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Mental Disorders Associated with Khat Use: A Scoping Review and Meta-Analysis

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Abstract

Background: Khat is the substance mainly used for its central nervous stimulation effects. The substance has been associated with several mental health problems, and there is an ongoing international concern about this causal relationship. Nevertheless, an effort to scope and systematically review mental health effects of khat based on the available studies is a much-ignored venture.

Objective: The objective of the study is to map, summarize and pool effect size of the association between khat use and mental disorders

Methods: The study has two phases. The first phase deals with the scoping review of the association between khat and mental disorders using PubMed, SCOPUS, Embase and CINAHL databases to map and clarify the existing published studies on the relationship between khat use and mental disorders. The second phase is a meta-analysis of the association between khat use and 'non-specific psychological distress' identified using scoping review as having rich evidence to warrant meta-analysis. Newcastle Ottawa Scale (NOS) is used to assess the qualities of studies used for meta-analysis. The meta-analysis employed RevMan version 5.4.1 and Comprehensive meta-analysis (CMA) software. Heterogeneity among estimates is quantitatively evaluated with the I^2-statistic. The Hedges method of pooling odds ratios is plotted using forest plots and pooled odds ratio (OR) is calculated. Publication bias is investigated by construction of funnel plots and Egger's test.

Results: The initial online search of the four databases yielded a total of 7,121 articles and the search of gray literature produced 5 eligible articles. A total of N=108 are considered eligible for the scoping review. The studies are conducted in 12 different countries, a dramatic increase in the number of studies was observed only during the last ten years and the studies mostly employed cross-sectional design. Khat use is mostly measured using a single item 'yes/no' question and attention to study the 'dose-dependent effect' of khat use on mental health is not given much attention. About 14 different categories of mental disorders and related conditions have been identified as having association with khat use. The meta-analysis shows that the pooled effect size of psychological distress among people who use khat in the form of odds ratio (OR) using Trim and Fill the imputed point estimate is 2.09 (1.56, 2.78), as compared to those who don't use khat.

Conclusion: Although most of the studies associated khat use with mental disorder, the development of conclusive evidence about cause-effect relation is impossible given the cross-sectional design dominating most of the studies, contradictory findings and the limited number of studies employing advanced designs.

Keywords: Khat and mental disorders, psychological distress, scoping review, meta-analysis

1. Introduction

1.1Background of the study

The use of psychoactive substances across the globe is rapidly increasing and has become one of the most pressing public health challenges affecting every country (1, 2). An estimate from the United Nations Office on Drugs and Crime indicates that 271 million people (5.5% of the global population) aged 15-64 had used substances in 2016, and compared to the 210 million people who used drug in 2009, this figure represents a 30% increase. Furthermore, 585,000 people are estimated to have died and 42 million years of healthy life were lost (premature deaths and years lived with disability) as a result of substance use disorder in 2017 (3).

Khat (*Catha edulis Forsk*) is one of the most used psychoactive substances in Ethiopia and other countries in East Africa and Arabian Peninsula. In this region, consumption of the plant is a deep rooted socio-cultural tradition (4) and is chewed by more than 20 million people on every day basis (5). In addition, khat chewing has gained global prominence recently due to migration, and improved transportation. As the result, the drug has been reported in Great Britain, Italy, The Netherlands, Canada, Australia, New Zealand, the USA and many other countries (6).

Khat is mainly used for its central nervous stimulation effects. Stimulation is achieved most commonly through chewing its fresh leaves. These leaves contain *cathinone* and *cathinone*, both are structurally related to amphetamine (7). Its effects on the chewer include increased levels of energy, increased self-esteem, euphoria, increased libido, excitement, and increased proclivity for social interaction (8) usually followed by tension, anxiety, irritability, and insomnia (7). Traditionally, the plant has been used as a socializing drug and this is still very much the case. However, it is also used by farmers and other laborers for reducing physical fatigue, and by vehicle drivers and students for improving attention (6).

Khat chewing is becoming routine behavior and increasing at an alarming rate (9). Studies reported a lifetime prevalence ranging from 13.4% to 41%, and past 30 days prevalence ranging from 6.3% to 33.1% of khat chewing among university students in Ethiopia (10). In the southwestern Uganda, a study conducted on three occupational groups revealed that 20.4% of the respondents were khat chewers at the time of the study, and 31.5% were ever users of khat (11). Among armed personnel in Somalia, 36.4% prevalence of khat use in the week before the interview was reported (12). In the capital city of Yemeni, Sana'a, 86% of

the males and 50% of the females were khat chewers, and the majority of the users were between the ages of 15 and 30 years (13).

In spite of its wide use, plentiful evidence showcases the adverse effects of excessive and prolonged use of khat on mental, physical and social wellbeing. Mentally, khat chewing is associated with a wide range of health effects extending from minor reactions (such as over talkativeness, hyperactivity, insomnia, anxiety, dizziness, impaired concentration, irritability, agitation and aggression) to the development of a psychotic illness. Khat use is also associated with a number of physical health problems, including mucosal problems, oral lesions, gastric cancers and duodenal ulcers, hypertension, cardiovascular complications, stroke, sexual dysfunction, hepatoxicity and reduced birth weight of infants born to khat-chewing mothers, to mention just a few (14). Socially, khat chewing results in diversion of household income among poor families, reduced productivity (8) and wasted time because a considerable amount of time is spent chewing (15). Khat chewing has also been implicated with use of illicit drugs, smoking, and alcohol (8). Khat is also usually considered as a 'gateway drug' to other drugs (8, 16). Khat use is most commonly associated with tobacco, alcohol use (2, 17, 18), shisha and cannabis (19-21).

Generally speaking, a number of mental and physical health problems are associated with the use of khat. Nevertheless, studies presenting such association are usually not supported with strong evidences, and as a result Odenwald described this study area as *a neglected topic* (22). Even more, the potentially adverse consequences of khat use on physical health have been relatively better documented than its effects on mental health. An effort to scope and systematically review mental health effects of khat on the basis of the few available studies is also a much-ignored venture. This scoping review is needed since primary studies on the mental health effects of khat are not still systematically and comprehensively mapped and summarized.

1.2 Statement of the problem

Mental disorders encompass a wide range of mental and behavioral disorders described in the International Statistical Classification of Diseases (ICD) and Related Health Problems (10th edition, ICD-10). These include depression, bipolar affective disorder, schizophrenia, anxiety disorders, dementia, substance use disorders, and intellectual disabilities and developmental and behavioural disorders that typically arise from childhood through adolescence, including autism (23). Mental disorders lead to poor health outcomes, premature death, human rights violations, and global and national economic loss (24). Persons with severe mental disorders, for instance, die 10 to 20 years earlier than the general population (25). In 2016, over one billion people or 16% of the world's population were affected by mental or addictive disorders and 162.5 million DALYs were lost due to these disorders (26).

In recent decades, there has been a growing recognition that the presence of psychiatric disorders associated with substance use represents a major challenge for public health responses. The relevance of the comorbidity of substance use and mental disorders is related not only to its high prevalence but also to its difficult management and its association with poor outcomes for the patients affected (27). Several studies indicate that substance users have higher prevalence rates of psychiatric illness compared with non-users (27, 28). It is a well-known fact that the use of drugs can induce psychiatric syndromes when people are intoxicated or are withdrawing from its effects (29). For instance, the prevalence of substance use disorders in persons with schizophrenia is significantly higher than in the general population, and several substances can cause psychosis during intoxication or withdrawal (30). A number of evidences also show that substances like alcohol, amphetamine, LSD, phencyclidine, ketamine, and synthetic novel psychoactive substances induce acute psychoactive substances (31).

Khat has been associated with a number of mental health problems, and there is ongoing international concern about a causal relationship between khat use and mental illness (32). The effects of khat were, indeed, reviewed by a WHO report in 1980 (33). In 1973 the WHO expert committee listed khat as a 'dependence producing drug', and in 1985 *cathine* and *cathinone* were assessed as meeting the criteria for control under the Convention of Psychotropic Substances and recommended for scheduling (32) though khat is still not

internationally controlled, rather different countries have their own policies which ranges from criminalization to non-regulation towards the substance.

In general, the potential risks and benefits of khat chewing are hotly debated, particularly regarding the association between khat and mental illness. There are many case reports on a possible association between excessive khat use and the occurrence of mental disorders, such as manic-like psychosis and the incidence of psychotic symptoms (34, 35). Sizeable number of studies has also pointed out khat use's effect on pre-existing psychosis (36-39) and khat chewing may also exacerbate symptoms in patients with pre-existing psychiatric disorder (40). The prevalence of depression, anxiety, and stress were higher among khat chewers (41, 42). Screening positive for khat dependence was associated with experiencing three or more psychological health problems (43). Excessive and prolonged use of khat were also associated with suicidal attempts and homicidal acts (44). A community-based study also found significant association between mental distress and khat use. It is stated that mental distress is higher among frequent and daily users and those who chewed for ≥ 2 years (45). Among special populations such as individuals with PTSD experiences, higher amount of khat consumption was associated with the higher odds for paranoid ideation (46).On the other hand, there are also studies that did not found significant association between khat use and mental disorders (32). In Yemeni, for instance, one study found that the incidence of adverse psychological symptoms was not greater in khat users. In fact, the study found that there was a negative association between the incidence of phobic symptoms and khat use (33). Warfa and Klein (32) also stated that there is no clear evidence as to the effects of khat use and the development of mental illness and they further indicated that khat use could only exacerbate psychological problems caused by pre-existing stressors. This makes association between khat use and mental illness a controversial issue. The lack of good quality studies examining dose–response relationship between khat use and mental illness was also stated (32). It is within this context that this study was conceived to summarize evidence on the association between khat use and mental disorders using scoping review and meta-analysis.

