BMJ Open

EXPLORING THE ASSOCIATION BETWEEN KHAT USE AND PSYCHIATRIC SYMPTOMS: A SYSTEMATIC REVIEW

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061865
Article Type:	Original research
Date Submitted by the Author:	10-Feb-2022
Complete List of Authors:	Edwards, Betsy; University of Birmingham, Atkins, Naomi; University of Birmingham
Keywords:	PSYCHIATRY, MENTAL HEALTH, Substance misuse < PSYCHIATRY, PUBLIC HEALTH, Adult psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

EXPLORING THE ASSOCIATION BETWEEN KHAT USE AND PSYCHIATRIC SYMPTOMS: A SYSTEMATIC REVIEW

Betsy Edwards[1*], Naomi Atkins[2]

[1] College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[2]College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[*]Correspondence: Betsy Edwards, BHE701@student.bham.ac.uk , 67 Peterborough Avenue Upminster RM14 3LL

Keywords: khat, psychiatric symptoms, mental health, review, meta-analysis

Word count (excluding title page, references, figures and tables): 3184

Abstract

Objectives: Consumption of the drug khat is high across East Africa and the South-Western Arabian Peninsula despite evidence for its adverse psychiatric effects. This systematic review aims to explore cross-sectional research in the field to determine the strength of the association between khat use and psychiatric symptoms.

Methods: Six databases were searched in October 2021 - Ovid Medline, Embase, APA PsycInfo, CINAHL, Scopus and Proquest - using the following search terms: "khat" OR "qat" OR "qaad" OR "catha" OR "miraa" OR "mairungi" AND "depression" OR "anxiety" OR "mania" OR "psych" OR "schiz*" OR "mental" OR "hallucinations" OR "delusions" OR "bipolar". Eligible studies were cross-sectional studies of any population or setting comparing the prevalence of psychiatric symptoms in long-term or dependent khat users with non-users. The quality of each study was appraised by the Newcastle-Ottawa scale. A meta-analysis was planned using a random effects model to produce an odds ratio with 95% confidence intervals - using the Mantel-Haenszel method - alongside an I^2 statistic to represent heterogeneity. The quality of this meta-analysis would be appraised using the GRADE scoring system.

Results: 35 studies were eligible for inclusion. Meta-analysis suggests that khat use is associated with an 122% increased prevalence of psychiatric symptoms (OR = 2.22, 95% CIs 1.76-2.79, $p<0.00001$, GRADE score: 'very low'). The high heterogeneity of the meta-analysis ($I^2=92\%$) suggests that variables not explored within this review also contribute to the differences between the studies, limiting confidence in the effect estimate.

INTRODUCTION

The stimulant drug khat consists of the buds and leaves of the plant *Catha edulis*, an evergreen shrub highly prevalent in East Africa and the South-Western Arabian Peninsula [1-2]. Ethiopia is the world's largest exporter of khat, however its consumption is highest in Yemen where up to 90% of adult males and 50% of adult females chew khat for three to four hours per day [3-5]. Within its local regions, khat chewing has been a cultural tradition for many generations and is thought to increase sociability, concentration, energy and spirituality [2, 6-7].

Psychiatric symptoms have been recognised as a consequence of khat use for several decades [8-9]. Milder psychological consequences related to its use include anxiety, restlessness, insomnia and dysphoric mood, all of which can reduce quality of life [2, 8-11]. More severe psychological harms associated with its use include psychosis and depression, which in some cases have resulted in acts of suicide and homocide [8-12]. Users most at risk of these sequelae are those abusing larger amounts of khat - some studies have provided evidence for a dose-dependent relationship - and those with pre-existing psychiatric disorders [8-10].

The association between khat use and psychiatric symptoms is supported by a large base of evidence, mostly of cross-sectional research. This systematic review aims to use these cross-sectional studies to investigate the strength of the identified association between khat use and psychiatric symptoms. This will help to guide further research in the field, and to evaluate the need for any widespread intervention for khat users, e.g. increased education about potential psychiatric side effects.

