidrug-resistant tuberculosis (MDR-TB) in South Africa. Soc Psychiatry Psychiatr Epidemiol. 2019;54(3):387-93.

36. Birhanu TT, Tadesse AW. Food Insecurity and Mental Distress among Mothers in Rural Tigray and SNNP Regions, Ethiopia. Psychiatry journal. 2019;2019:7458341.

37. Sweetland AC, Norcini Pala A, Mootz J, Kao JC, Carlson C, Oquendo MA, et al. Food insecurity, mental distress and suicidal ideation in rural Africa: Evidence from Nigeria, Uganda and Ghana. Int J Soc Psychiatry. 2019;65(1):20-7.

Statement on Pre-release and Contribution

Some parts of this thesis are published in peer-reviewed journals. The first publication was on Magnitude and predictors of khat use among patients with tuberculosis in Southwest Ethiopia: A longitudinal study. I'm the first and corresponding author of this paper. Also, I contributed to proposal preparation, data collection, analysis and manuscript preparation, and publication. Also, I sent the second manuscript for publication on July 2020. The first and second reviewers' comments were addressed and waiting for publication. I contributed to proposal preparation, data collection, analysis, and manuscript preparation. Moreover, the third manuscript was submitted in September 2020 and waiting for reviewer comments.

I prepared all manuscripts and edit based on the feedback from supervisors. In general, I contributed to the conceptualization, design, searching for funds, data collection, statistical analysis, manuscript preparation of this thesis.

Acknowledgments

First of all, I would like to thank God for His great support during day and night. Then I would like to extend deep gratitude to Professor Eva for her support and guidance during the development of my proposal to the end of this thesis. I want to extend warm gratitude to Professor Markos Tesfaye for his great support and constructive comment from proposal development up to the end of this thesis. Also, I want to thank Dr. Kristina Adorjna for her great support and constructive comment starting from the proposal development till the end of this thesis. I want to extend warm gratitude to Dr. Wolfgang Krahl for his great support and constructive comment from proposal development up to the end of this thesis. Additionally, I want to thank Jimma University for giving me this chance and financial support. Also, I want to thank the Institute of Psychiatry Phenomics and Genomics for the financial support. My warm gratitude goes to Dr. Michael Odenwald for the financial support he provided me from his pocket. Also, I want to thank Dr. Ralf Strobl for his support during data analysis. I would like to thank my family member for their support to reach this level. Additionally, my warm gratitude goes to my wife Maireg Sori for all her necessary support for the success of my thesis. Last not least, I would like to thank the study participants for compromising their time to participate in the study.

List of Publications

1. **Soboka M**, Tesfaye M, Feyissa GT and Hanlon C, 2014. Alcohol use disorders and associated factors among people living with HIV who are attending services in south west Ethiopia. BMC Research Notes, 2014; 7:828
2. **Soboka M**, Tesfaye M, Feyissa GT and Hanlon C, 2015. Khat use in people living with HIV: a facility-based cross-sectional survey from South West Ethiopia. BMC Psychiatry, 2015; 15:69
3. **Soboka M**, Gudina EK, Tesfaye M. Psychological morbidity and substance use among patients with hypertension: a hospital-based cross-sectional survey from South West Ethiopia. Int J Ment Health Syst . 2017; 11:5
4. Molla Z, Dube L, Krahl W and **Soboka M**. Tobacco dependence and associated factors among people with mental illness from South West Ethiopia. BMC research note, 2017 ; 10:289
5. Dires E, **Soboka M**, Kerebih H, Feyissa GT. Factors Associated with Khat Chewing among High School Students in Jimma Town Southwest Ethiopia. Journal of Psychiatry. 2016; 19:4
6. Adorjan K, Odenwald M, Widmann M, Tesfaye M, Tessema F, Toennes S, Suleman S, Papiol S, **Soboka M** et al. Khat use and occurrence of psychotic symptoms in the general male population in Southwestern Ethiopia: evidence for sensitization by traumatic experiences. World Psychiatry. 2017, 16(3).
7. Adorjan K, Widmann M, Tesfaye M, Tessema F, Toennes S, Suleman S, Susser E, Papiol S, **Soboka M** et al. Khat abuse as risk factor for development of psychotic symptoms in trauma patients. A feasibility study for further genetico-epidemiological studies in the GGFRC, Ethiopia. European Neuropsychopharmacology. 2017, 27(3):S468
8. Asrat B, Girma E, **Soboka M** and Tesfay K. Mental Distress and Associated Factors among Health Professionals Working in Tertiary Teaching Hospital, South West Ethiopia. Depression & Anxiety, 2015; 4:3
9. Asrat B, Tesfay K, **Soboka M** and Girma E. Burnout status at Work among Health care Professionals in a Tertiary Hospital. Ethiop J Health Sci. ,2016; Vol. 26, No. 2
10. Derajew H , Tolessa D, Feyissa GT, Addisu F and **Soboka M**. Prevalence of depression and its associated factors among primary caregivers of patients with severe mental illness in southwest, Ethiopia . BMC of psychiatry. 2017;17:88