1.3 Significance of the study

The rapidly growing use of khat, especially in East Africa and Arabian Peninsula, is a major concern for public health. Specifically, studying the mental health effects of khat represents an important area of public health concern. A synthesis of evidence on the link between khat use and mental disorder, therefore, may provide strong scientific base for healthcare practitioners to tailor their treatment regimens for mental illness by taking in to account khat use history of their patients. For policy makers and international stakeholders like WHO and UNODC, the result of this review could strongly help them to figure out how khat should be dealt with at national and international level.

Furthermore, this study has identified gaps in research in the area of the association between khat use and mental health, and provided impetus for researchers to employ appropriate study designs to carry out such studies.

2. Literature review

2.1 Prevalence and pattern of khat use

Although the exact number of global khat users is not known, it is usually stated that more than 20 million people worldwide regularly use khat (53) with more than 10 million people using khat daily (54). Overwhelming majority of global khat chewing population is located in the traditional khat consuming regions of East Africa. A cross sectional study on the students of Bahir Dar University found a life time prevalence of 24% and a current prevalence 12.7% of khat chewing among students. Habitual use, defined as khat chewing at least once a week, was reported by 4.8% of the students. The study indicated the reported prevalence as being higher than reports from previous studies, and described the trend as a growing concern (55). A meta-analysis on the epidemiology of khat consumption among university students found a pooled prevalence of 13.59% of current and 24.82% of lifetime khat chewing prevalence among university students in Ethiopia (56). Similarly, a meta-analysis of 24 studies on the prevalence and predictors of khat chewing among Ethiopian university students found a khat chewing pooled prevalence of 23.22%. a subgroup analysis shows that the highest prevalence was from Oromia with a prevalence of 31.6% and followed by SNNP (24.7%). The prevalence of khat chewing was to some extent higher in studies having a sample size $\geq$ 700 as compared to studies involving a sample size $<$ 700 (9).

A large house-to-house survey of the prevalence and socio-demographic correlates of khat chewing in Butajira, a small town in the south-central Ethiopia, sampled 10,468 adults. The study found 55.7% lifetime prevalence of khat chewing, 50% prevalence of current use, and 17.4% use of khat on a daily basis (57). A more recent study of khat use among adolescents in the selected secondary schools in Uganda reported 10.8% of khat use. In the study, khat is the third most used substance, following alcohol (23.3%) and *kuber* (10.8%) (58). Yemeni and Saudi Arabia are the two countries in Arabian Peninsula where significant numbers of khat chewing population are reported. Yemen National Health and Demographic survey (59), reported 52% of the individuals aged 15 or older as current users of khat. In terms of gender, the same study described khat use to be more prevalent among male (71.3%) as compared to female (33.6%). A cross-sectional study in the Jazan region of Saudi Arabia showed 28.7% prevalence of current khat chewing, 36.9% among males and 8.7% among females.(60)

2.2 Motives and predictors of khat use

Research evidences show a number of motives behind the use of khat. The consumption of khat was traditionally meant to assist with religious studies, arduous work demands, food shortages, social cohesion, and medication for ailments like depression (61). Moreover, khat was pretty much used in the olden days mainly on ceremonial occasions, and predominantly by men. With changes in lifestyles, more young men seem to have taken to the khat chewing habit with frequent use pattern (62).

The main reasons reported for chewing khat among undergraduate medical students of Addis Ababa University included for effective reading and studying (68%), for enjoyment (63%) and to get rid of sleeplessness (43%) (2). A considerable broader set reasons for khat chewing haven mentioned by the students of Haramaya University. The reasons were to increase academic performance (45.4%), to get personal pleasure (25.8%), get relief from tension (23%), to stay awake (16.2%), due to peer influence (16.2%), due to academic dissatisfaction (10.3%), to get acceptance by others (6.4%), to be sociable (5.5%), to increase pleasure during sex, (4.1%) and due to religious practice (2.6%).

Pleasurable central stimulation effects of khat are utilized to boost work capacity and to prevent sleep where there is the need among long distance lorry drivers, night watchmen, and farmers. Khat is also valued at social occasions, where the effects help to enhance communications (63).

With regard to predictors, a study in Jimma found male students, students living in off campus housing, students who have khat user friends, and students who perceive khat use improves academic performance are more likely to use khat (55).

A study in Hawassa also reveals that those who had family history of substance use were about five times more likely to chew khat than the those who had no family history of substance use, having a friend who used khat increased the odds of khat chewing by 4.6 times, and ever using shisha increased the risk of khat chewing by 32.1-fold. Ever smoked increased the risk of khat chewing by seven fold, and having used alcohol increased the risk of having khat chewing by three times (64).

A systematic review and meta-analysis conducted using a total of nine studies indicates that gender was significantly associated with khat chewing practice, with males 2.76 times more

likely to chew khat as compared to females. The presence of khat chewing family members and friends was strongly associated with the khat chewing practice of students in the universities with students having family members and friends chewing khat were 2.91 and 4.74 times more likely to chew khat as compared to their counterparts respectively (9).

2.3 Mental health effects

There have been serious concerns about psychological harms of khat chewing on users. Studies on the health effects of khat use are diverse and findings are usually inconsistent and at odds.

Consumption of small amount of khat leads to positive subjective experience among chewers such as euphoria, and increases in energy levels, alertness, ability to concentrate, self-esteem, increase in libido, imaginative ability, ability to communicate, and work performance (51), and limited use of khat has also no accompanying serious mental health consequences (14). However, prolonged exposure could lead to dependence, and other psychiatric disorders (14). The alkaloid in khat principally responsible for producing dependence and mental illness is believed to be *cathinone*.

Consumption of khat in large amount leads to hyperactivity, and sometimes manic behavior. When a chronic khat chewer stops chewing the leaf, withdrawal symptoms that follow are feeling hot, lethargy, a desire to chew khat in the first few days, a nightmare for 1-2 days (4), insomnia, numbness, lack of concentration and low mood (51). Depression is encountered following khat use withdrawal (65), occasionally ensuing self-harm and suicide in a similar ways with the cessation of amphetamine use (51). However, physical symptoms of withdrawal related with substances like morphine and alcohol do not occur in khat users (4).

Khat chewing is associated with a wide range of mental health effects extending from minor reactions to the development of a psychotic illness. Minor reactions that follow moderate intake of khat may include overtalkativeness, hyperactivity, insomnia, anxiety, dizziness, impaired concentration, irritability, agitation and aggression which usually occur after a moderate intake of khat (66). A community based study also reveals that khat chewing was associated with mental distress (45). The most reported psychiatric complications resulting from khat chewing is psychosis (51). According to Cox and Rampes (51) psychosis following khat chew can be two main types: paranoid or schizophreniform psychosis (similar to an amphetamine-like psychosis) and a manic psychosis. In the Schizophreniform psychosis

subjects typically display paranoid delusions, fear, a hostile perception of the environment, auditory hallucinations (frequently of a persecutory or threatening type), ideas of reference, thought alienation and a tendency to isolate themselves, or alternatively displaying aggressive behavior towards others. Manic psychosis subjects present with hyperactivity, shouting, pressure of speech, grandiose delusions with flight of ideas and tangential thought processes, and a labile mood varying from euphoria to anger. Schizophreniform psychosis is thought to cease within 3-11 days and symptoms of manic psychosis wear-off spontaneously within 8 hours of chewing (51). Most reported cases of psychosis has set on after excessive use, and the symptoms are said to settle with the withdrawal of chewing (65). Owing to the mode of consumption, the dose of khat tends to be self-limiting, unlike amphetamines that are available in a pure form for oral or parenteral administration. Therefore, toxic psychosis as a result of excessive use is much less frequent with khat than with amphetamines (51). On the other hand, a cross-sectional exploratory study of adverse psychological symptoms in Yemeni khat users employing the Symptoms Checklist-90 (SCL-90) indicates that incidences of adverse psychological symptoms were not greater in khat users. The other way round, the study showed negative association between the incidence of symptoms and khat use.

3. Objectives

3.1 General Objective

The objective of the study is to map, summarize and pool effect size of the association between khat use and mental disorders

3.2 Specific objectives

The scoping review will be conducted to address the following specific objectives

1. To map and summarize the evidence available on the association between khat use and mental disorders
2. To identify area for (and compute effect size of) the association between khat use and mental disorders

4. Methods

4.1 Introduction

This study has two phases. The first phase addresses the scoping review of the association between khat and mental disorders. The process involved extensive literature search, and structured mapping of available evidence on the link between khat use and mental disorders. The results of scoping reviews helps to identify areas where a sufficient depth of literature exists to warrant a meta-analysis (75). Accordingly, the second phase involved a meta-analysis of the association between khat use and a specific form of mental disorder (non-specific psychological distress) identified using scoping review as having rich evidence to meta-analysis.

4.2 Protocol design for scoping review

This objective is addressed using a scoping review approach. The function of a scoping review is to map the literature and evidences available in a given research area (76), summarize and share existing research findings with policymakers, practitioners and other relevant stakeholders; and identify research gaps in the existing literature (77). To this end, the evidence methodology of a scoping review has been employed for mapping and clarifying the existing studies on the relationship between khat use and mental disorders.