METHODS

The protocol for this systematic review can be found on Prospero, with registration number CRD42020224510 [13]. Originally, this systematic review had two objectives; to investigate the strength of the association between khat use and psychiatric symptoms, and secondly to investigate the role of trauma within this relationship. Due to the vast amount of literature in the field, the second objective was removed from the protocol to ensure that the findings would be suitable for one single review. It is recommended that a follow-up review should be conducted to explore the role of trauma.

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines at all times [14]. Ethical approval was not necessary as only secondary data was used.

Patient and Public Involvement

No members of the public or patients were involved in the design of this systematic review.

Literature Search

A literature search was carried out independently by authors BE and NA in October 2021 using the following search terms:

"khat" OR "qat" OR "qaad" OR "catha" OR "miraa" OR "mairungi"
AND
"depression" OR "anxiety" OR "mania" OR "psych" OR "schiz*" OR "mental" OR "hallucinations" OR "delusions" OR "bipolar"

These search terms encompass all previously reported psychiatric symptoms associated with khat, and include all predominant cultural variations of the term 'khat' as identified by the Medical Subject Headings Thesaurus (MeSH) [15]. Advice was provided by the library team at the University of Birmingham. Note that studies surrounding suicidality were excluded, as suicidality is often but not always associated with psychiatric dysfunction [16]. Disagreements between the authors were discussed in person. Removal of duplicates was automated for the databases Ovid MEDLINE, Embase and APA PsycInfo, and was performed manually for the remaining databases.

Six electronic databases were searched. Five of these were databases of published literature: Ovid MEDLINE, Embase, APA PsycInfo, CINAHL and Scopus. Additionally, Proquest was searched to obtain any relevant grey literature.

Study Eligibility

The literature search used the following inclusion criteria:

- Population: adults (aged 18+)
- Exposure: long-term or dependent khat use
- Comparator: no khat use or non-dependent khat use*
- Outcome: prevalence of psychiatric symptoms in khat users and prevalence of psychiatric symptoms in non-users

- Study design: cross-sectional studies; note that mixed-method studies are considered eligible but only the cross-sectional data will be considered for the review
- Language: all
- Publication type: must be a complete study but no restriction on publication status
- Setting: all

Each potentially eligible study was compared to a checklist of the above criteria to determine whether or not it should be included within the review.

*Note that non-dependent khat use was only considered a suitable comparator for studies where the exposure group were dependent khat-users, where both dependence and non-dependence were validated by a recognised tool such as the Severity of Dependence Scale (SDS).

The literature search used the following exclusion criteria:

- Population: children, animals
- Exposure: substance abuse other than khat
- Comparator: 'substance users' where khat use is not specifically described
- Outcome: neurobehavioural processes, withdrawal symptoms, suicide, substance use disorders
- Study design: any study design other than cross-sectional, e.g. case control, randomised controlled trial, case report, review
- Language: no exclusion criteria
- Publication type: unfinished studies including abstract only, conference abstracts, letters, retracted articles, book chapters
- Setting: no exclusion criteria

Data Collection and Quality Assessment

A summary of findings table - see Supplementary Material 1 - was created to present the following study features: population, sample, criteria for 'khat user', psychiatric measure, effect estimate. In addition, the quality of each primary study (e.g. risk of bias due to inadequate reporting methods or missing data) was assessed using the Newcastle-Ottawa Scale (see Supplementary Material 2)[17-18]. Data was collected manually by both authors independently, with any disagreements between the independent assessments resolved by discussion.

Synthesis of Findings

The prevalence of khat-users and non-users with psychiatric symptoms from each study was entered into a meta-analysis using the software Revman, provided by the Cochrane organisation. After inputting all dichotomous values, this software created a forest plot of odds ratios, each with 95% confidence intervals, using the Mantel-Haenszel method [19]. A random effects model was used as this assumes that the outcome is normally distributed rather than always the same, hence attributing the differences between studies to both chance and genuine variation [19]. An I^2 statistic was given to indicate variability between studies, as this is again recommended by the Cochrane organisation [20].

A subgroup analysis will also be included, grouping studies investigating similar symptoms. An odds ratio and I^2 statistic will be provided for each subgroup, as well as a chi-squared test and p-value for overall subgroup differences.