11. Fikreyesus M, **Soboka M**, Feyissa GT. Psychotic relapse and associated factors among patients attending health services in Southwest Ethiopia: a cross-sectional study. BMC Psychiatry .2016; 16:354.
12. Kerebih H, **Soboka M**. Prevalence of Common Mental Disorders and Associated Factors among Residents of Jimma Town, South West Ethiopia. Journal of Psychiatry. 2016; 19:4
13. . Kerebih H, Abera M, **Soboka M**. Pattern of Help Seeking Behavior for Common Mental Disorders among Urban Residents in Southwest Ethiopia. Quality in Primary Care (2017) 25 (4): 208-216
14. **Soboka M** and Feyissa GT. The effectiveness of counselling, material support and/or nutritional supplementation on improving adherence to anti-retroviral therapy and clinical outcomes among HIV patients: a systematic review of quantitative evidence protocol. JBI Database of Systematic Reviews & Implementation Reports. 2015; 13(7) 142 – 152
15. **Soboka M** and Feyissa GT. The impact of maternal postnatal depression on infant growth in sub- Saharan African countries: a systematic review protocol
16. **Soboka M**, Adorjan K, Dehning S, Asaminew A, Abera M, Siebeck M, Tesfaye M, Jobst A. Evaluation of a Master of Science in Integrated Clinical and Community Mental Health (MSc ICCMH) program in Ethiopia. GMS German Medical Science 2018, (16): 1612-3174.
17. Mekuriaw B, Abera M, Tessema W, Agenagnew L, Dawud B, Abdisa E, Tesfaye M, Tolosa D, Hailsilassie H, **Soboka M**, Mamaru A, Yeshgeta E and Kerebih H. Medication Non adherence and Use of Traditional Treatment Among Adult Psychiatric Patients in Jimma Town Treated at Jimma University Teaching Hospital Psychiatric Clinic. Community Based Cross-sectional Study, 2016. J Psychiatry , 21:434
18. Yitayih Y, Abera M, Tesfaye E, Mamaru A, **Soboka M†**, Adorjan K†. Substance use disorder and associated factors among prisoners in a correctional institution in Jimma, Southwest Ethiopia: a cross-sectional study. BMC Psychiatry (2018) 18:314
19. Slabbert I, Greene IC, Womersley JS, Olateju OI, **Soboka M**, Lemieux AM. Women and substance use disorders in low- and middle-income countries: A call for advancing research equity in prevention and treatment. Substance Abuse, DOI: 10.1080/08897077.2019.1680481

20. Yitayih Y, **Soboka M**, Tesfaye E, Abera M, Mamaru A, Adorjan K. A cross-sectional study of psychopathy and khat abuse among prisoners in the correctional institution in Jimma, Ethiopia. PLoS ONE 15(1): e0227405.
21. Yitayih Y, Feyissa GT, Adorjan K, **Soboka M**. Effectiveness of symptom-triggered regimen versus fixed-dosage regimen of benzodiazepine treatment for alcohol detoxification: a systematic review protocol. JBI Database System Rev Implement Rep 2019; 17(0):1–6.
22. Adorjana K, Mekonnen Z, Tessema F, Ayanad M, Degenhardt F, Hoffmann P, Fricker N, Widmannh M, Riedkeh H, Toennes SW, **Soboka M**, Suleman S, F.M. Andlauerm T, Tesfaye M, Rietschel M, Susser W, Odenwaldh M, Schulzea TG, Mattheisen M. Genotype-phenotype feasibility studies on khat abuse, traumatic experiences and psychosis in Ethiopia. Psychiatric Genetics 2020, 30:34–37.
23. Agenagnew L, Mamaru A, Hailesilassie H, Mekuriaw B, Dawud B, Abdisa E, Tolosa D, Abera M, **Soboka M**, Kerebih H, Yeshigeta E, Tesfaye E. Disability among Patients with Mental Illness in Jimma Town, Southwest Ethiopia, 2017, Communitybased Crosssectional Study. Mental Health Hum Behav 2019; 24:27-35.
24. **Soboka M** , Tolessa O, Tesfaye M, Adorjan K, Krahl W, Tesfaye E, Yitayih Y, Strobl R, Grill E. Magnitude and predictors of khat use among patients with tuberculosis in Southwest Ethiopia: A longitudinal study. PLoS ONE, 2020; 15(7): e0236154.
25. Alemu D, **Soboka M**, Tesfaye E, Ahmed G, Tesfaye Y. Alcohol Use Disorder and Associated Factors Among Jimma University Undergraduate Students. Psychol Res Behav Manag, 2020; 13: 609–618.
26. Teshome M, **Soboka M**, Feyissa GT, Salelew E, Kerebih H. Medical comorbidity among psychiatric patients treated at Jimma University Medical Center, Southwest Ethiopia: Retrospective record review. Neurology, Psychiatry and Brain Research, 2020;38:33-38
27. **Soboka M,** Tesfaye M, Adorjan K, Krahl W, Tesfaye E, Yitayih Y, Strobl R, Grill E. Effect of food insecurity on mental health of patients with tuberculosis in Southwest Ethiopia: a prospective cohort study. BMJ Open, 2021; 11(9): e045434.
28. **Soboka M**, Tesfaye M, Adorjan K, Krahl W, Tesfaye E, Yitayih Y, Strobl R, Grill E. Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: a prospective cohort study. BMJ Open, 2021;0:e043050. doi:10.1136/ bmjopen-2020-043050.