4.2.1 Procedures

This scoping review followed the methodological framework presented by Arksey and O'Malley (76). The review followed the five stages specified in the methodology of scoping review: (1) identifying the research question(s); (2) identifying potentially relevant studies; (3) selecting eligible studies; (4) charting the data; (5) collating, summarizing and reporting the results (76).

Stage 1: Identify the research question

The main research question that guided this scoping review is “what is known about the association between khat use and mental disorders?” It is quite comprehensible that the term mental disorders is a very wide concept and search results could be unmanageably high. But this wide research question is designed since Arksey and O’Malley (76) recommend that very

wide research question could reduce the likelihood of missing relevant articles, and once the breadth of existing literature and the number of bibliographic reference is identified, a decision of whether it is important to revise the scope of the research question is determined. In the case of the current project, this research question is maintained up to the end since it was desired to come up with a comprehensive picture about the general relation between the use of khat and mental disorder.

Stage 2: Identifying relevant studies

a. Eligibility criteria

The following inclusion and exclusion criteria have been utilized to guide the search and selection of review articles.

Inclusion criteria:

Population

- All age groups[1] and both sexes of participants
- Research that looks at the general population, as well as at specific population groups

Concept

- Research articles should examine the link between khat use and mental disorders
- The articles should be empirical studies
- Any pattern of khat use
- Any mental health condition
- Published primary studies as well as primary grey literature including unpublished thesis/dissertations and conference proceedings.
- Any study design
- Both quantitative and qualitative study approaches

Context

- All geographical locations
- Any publication year

[1] Though khat is usually not chewed among children, such evidences will be charted in case it is available.

Exclusion criteria:

- Opinions, letter to the editor, magazine and newspaper articles.
- Published in other languages than English
- Articles not based on empirical data

b. Search strategy and databases

A comprehensive literature search has been conducted on the following four databases to search for the articles which fulfill the aforementioned eligibility criteria: PubMed, SCOPUS, Embase and CINAHL. Secondary search has also been performed in Google Scholar to identify articles that are not indexed in the databases listed above. In addition, hand searches have been conducted on Google, OpenGrey and institutional repositories of different universities to identify grey literature like theses and articles included on the reference list of the already identified studies.

The following terms were used to search for articles from the databases and search engines ("Catha"[Mesh] *OR "Catha edulis"*[tw] OR khat[tw] OR Murungi[tw] OR Miraa[tw] OR Chat[tw] OR Qat [tw]) AND ("Mental Disorders"[Mesh] OR "Mental health" [tw] OR "mental illness" [tw] OR "mental disorder" [tw] OR "mental problem*"[tw] OR "mental distress" [tw] OR psycho*[tw] OR psychiatr*[tw]). Finally, references were extracted and imported to the EndNote X9 reference management system.

Stage 3: Study selection

This stage consists of two steps: (1) Titles and abstracts identified by the search strategy have been evaluated against the eligibility criteria by the lead researcher and a research assistant. Both advisors of the thesis completed the same process on a random sample of 10% of titles and abstracts as a quality check (2). After title and abstract review, a full-text of included articles have been read by the lead researcher. After full-text review, the final sample size of the included studies was determined. Following this, the full text sourced for all articles meeting the inclusion criteria were used for analysis. A PRISMA flow diagram is used to report the whole process of the search process.

Stage 4: Charting the data

Eligible studies was charted using a data extraction fields presented on *guidance for conducting systematic scoping reviews (78)* and other fields relevant to the research question have been added. The data extraction form is used to extract details pertaining to the following information.

1. Author (s)
2. Year of publication
3. Origin (where the study was conducted)
4. Aims/purpose
5. Study population and sample size
6. Study design
7. Outcome
8. Predictor variable and its measurement
9. Key findings that relate to the scoping review research questions
10. Gaps of the studies and their recommendations

Stage 5: Collating, summarizing and reporting the results

The results are summarized both quantitatively and qualitatively to give an account of collected data.

1. A quantitative analysis is used to map the studies in tabular and diagrammatic form, showing distribution of studies by theme, period of publication, country of origin and study design.
2. A qualitative summary is used to provide a thematically organized narrative synthesis describing how the studies identified relates to the research question of this review and the main findings from these.

4.3 Protocol design for meta-analysis

4.3.1 Searches

The scoping review identifies non-specific psychological distress as the most common category of mental disorder associated with the use of khat. Meta-analysis part of the study focused on pooling the effect size of these studies.

4.3.2 Eligibility criteria

All studies categorized under non-specific psychological distress are reviewed and checked for their eligibility to be included in the meta-analysis based on the eligibility criteria listed below:

4.3.2.1 Inclusion criteria

Population

- All age groups[2] and both sexes of participants
- Research that looks at the general population, as well as at specific population groups
- Studies conducted in every country of the world

Exposure of interest

- Any pattern of khat use

Outcome of interest

- Non-specific psychological distress

Study design

- All study designs are eligible for inclusion: cross-sectional, case-control, cohort studies, and randomized controlled trials.
- All human studies that examine the relationship between any measure of the use of khat and common mental disorders.

Language

[2] Though khat is usually not chewed among children, such evidences will be charted in case it is available.

Studies written in English language are included

Publication date

The review includes studies published up to the time of literature search

4.3.2 Exclusion criteria

Reasons for non-eligibility are:

- Non-English language
- Animal and non-human studies
- No empirical data
- Low quality score
- Khat use alone is not clearly identified or is blended together with other substances

4.3.3 Data extraction

A structured data extraction template is prepared. The template covers: Author, study location, participant information, sex, sample size, cut-off points, diagnostic tool used, and prevalence of psychological distress.

4.3.4 Quality assessment

Eligible studies were reviewed for their overall quality. Newcastle Ottawa Scale (NOS) is used in this regard to assess the risk of bias (79). The NOS is one of the most known scale for assessing quality and risk of bias as it is relatively quick to do, the adaptability of its indexes on the basis of the investigated topic, and as it is validated for different study designs (80). NOS gives a score between 0 and 9 based on three quality parameters: selection, comparability and outcome (79). The adapted version of NOS, which gives a score between 0 and 10, is used for cross-sectional studies (81).

Thresholds for converting the NOS to good, fair, and poor standards are the following (79).

- **Good quality:** 4 or 5 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- **Fair quality:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

- **Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Only studies with good quality or fair quality are considered for the review.

4.3.5 Data analysis

Microsoft Excel, RevMan version 5.4.1 and Comprehensive meta-analysis (CMA) software are used for data entry and meta-analysis. A narrative description of the study population, the included studies, and the nature of association between khat use and common mental disorders is made. Moreover, tables and chart are used to summarize results of the review. Heterogeneity among estimates is quantitatively evaluated with the I^2-statistic. Due to significant heterogeneity among studies, pooled estimates is based on random-effect models. The Hedges method of pooling odds ratios is plotted using forest plots and pooled odds ratio (OR) is calculated. Publication bias is investigated by construction of funnel plots and Egger's test. The review considered $p<0.1$ as statistically significant publication bias and in such cases Duval and Tweedie's trim and fill method is employed.

4.4 Operational definitions

Mental disorders: the existence of a clinically recognizable set of symptoms or behavior associated in most cases with distress and with interference with personal functions. These include depression, bipolar affective disorder, schizophrenia, anxiety disorders, dementia, substance use disorders, and intellectual disabilities and developmental and behavioral disorders that typically arise from childhood through adolescence, including autism (23, 82).

Non-specific psychological distress: a constellation of psychological and somatic symptoms that are common among individuals with a wide range of mental disorders but are not specific to any single disorder (83).

Khat use: any self-reported or clinically diagnosed use of khat

4.5 Dissemination plan

The results of this review will be presented at national and international research conferences and published in a peer-reviewed reputable journal.