A sensitivity analysis will be conducted to look for any studies that are prominent outliers. Each study will be removed from the meta-analysis one at a time, and the odds ratio, 95% confidence intervals, I^2 value and p-value reported within a table.

The quality of the meta-analysis was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework [21].

RESULTS

Included and Excluded Studies

The PRISMA flow chart in Figure 1 shows the number of studies included and excluded at each stage of the literature search [14]. When searching the relevant databases, 1641 results were found that included the relevant terms within their title or abstract. After removing duplicates, this number was reduced to 616.

Each title and abstract were screened, and 567 results were removed for the following reasons:

- 119 were not research studies, e.g. these included conference abstracts, letters, and newspaper/magazine articles
- 30 were animal studies
- 71 were reviews, including systematic reviews and meta-analyses
- 20 were case studies or case reports
- 4 were case control studies or randomised controlled trials
- 11 were qualitative studies
- 312 did not explore the relationship between khat use and psychiatric symptoms

49 studies were read in full in order to determine their eligibility. Of these, 14 were excluded for the following reasons:

- 9 explored both khat use and psychiatric symptoms but not their prevalence [22-30]
- 4 did not report khat-use alone, and instead reported substance use or equivalent [31-34]
- 1 only reported the prevalence of khat use alongside ‘three or more psychiatric issues’[10]

35 studies were included in the final review [7, 35-68].

Summary of Included Studies

The summary of findings table – Supplementary Material 1 – contains the effect estimates of each individual study, alongside each study’s characteristics (i.e., target population, sample, and methods of measuring khat use and psychiatric symptoms).

A subsequent table - Supplementary Material 2 - provides information regarding the quality of each primary study, assessed using the Newcastle-Ottawa Scale [17-18]. According to Mekuriaw et al. 2020, a score of 5/10 indicates a medium-quality study whilst a score of

6/10 indicates a high-quality study [69]. In this systematic review, the average quality score was 6.8 , with a range of 4-8. No issues due to missing data arose.

Symptoms Explored within Included Studies

The included studies explored a range of symptoms in association with khat usage. These have been grouped into the following subgroups:

- 12 studies explored symptoms of 'depression'; this subgroup includes 'depressive symptoms', 'feeling depressed', diagnoses of depression, and the presence of 'depressive episodes' within the last month
- 6 studies explored symptoms of' anxiety'; this subgroup includes 'feeling anxious', 'obsession-compulsion', 'phobic anxiety' and diagnoses of anxiety disorders
- 16 studies explored symptoms of 'psychological distress'; this subgroup includes 'psychological stress', 'psychological distress', 'mental distress', and 'stress'
- 6 studies explored symptoms of psychotic disorders; this subgroup includes 'psychotic symptoms', 'psychosis', 'paranoid ideation', 'psychoticism', and diagnoses of 'schizophrenia'
- 1 study explored psychopathy
- 5 studies explored unspecified psychiatric symptoms and disorders; this subgroup includes common mental disorders', 'psychiatric dysfunction', 'mental illness' and 'mental problems that prevent employment or household tasks'
- No studies explored bipolar disorder or mania

Meta-Analysis

The meta-analysis of the 35 included studies can be seen in Figure 2. This meta-analysis suggests that khat use is associated with an 122% increased prevalence of psychiatric symptoms (OR = 2.22, 95% CIs 1.76-2.79, p<0.00001). All but one of the 35 studies were scored as at least medium or high-quality when assessed using the Newcastle-Ottawa Scale; the remaining study scored 4/10 - where 5/10 is medium-quality - and had a very small weighting within the meta-analysis of 1.5%. The heterogeneity of this meta-analysis is 92%, which is classified as high [20-21].

Subgroup Analysis

The accompanying subgroup analysis - grouping studies investigating similar symptoms - shows that there is a statistically significant subgroup effect of p=0.04; usually, a p-value of less than 0.1 is regarded as a statistically significant subgroup effect [70]. This means that khat use has a varying association with the symptoms investigated.