5. Results

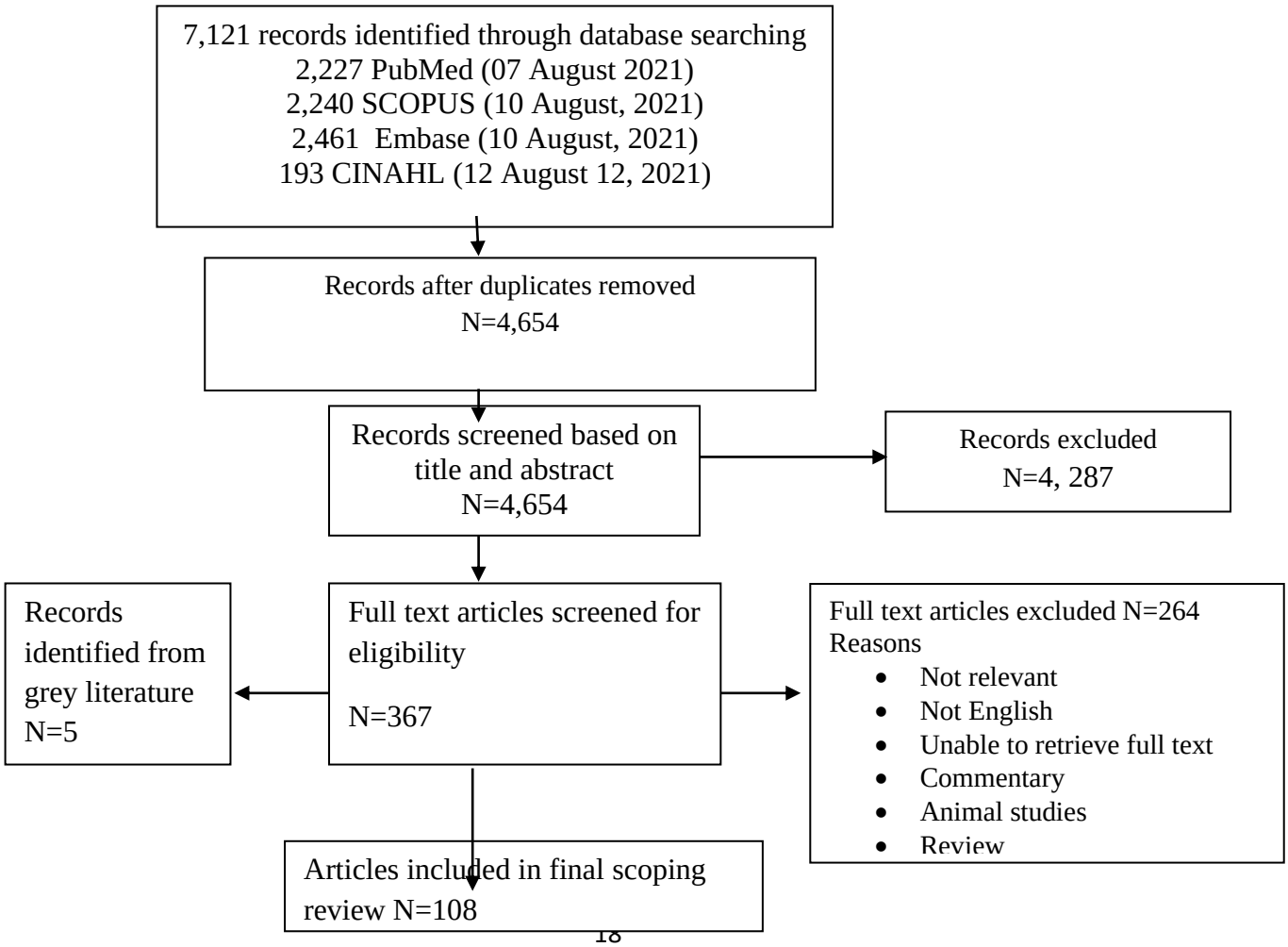
The first part of this chapter presents the scoping review results and the second part will address the meta-analysis of the association between khat use and mental disorder.

5.1 Scoping review

5.1.1 Study selection

The initial online search of four databases (PubMed, SCOPUS, Embase and CINAHL) yielded a total of 7,121 articles. After the removal of duplicates, the number of articles is reduced to 4,654. The titles and abstracts of these 4,654 articles were then reviewed, and 4, 287 articles were excluded because of ineligibility. Full text articles screened for eligibility was 367 and from these, 264 articles were excluded because they are irrelevant as per the specified inclusion criteria or full text articles were unable to be retrieved. The search of gray literature produced 5 eligible articles, and finally N=108 articles are included in this scoping review.

Fig. 5.1: Flow diagram of screening process



5.1.2 Geography of the included studies

The articles included in this scoping review resulted from 12 different countries. Half of the included studies (50%) are from Ethiopia, 10.2% from Yemen and 8.3% from Saudi Arabia. These are the countries where khat has been traditionally consumed on a regular basis by significant number of people. The remaining 9 countries share the rest of the percentage, 31.5%.

Table 5.1: Geographical distribution of the studies

Country	Number of studies	Percentage of studies
Australia	5	4.6
Ethiopia	54	50.0
Germany	3	2.8
Israel	1	.9
Kenya	5	4.6
Saudi Arabia	9	8.3
Somalia	4	3.7
Somaliland	2	1.9
the Netherlands	4	3.7
UK	7	6.5
USA	3	2.8
Yemen	11	10.2
Total	108	100.0

5.1.3 Study designs

The studies included are of considerable variety in terms of designs. The majority of the studies (70.4%%) assessing the relation between khat use and mental disorders come from cross-sectional studies. From the cross-sectional category also, institution-based design takes the largest share (38%), a community based cross-sectional study accounts for 29.6% and lastly, 2.8% are mixed method (cross-sectional and qualitative) studies. Only 3.7% of the articles used prospective cohort and 1 (0.9%) article employed RCT.

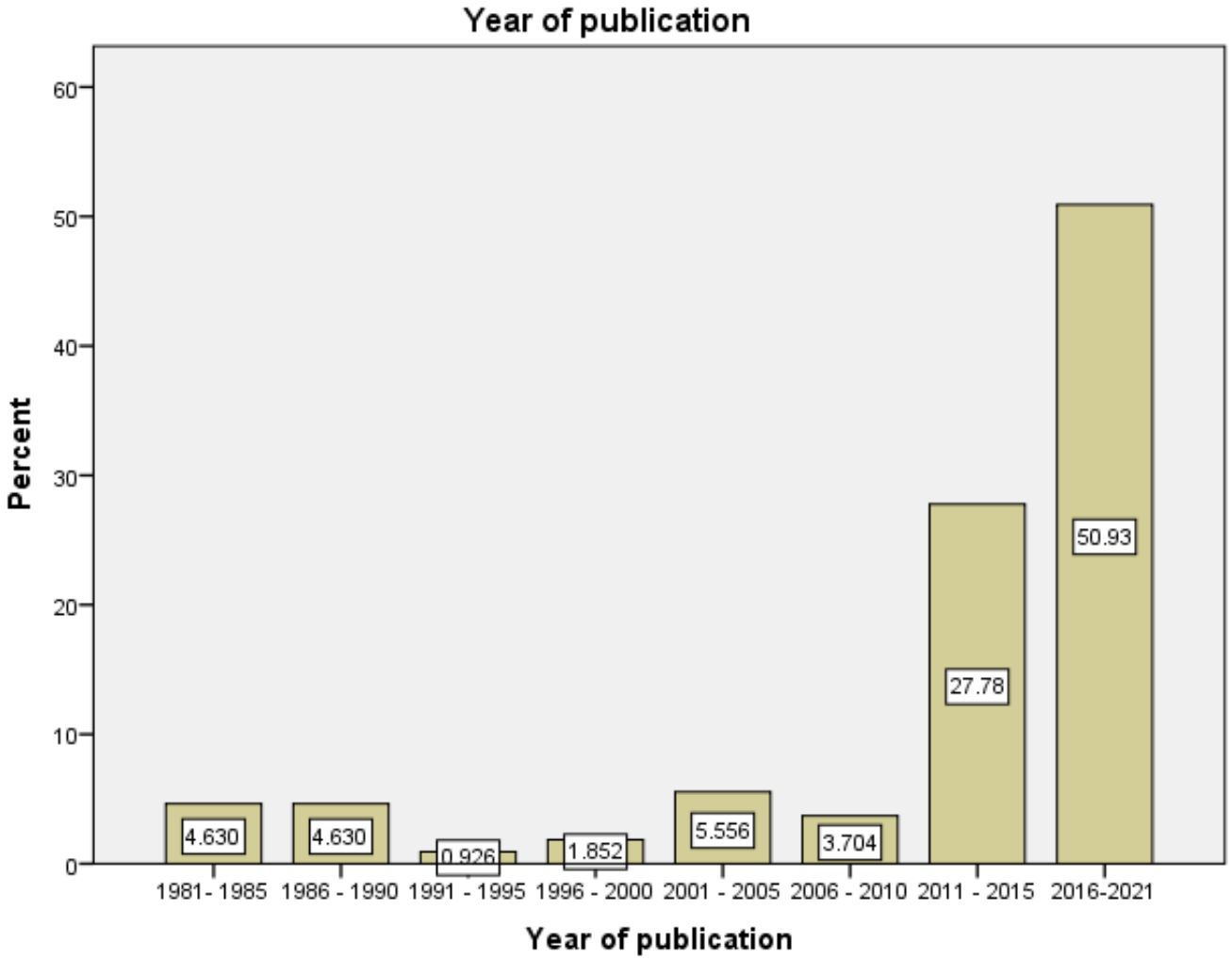
Table 5.2: Study designs

Designs	Frequency	Percent
A community based cross-sectional study	32	29.6
A prospective Cohort	4	3.7
Case report/ Case series	14	13.0
Case-control	3	2.8
Electronic patient record database	1	.9
Institution based cross sectional study	41	38.0
Mixed method (cross sectional + qualitative)	3	2.8
Qualitative	6	5.6
RCT	1	.9
Retrospective cohort	1	.9
Single arm pre-post study design	2	1.9
Total	108	100.0

5.1.4 Year of publication

The studies assessing the link between mental disorder and khat use have been around starting from Dhadphale, Mengech (84) case report publication of 'Miraa (*Catha edulis*) as a cause of psychosis.'

Fig. 5.2: Year of publication



It seems that there had been a stagnation in the growth of studies interested in the topic for the first three decades and it was only starting from 2011 that an outburst in the number of publications is observed. The period from 2011 to 2021 comprises 78.7% of the studies, indicating increasing interest in the topic.

5.1.5 Khat chewing measurement

After removing qualitative studies and case reports/case series, assessment of how N=86 studies measured khat use to examine its link with mental disorders has been made. Khat chewing measurement used are very diverse. About 70% of the studies measured khat use with 'yes/no' by neglecting the possible dose dependent effects of khat use. The rest of the measurement items used are provided in the following table.

Table 5.3: khat use measurement tools

	Frequency	Percent
Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV)	2	2.32
Khat only users, co-users of khat and tobacco	2	2.32
4-point scale	5	5.8
Amount, frequency and duration of use	5	5.8
Current users, former users, non-users	2	2.32
Drug Abuse Screening Test (DAST)	2	2.32
Khat chewing index	1	1.16
Age of onset of khat chewing	1	1.16
Moderate users vs heavy users	2	2.32
Severity of Dependence Scale	2	2.32
Never chewing, chewing less than once per week, and chewing at least once per week	1	1.16
Regular, occasional and non-users	1	1.16
Yes/no	60	69.7
Total	86	100.0

5.1.6 Mental health problems and related conditions associated with the use of khat

The identified studies are of different designs, making a direct comparison among them and comprehensive meta-analysis impossible. Attempt is rather made to descriptively indicate the mental health problems associated with the use of khat. Of all the included articles, 101 of them used khat use as a predictor variable and the remaining 8 articles (7.3%) considered khat use as an outcome variable. The different types of mental disorders associated with the use of khat are provided in the table 5.4 and the description of each identified association is detailed in the subsequent sub-sections.

Table 5.4: Mental disorders and related conditions associated with the use of khat

	Frequency	Percent
Adherence and response to antipsychotic medication	2	1.9
Mental disorder induced suicide	2	1.9
Depression, anxiety, stress	17	15.7
Non-specific (general) psychological distress	29	26.9
Insomnia	1	.9
Mood status	4	3.7
Neurocognitive disorder	8	7.4
Psychopathy	2	1.8
Psychosis	17	15.7
Quality of Life (Mental health component)	4	3.7
Readmission for mental disorder treatment	1	.9
Social phobia	1	.9
Substance use disorder	16	14.9
Suicidal ideation	5	4.6
Total	108	100.0

A. Non-specific psychological distress

Table 5.4 shows that 27.5% of the identified associations are general, 'non-specific' psychological distress. This makes non-specific psychological distress the most studied mental disorder in connection with khat use

The evidences about the association between khat chewing and non-specific psychological distress is mixed with some indicating the existence of significant associations (85-87) and others reporting the absence of such associations (88). The lowest reported AOR was 2.23

(89) and the highest AOR was 6.91 (90). A hospital-based cross-sectional survey among patients with hypertension reported the absence of association between psychological morbidity and khat chewing (87). Some of the articles are indicative that it is not khat in and of itself that is associated with non-specific psychological distress but the frequency of use matters. For instance, (85) found that regular or daily khat users had a five times higher chance of experiencing mental distress than non-users of khat while other use patterns of khat (occasionally and one or more per week) have no significant chance of experiencing non-specific psychological distress than non-chewers. There is also a finding that 'current use of khat' is not associated with non-specific psychological distress while ever use of khat is associated (91). Qualitative findings, on the other hand, show that khat users employ khat for the treatment of psychological distress (92).

B. Psychosis

Of all studies included in this review, 15.7% of them associated psychosis with the use of khat. This makes psychosis the most common specific mental disorder associated with khat chewing. However, evaluation of the strength of this evidence shows that about 64.7% (11 out of the 17 articles) relied on case report or case series designs and 58.8% (10 out the 17 articles) of the studies were conducted among khat chewing migrants from traditionally khat chewing regions.

C. Depression, anxiety and/ or stress

Depression, anxiety and/or stress are reported by 15.7 % of the articles included in this scoping review. However, there is no conclusive evidence about the effects of khat use as several studies show significant association, some studies reporting the absence of such association and other studies reporting the use of khat for alleviating depression and stress.

In a cross-sectional study among university students, khat use was not associated with depression, anxiety, and stress in the univariate analysis. After stratification of the sample by gender, however, a significant association was found between only male gender khat users and depression, female gender khat users and depression and female gender khat users and anxiety (42). Another study on khat chewing among intermediate and secondary school students found that depression is insignificantly related with khat chewing in the multivariate logistic regression (15). Moreover, the multivariate logistic regression analyses didn't show significant association between khat chewing, and stress and depression (93). A similar cross-

sectional study among students of higher education didn't find significant association between khat use, feeling depressed and feeling stressed (15).

On the other hand, there are also evidence showing history of khat chewing as being significantly associated with depression, stress and anxiety. Prisoners who chew khat prior to incarceration were about two times more likely to develop depression than those who did not chew khat (94). Among currently married reproductive age women in rural Ethiopia also, a frequent khat use is independently associated with depression after adjusting for common sociodemographic characteristics (95). Among Jimma university staff, khat chewing was associated with depression, anxiety and stress (96). Another study shows that it is not just khat use which matters in causing anxiety and depression. The study revealed statistically significant difference in the levels of anxiety and depression among non-khat users (NKU), Non-dependent khat users (NDKU) and dependent khat users (DKU). After conducting Scheffe's Post-hoc multiple comparisons, DKU scored significantly higher mean value in both anxiety and depression as compared to NKU and NDKU. NDKU have almost the same mean score in anxiety and depression with NKU (97).

The functional use of khat to relieve anxieties and depression have also been reported in a mixed method study. The survey part of the same study didn't find significant correlation between SRQ-20 symptoms of depression and anxiety and khat use (98).

D. Substance use disorder

The third top ranked category of mental disorder associated with the use of khat is substance use disorder. About 15% of the included studies have reported such association. A measurement of khat dependence based on Drug Abuse Screening Test-10 (DAST-10) among khat users shows that 2% have reported no problems, 17.3% reported low level, 73.6% reported moderate level and 7.1% reported substantial level of dependence. The odds of being moderately addicted to khat for those who live in rural areas was 1.67 as compared to those living in urban areas. The risk of being moderately dependent increases by 4.8 for the daily chewer as compared to irregular chewer (99). Assessment of khat use disorder among samples recruited from the general community and university students using DSM-5 criteria shows that 10.5% were categorized as experiencing mild, 8.8% moderate and 54.5% severe khat use disorder. Greater frequency and quantity of khat use are shown among individuals experiencing khat use disorder (21).

The use of khat has also been associated with alcohol use disorder and nicotine dependence. Along with educational status, social support, family history of alcohol use and cigarette smoking, khat chewing was a predictor of alcohol use disorder among human immunodeficiency virus infected patients attending antiretroviral therapy clinic (100). Chewing khat is one of the significant factors associated with increased alcohol use disorder among university undergraduate students (101). Concerning nicotine dependence, the odds of nicotine dependence for khat chewers were 3 times higher when compared to non- chewers among adult psychiatric patients (102). Similarly, among people with mental illness, there was a significant association between tobacco dependence and daily khat chewing, chewing khat 2-3 times per week, chewing khat once a week (103).

E. Suicidal ideation

Two studies have examined the association between khat use and suicidal ideation. The odds of suicidal ideation was higher among those having khat use history (104, 105).

F. Neurocognitive disorder

Neurocognitive disorders have been studied in the 7.4% of the studies. Khat users scored less in tasks tapping into cognitive flexibility, which is the ability to adapt and restructure cognitive representations in response to changing situational demands (106). Studies also found the negative effect of khat use on working memory (106, 107). Although statistically significant, the magnitude of performance decrement seen in khat users is modest (107). On the other hand, statistically significant difference is not found in speed of information processing between the group of chronic khat users and non-khat using control group (107).

The importance of considering the use of other substances has been pronounced in the study of neuropsychological impacts of khat use. As compared to the khat-only group and the control group of non-users of khat and cigarettes, the concurrent khat and cigarette users had statistically significant difference ($P < 0.05$) in verbal learning and recall. In comparison, the concurrent users recalled fewer words, had a slowed rate of verbal learning, and demonstrated delayed recall of previously learned verbal material. The authors suggested that khat use alone may not affect immediate or delayed recall of previously learned words. Post-hoc test didn't show statistically significant differences in performance between controls and khat-only users (108).

Khat chewers demonstrated deficits in 3 out of 14 neuropsychological functions compared with the control group, representing serial digit learning, motor speed/coordination, and set-shifting/response inhibition functions. There was no significant difference in performance on the rest of the subsets of neuropsychological functions. Age and educational level were identified as predictors of neuropsychological outcomes of khat chewers. One test showed improvement with increasing age of Serial Digit Learning test, 3 other tests showed decrements in performance as age increased in Trail Making, Continuous Performance latency, and Block Design tests. Increasing years of education was associated with improvement in performance of 4 subtests: Block Design test, latency in the Trail Making and Symbol Digit subtests. Since measures taken to control confounding factors were not indicated in the study, whether the observed associations described above are due to random chance or not is clear. The study suggests that that the effects of khat are rather moderate and may not be noticeable after the ingestion of a low dose or in habituated users (109)

G. Others mental disorders

Under this section those mental disorders with each accounting less than 5% are described. Among patients with schizophrenia, the use of khat has been associated with less medication adherence. In a retrospective study to assess response to standard anti-psychotic treatment, significant difference ($P < 0.001$) in the retention rate of the initial drug was observed among the khat users and nonusers (53.8% vs 78.4%). Changing the initial drug was also significantly higher among moderate and heavy khat users than low and mild khat users (55% and 49.2% vs. 35.6% and 44.7% respectively, $P < 0.001$). The primary reason for substituting the initial drug among moderate (51.7%) and heavy khat users (48.4%) was lack of drug efficacy, for which khat could have hampered response to initial antipsychotic drug treatment (110). Concerning quality of life, the use of khat has been associated with lower mental health component of quality-of-life sores (111-113). Contrarily, among patients with schizophrenia, khat users had higher scores in the mental health components of quality of life than non-users (71.76 vs. 69.59) (114)

A study has shown the indirect effect of khat chewing in causing death. In a case series study of khat related death in the UK, four cases of suicide (three confirmed and one possible cases) due to psychoses caused and/ or exacerbated by long-term khat consumption has occurred (53). Though life-time khat use is associated with social phobia among college students in a

univariate analysis, in the multivariate regression model the association found to be insignificant (115).

Other mental disorders and related conditions associated with khat use are insomnia (116), disturbed mood state (117-120), psychopathy (121, 122) and readmissions of people with schizophrenia (38).

5.1.7 Gaps and recommendations

The gaps identified from the included studies and recommendations for future studies are discussed in the following table.

Table 5.5: Main gaps of the studies and avenues for future research

Main gaps	Description of the gaps	Suggested research avenue
Design	Most studies employed cross sectional study design in which is it is difficult to establish cause-effect relationship	• Further studies with robust designs are needed to examine mental health effects of khat use • Prospective studies are needed to follow up chewers for a period of time to record the start of the appearance of psychiatric symptoms and relation to khat chewing.
Biases	Social desirability bias due to • Administering the questionnaire through a face-to-face interviews • Conducting studies in institutions like health facilities, correction centers and schools Recall bias • due to the use of retrospective items in questionnaires Measurement bias due to	• Measuring the levels of biomarkers (dopamine, serotonin, cathinone, etc) is needed in future studies rather than purely relying on self-report of khat use • Specific measurement of khat use pattern (amount, frequency, duration, etc.) and its association with specific forms of mental disorders needs attention

	• Lack of an objective and standard measure of khat use • Some studies relied on the report of lifetime khat use to examine its association with mental disorder, which might not be the most sensitive indicator • In many instances, instruments employed in measuring mental disorders are general, and non-specific mental disorders are reported • Most studies did not show the association between the level of khat use (frequency, amount, age at first use etc) and mental disorders • The studies utilized self-reports measurement for assessing khat chewing behavior and associated mental health problems, instead of standard clinical interview or other objective measurements like urine or blood tests	• Future studies should focus on the dose-related effects of khat use on mental health • Standard scales with multiple items need to be employed to address the actual khat use experiences
Confounding variables	• The mediating role of pre-existing genetic, neurodevelopmental factors, use of other substances, pesticides used by khat growing farmers and environmental factors are not considered in many studies	• Study designs and statistical control capable of addressing such confounding variables are needed
Study population and sampling	• In some cases, the surveys use convenience sample, and results may not be	• More community-based studies with the use of probability sampling are

	generalizable. • In many instances, the studies are institution based, confining generalizability.	suggested
Comparison	• Findings of the studies are usually compared with findings from amphetamine studies.	• Although cathine and cathinone alkaloids are similar in structure and pharmacological activity to amphetamines, the fact that khat is slowly chewed means there is slow absorption of these alkaloids. The effects of this might be different from the one from pure ingestions of amphetamine. Additionally, cathinone is only half as potent as amphetamine, and cathine is about 7–10 times less potent than amphetamine (123). These differences have to be explicitly stated while comparing results from khat and amphetamine studies.
Mechanism of action	• The neurobiological mechanism of action in causing mental disorder is not clearly understood. Associations are based on pure statistical rules and discussions are mainly based on guessing	• Studies designs capable of providing such explanations are needed.

5.2 Meta-analysis

5.2.1 Selection process

The scoping review has shown that the most assessed mental disorder in connection with khat use is ‘non-specific psychological distress.’ To meet objective two, the second part of this

thesis conducted meta-analysis of the association between khat use and non-specific psychological distress. Of the total N=29 articles classified under the 'non-specific psychological distress,' N=15 of them are used for meta-analysis. N=14 articles are removed based on the exclusion criteria listed under 4.3.2.

5.2.2 Characteristics of the studies

This meta-analysis included 7696 study population. The studies included here used different psychometric instruments for measuring psychological distress. Accordingly, 10 of the studies used SRQ-20, 2 studies used Kessler Psychological Distress Scale (10), one study used Brief Psychiatric Rating Scale (BPRS), one study employed Impact of Event Scale Revised (IES-R) and the remaining one study has not mentioned the type of measurement used. In terms of study population, 7 of the studies focused on university/college students, 3 studies are based on general population, two studies are facility based, one study focused on holy water users, and the last one study is prison based. Except one study which was conducted in Somaliland (126), the rest of the studies were conducetd in Ethiopia. The studies included in this scoping review demonstrated fair quality based on the adapted version Newcastle Ottawa Scale (NOS) for cross-sectional studies.

Author	Participant information, country	Age (mean, median or range)	Gender Female	Sample size	Used term to denote psychological distress	Cut-off points	Prevalence of psychological distress (%)	Psychometric instruments
Gebrekidan Abbay, Tibebe Mulatu (85)	General population, Adult, Ethiopia	36.18 (range 19-85)	58%	260	Mental distress	7	25.4%	SRQ-20
Adraro, Kerebih (124)	Prisoners, Ethiopia	30	6.3%	300	Common mental disorders	8	62.7%	SRQ-20
Dachew, Azale Bisetegn (91)	University students, Ethiopia	20	35.6%	863	Mental distress	8	40.9%	SRQ-20
Damena, Mossie (45)	General population, Ethiopia	-	44.2%	1200	Mental distress	7	25.8%	SRQ-20
Dessie, Ebrahim (89)	University students, Ethiopia	20.9	12.1%	413	Mental distress	11	21.6%	SRQ-20
Fekadu, Mulat (86)	Holy water users, Ethiopia	33.7	51.2%	416	Mental illness	31	60.1%	Brief Psychiatric Rating Scale

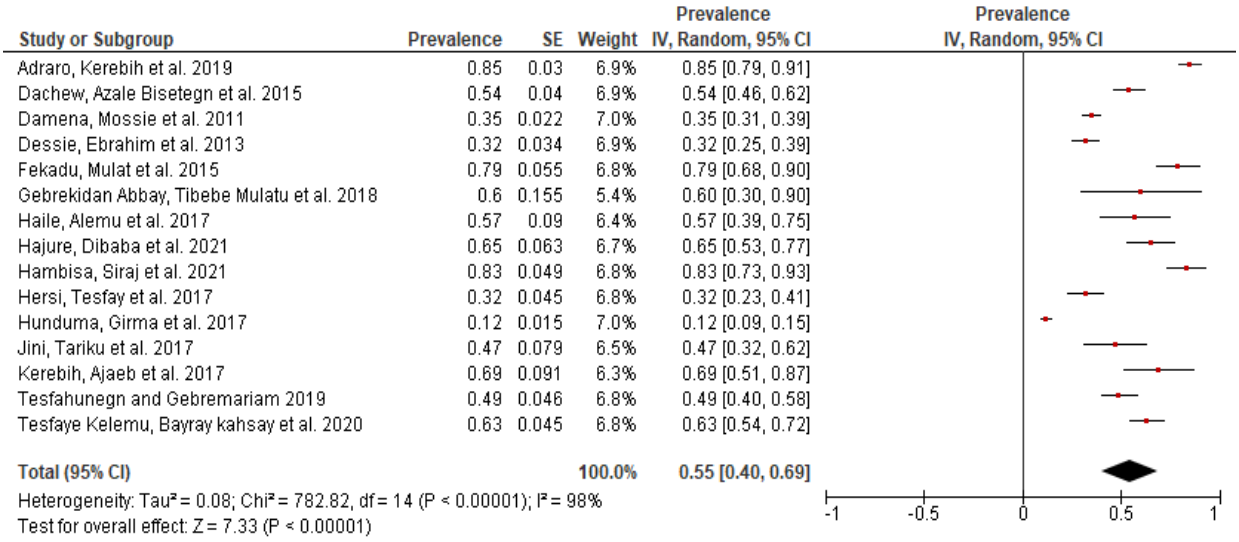
								(BPRS)
Hajure, Dibaba (125)	Health Care Workers, Ethiopia	31.89	32.3%	127	Psychological distress	33	40.2%	Impact of Event Scale Revised (IES-R
Hambisa, Siraj (126)	Hospitalized Patients During the COVID-19, Ethiopia	32.83	45.1%	337	Psychological distress		57.9%	Kessler Psychological Distress Scale (10)
Hersi, Tesfay (127)	University students, Somaliland	23.5	39.3%	570	Mental distress	11	19.8%	SRQ-20
Hunduma, Girma (128)	Adult general population, Ethiopia	34.4	38.1%	901	Common mental illness	6	14.9	SRQ-20
Kerebih, Ajaeb (90)	University students, Ethiopia	18-30	29.3%	290	Common mental disorder	8	35.2	SRQ-20
Jini, Tariku (129)	College students, Ethiopia	19.25	73.7%	308	Mental distress	-	29.2%	-
Tesfaye Kelemu, Bayray Kahsay	University students,	-	43.1%	404	Mental distress	8	53.2%	SRQ-20

(130)	Ethiopia							
Haile, Alemu (131)	University students, Ethiopia	22.13	21.6%	388	Common mental disorder	7	63.1	Kessler psycho-logical distress (K10)
Tesfahunegn and Gebremariam (132),	University students, Ethiopia	21.5	35%	919	Mental distress	8	39.6%)	SRQ-20

5.2.3 Prevalence of psychological distress among khat users

In this study, the pooled prevalence of general psychological distress among khat users was 55% (95% CI: 40, 69). A random-effect model was employed to estimate the pooled prevalence of psychological distress due to severe heterogeneity (I^2 =98, p-value < 0.00001) observed between the studies (Fig 5.3).

Fig. 5.3: Prevalence of psychological distress



4.1.1 Publication bias and heterogeneity

The I^2 test for heterogeneity showed significant difference among studies (I^2 = 73%, p < 0.00001). Publication bias was observed (Egger's test: p (two tailed)= 0.03866). Duval and Tweedie 'Trim and Fill' is used to trim the asymmetric studies from the right-hand side to locate the unbiased effect (in an iterative procedure), and then filled the plot by re-inserting the trimmed studies on the right as well as their imputed counterparts to the left the mean effect. The program looked for missing studies based on a random effect model, and looked for missing studies only to the left side of the mean effect. Using these parameters, the method suggests that 4 studies are missing, indicating the existence of publication bias (Fig 5.4 and Fig 5.5).

Fig. 5.4: Observed funnel plot

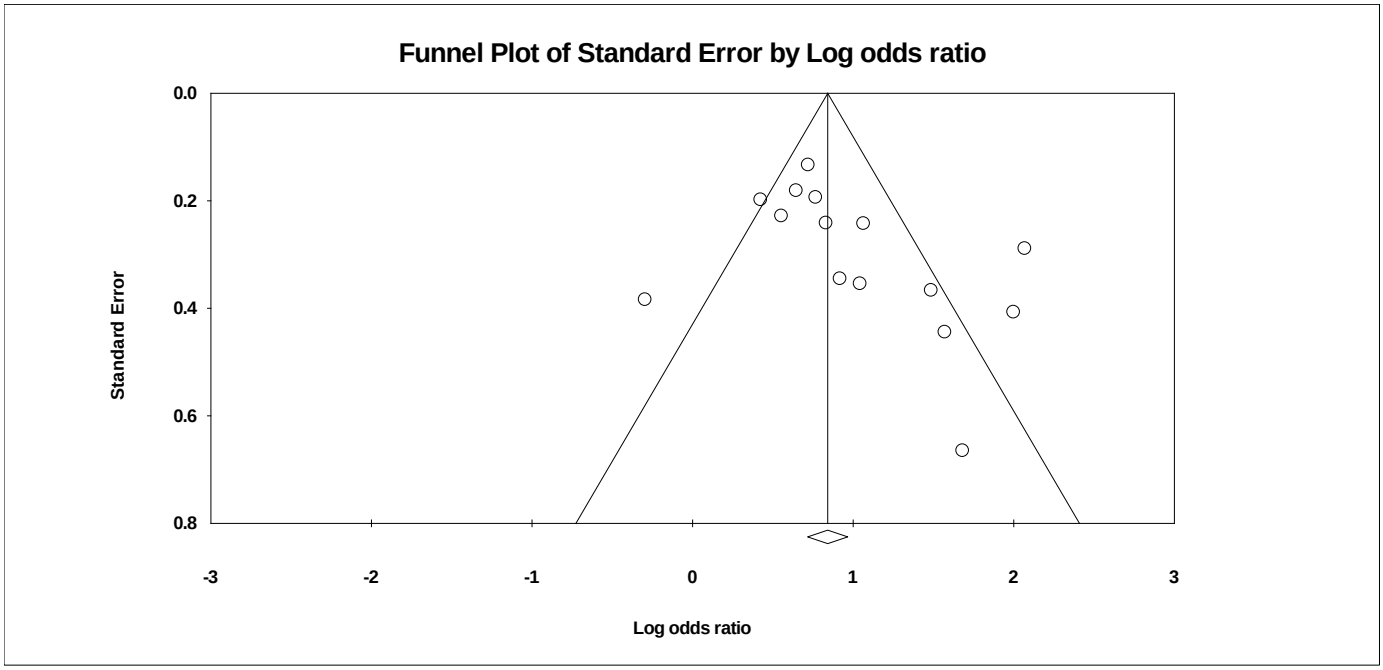
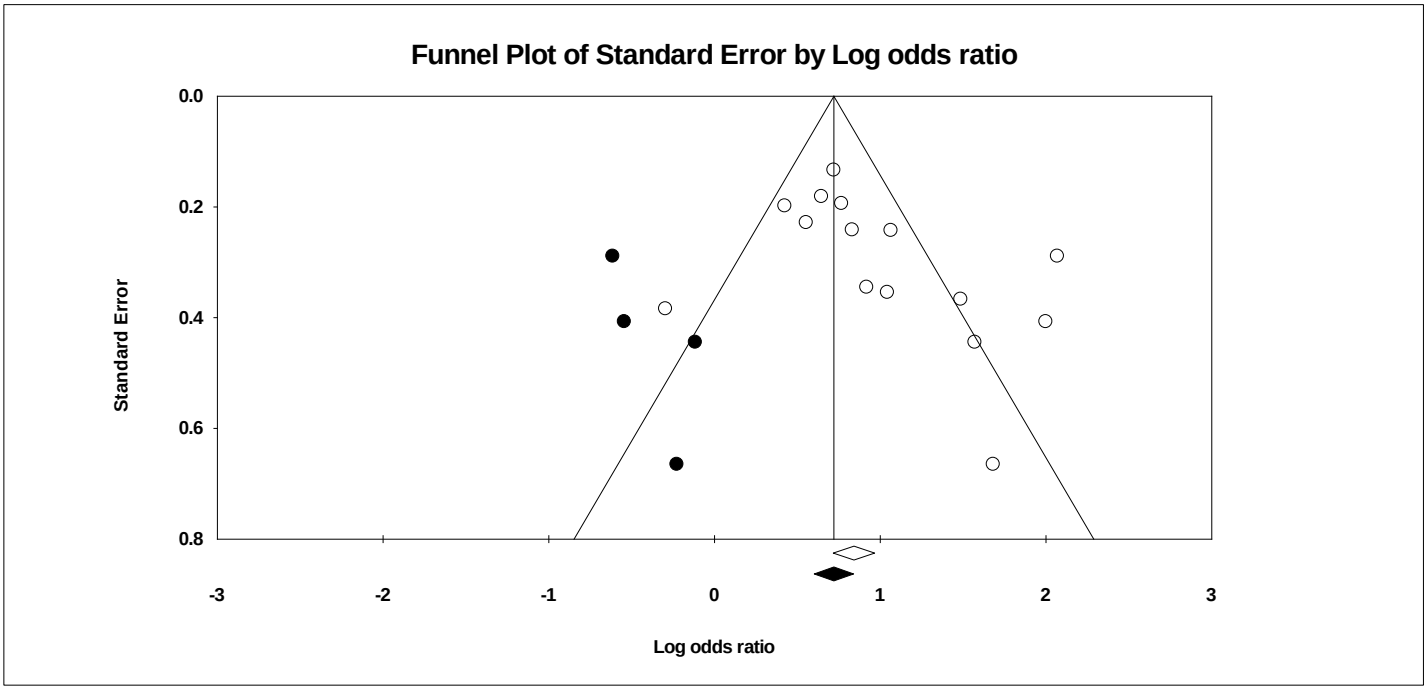


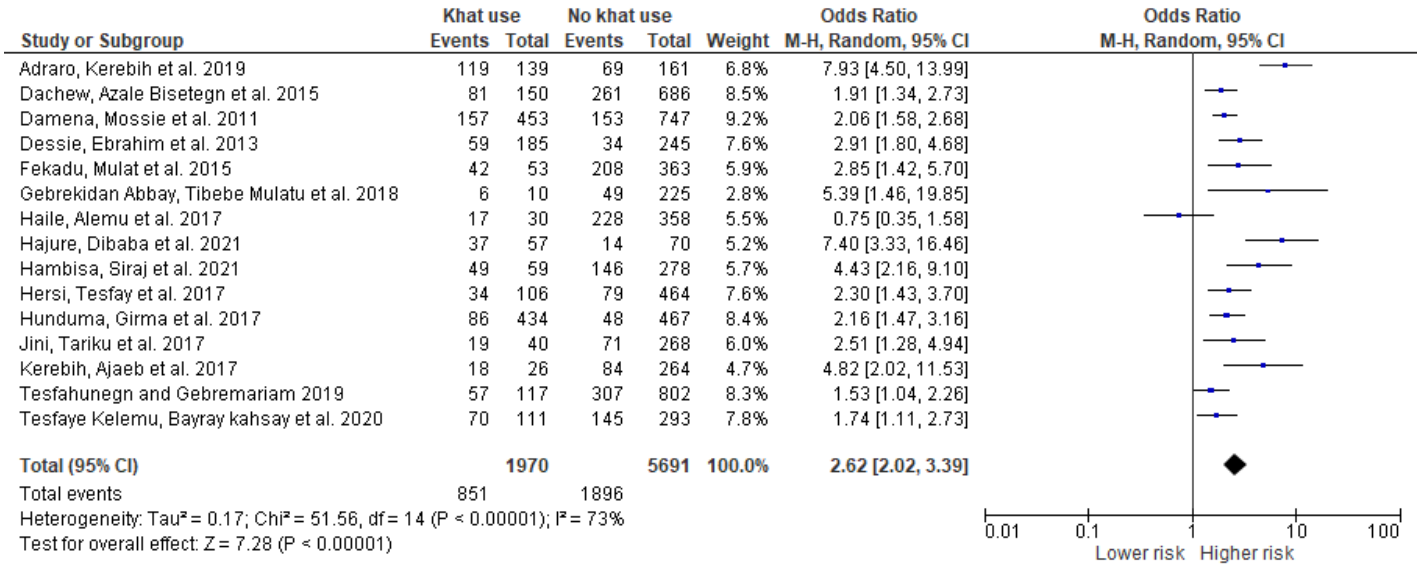
Fig. 5.5: adjusted funnel plot



5.2.4 Pooled effect size

The pooled effect size of psychological distress among people who use khat in the form of odds ratio (OR) using Trim and Fill the imputed point estimate is 2.09 (1.56, 2.78), as compared to those who don't use khat. Under the random effects model, the point estimate and 95% confidence interval for the combined studies is 2.61631 (2.01975, 3.38905).

Fig 5.6: Pooled effect size of the association between khat use and psychological distress



6. Discussion

This study represents the first attempt to systematically scope review the mental disorders associated with the use of khat and to evaluate the strength of available evidence. The scoping review part of the study mapped and summarized evidence on the relation between khat use and mental disorders, specifically evidence relating to the place studies were conducted, publication trend, study design or strength of evidence, khat use measurement issues, mental disorders associated with khat use, and finally limitations of previous studies and avenues for further research. The meta-analysis section of the study pooled the effect size of the association between psychological distress and khat use.

Most of the studies are sourced from Ethiopia and that is expected given that Ethiopia is where the largest proportion of global khat production takes place (133) and probability holds the largest population of khat chewers globally. However, more studies are still needed from other traditionally khat using countries in East Africa and Arabian Peninsula states to comprehensively understand the mental health effects of khat use and the modifying role of socio-cultural and ecological factors in this regard. Additionally, comparative studies across countries about the mental health effects of khat are absent.

Although studies assessing the association between khat use and mental disorder have been around for at least the last three decades (since 1981), remarkable increase in the number of studies was observed only after 2011. Nevertheless, this dramatic increase in the number of studies during the last one decade was not complemented with the employment of advanced study designs.

The studies included in the scoping review are diverse in their designs. This makes tough comparison among the studies and made a meta-analysis of the whole study results impossible. The fact that majority of the studies are cross-sectional limited the development of definite conclusion about the cause-effect relation, and interpretation of the results should be made with such caution. This review found that robust, advanced study designs that warrant strong evidence about the association are very less.

This scoping review shows that majority of the studies assessing the association of khat use with mental disorder didn’t employ standardized instrument of khat use measurement. The instruments

used varies considerably from a single item question to multiple-item questionnaires. However, more than two of every three articles included in this scoping review measured khat use with a single item 'yes/no' question, and the rest of the studies emphasized more on the frequency of chewing than the amount of chewing. The single item 'yes/no' measurement approach has a limitation since it lumps together khat users with diverse chewing amount/frequency and duration of khat use experience. Single item 'yes/no' question also neglects the potential 'dose-dependent' effect of khat use on mental health. The standardized khat chewing measurement instruments used in a few studies are also adopted from the studies of alcohol use disorder and measurements for disorders associated with other drugs. The use of such instruments could be less sensitive to screen khat disorders since they are not clinically tested and are not informed with the qualitative study of culture-specific khat use patten and behaviors. The reference periods used to measure khat chewing also considerably varies from the last one month to the life-time use. Studies in other psychoactive substances, for instance alcohol, indicates that while the previous-month measures are better to avoid recall bias, the 12-months measures are preferred if capturing seasonal variability in consumption and measuring long term effects of such consumption are needed (134). In studies where the interest is to assess the mental health effects of khat chewing, thorough consideration of these pros and cons of different reference periods are needed. More importantly, whether the specific mental disorder being studied is better explained using which reference period needs consideration when designing a questionnaire.

About fourteen categories of mental disorders and related conditions have been identified as having association with the use of khat. These are: non-specific (general) psychological distress; depression, anxiety, stress; mental disorder induced suicide; adherence and response to antipsychotic medication; insomnia; mood status; neurocognitive disorder; psychopathy; psychosis; quality of life (mental health component); readmission for mental disorder treatment; social phobia; substance use disorder; and suicidal ideation. Although contradictory findings are present, most of the evidence associate khat use with mental disorders. General, 'non-specific' psychological distress is the most reported category. Different terms are used in the included studies as denoting this category of mental health condition. The terms are mental disorder; poor mental health; mental illness; mental distress; mental health problems; psychological distress; common mental illness; psychological morbidity; mental health; mental health problems; psychiatric morbidity; psychiatric symptoms; common mental disorders. Four conflicting

findings have been reported in this category: khat is associated with greater risk of general psychological distress (86), there is no association between khat use and mental disorder (87), frequent khat use is associated with general psychological distress whereas occasional use is not (85) and khat is used to treat psychological distress (92). Although psychosis is the most studied specific mental disorder in connection with khat use, most of the studies are case reports/ case series and majority of the studies are conducted on immigrants from traditionally khat chewing regions. Very few studies used quantitative analysis of the connection between khat use and psychosis (46, 135-137). More interest to study the link between psychosis and khat use among migrants as compared to countries where khat is widely used could show the mediating role of traumas associated with migration or the weakening khat use norm among khat users in the countries of destination. Similar with general psychological distress, in studies where depression, anxiety and/or stress are specifically assessed for their association with khat also presented conflicting findings. On the one hand, khat is considered as a risk factor (42, 94-96) and on the hand insignificant association are reported (15, 93, 98).

Khat use disorder is the category where a better in-depth assessment of khat use patterns in terms of frequency and amount are relatively better assessed. Moreover, standardized instruments like DAST (99) and DSM-5 are employed for assessing khat use disorder (21). The available evidence indicates that khat use disorder is more associated with daily chewing and greater quantity/frequency of khat use.

This review identified several biases, limitations related with designs and generalizability, failure to control confounding variables, making comparison between the results of khat and amphetamine studies and finally the absence elaborate explanation about mechanism of khat use's impact on mental health as stunting the level of available evidence. Nevertheless, it is against this weak level of evidence that many countries in the west criminalized the possession and chewing of khat. This in turn affects the personal and cultural right of migrants from khat chewing regions and the economy of subsistence, small scale farmers relying on khat farming in east Africa and Yemen. In UK, the country with the most recent criminalization of khat, khat was indeed criminalized due to political decisions rather than its potential public health effect. Advisory Council on the Misuse of Drugs (ACMD), the organ responsible for counseling ministers in the UK on the appropriate control measures, advised that 'the harms of khat does not

reach the level required for classification' and 'that the potential of misuse did not merit controls.' Despite the evidence, the Home Secretary announced in 2013 that khat would classified as Class C drug and 'be banned because of 'broader concerns', including the UK's role as a hub for khat export to other countries and compliance with general practice in other EU and G8 countries, where khat is banned already' (138). Although studies of good quality and robust designs are generally absent to confirm the causative role of khat use in mental disorder, arguments of causal association between khat use and mental disorder have been used in the policy debate to prohibit the use of khat (32). On the other hand, keeping the pace with the very fast growing khat production and consumption (139), methodological advancement in studying khat chewing impact on mental health has not been made.

The meta-analysis part of the study relied on N=15 articles assessing the association between khat use and general psychological distress among N=7696 study population. All the studies, except one (126), was conducted in Ethiopia. The pooled prevalence of psychological distress among khat users was 55%. This figure is much larger than the pooled prevalence of psychological distress among the general population in Ethiopia, 21.58% (140). The result of the meta-analysis also shows that khat chewers are about two times more exposed to the risk of non-specific, general psychological distress as compared to those who don't chew khat. Given the cross-sectional nature of the studies and higher level of heterogeneity in the included studies for meta-analysis, this result needs to be read with caution. The studies also didn't consider the dose-effect relationship of khat use with psychological distress. Studies included in this meta-analysis have also not specifically indicated measures taken to control the confounding role of the use of other substances like cigarette and alcohol. Studies, however, show that khat is 'gateway drug' to other drugs (8, 16).

Limitation of the review

Although this review has undergone a rigorous search process of major public health databases, the review might not have included every eligible studies. Since the search process mainly focused on the titles and abstracts of studies, articles on mental disorders where khat use have not been mentioned in their abstracts due it's insignificant association might have been excluded from the review. Since this review also focused on publications in English language, studies in other languages might have been excluded.

7. Conclusion

The review reveals that the scientific interest in the study of khat uses effect on mental disorder have been increasing from time to time. However, this increasing interest is not supplemented with the employment of robust study designs capable of generating definitive conclusion about cause-effect relationship. Although most studies associate khat use with mental disorder, the level of available evidence is weak since cross-sectional studies dominated the studies. The lack of valid and standardized measurement tool for khat use has also impeded attempts to study mental health effects of khat use. Although the meta-analysis part of the study shows that khat chewers are about two times more likely to face the risk of non-specific, general psychological distress as compared to those who don't chew, the interpretation of this result needs care due to cross-sectional nature of all the included studies and higher level of heterogeneity in the effect sizes of the included studies. Given that khat use is fast growing, there needs to be studies with better design and instruments to document the mental effects of khat, which pattern of use is riskier, and the combined effect of simultaneous khat and other substance use.

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Declaration

I, the undersigned, declare that this thesis is my original work, has not been presented for a degree in this or any other university, and that all sources used for the thesis have been fully acknowledged.

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This thesis has been submitted with my approval as internal examiner