The largest association found is between khat use and symptoms of psychological distress (OR = 2.56, 95% CIs 1.82-3.61, p<0.00001). A higher odds ratio can be found in the psychopathology category (OR = 6.10, 95% CIs 2.81-13.28), but as this is only comprised of one single study this has not been considered as a subgroup.

The two subgroups of symptoms with the lowest odds ratios are anxiety (OR = 1.68, 95% CIs 0.93-3.04) and psychotic symptoms/disorders (OR = 1.47, 95% CIs 0.93-2.30). As the confidence intervals cross the null value in both of these subgroups, this meta-analysis suggests that neither anxiety nor psychotic symptoms are associated with khat use.

Every subgroup - with the exception of psychopathy - has at least five studies to support it, a reasonable amount of supporting evidence. Most of these subgroups have a high level of

heterogeneity, apart from the subgroup of unspecified psychiatric symptoms/disorders, which has a heterogeneity of 0%.

Sensitivity Analysis

A sensitivity analysis of the meta-analysis data was conducted and can be seen in Supplementary Material 3. Each study was removed in turn and the odds ratio, confidence intervals, I^2 value and p-value recorded. Removing the depression data from Wondemagegn et al. 2017 caused the largest change in odds ratio, from 2.22 to 2.11. The I^2 value for heterogeneity remained at 91% or 92% regardless of which study was removed, and the p-value was always <0.00001.

GRADE Analysis

The meta-analysis shown in Figure 2 received a GRADE score of 'very low' [21]. As per guidance in the GRADE handbook, the score automatically starts as 'low', because the meta-analysis focuses on observational studies [21]. The score was then downgraded for the following two reasons: 'inconsistency of results' demonstrated by the high I^2 statistic, and 'indirectness of evidence' due to the differences between studies including populations investigated and methods of measuring khat use [21]. The score was not downgraded for publication bias, as despite occasional outliers, overall the funnel plot for the included studies was fairly symmetrical (see Figure 3).

DISCUSSION

Our findings suggest that khat use is associated with a 122% increased prevalence in overall psychiatric symptoms (OR = 2.22, 95% CIs 1.76-2.79, p<0.00001). When subgrouped into groups of similar symptoms, the strongest relationship is between khat use and psychological distress (OR = 2.56, 95% CIs 1.82-3.61, p<0.00001). Khat use and psychopathology potentially have a relatively large association as well (OR = 6.10, 95% CIs 2.81-13.28), however only one study investigated this symptom so more supporting evidence would be needed to make a conclusion. The subgroup analyses also found that the associations between khat use and anxiety, and khat use and psychotic symptoms/disorders is statistically insignificant (OR = 1.68, 95% CIs 0.93-3.04 and OR = 1.47, 95% CIs 0.93-2.30 respectively).

The overall prevalence of psychiatric symptoms and disorders within this systematic review is 29%. Most of the included studies were conducted in Africa, which the WHO estimates has a 5.5% prevalence of common mental disorders [71]. The prevalence of symptoms is higher in this review than expected, as many of the studies focus on populations with an increased risk of mental illness, e.g. students, migrants, combatants, refugees, prisoners and psychiatric outpatients [72-76].

This review has many methodological strengths, as it follows the PRISMA guidelines for systematic reviews [14]. However, the usefulness of the review is limited by the high heterogeneity of its meta-analysis (I^2=92%)[20]. High heterogeneity indicates that the studies combined within the meta-analysis may be too different to meaningfully compare [20]. The differences in symptoms studied may have some contribution towards this, but the heterogeneity values of each subgroup analyses are also high, e.g. the depression subgroup has an I^2 value of 95%; as inconsistencies are present between studies investigating similar symptoms, other differences in variables must be present, which make the overall effect estimates uncertain. These differences may include the populations studied, the differences in

defining khat use, and the varying methods of measuring psychiatric symptoms within the same subgroup. These variables should be investigated in future reviews.

Similarly, the meta-analysis of this systematic review has a GRADE score of 'very low', indicating that the effect estimate produced may be inaccurate [21]. Having said this, a large contributor to this low score is the focus on observational studies rather than experimental data, the latter of which would be both pragmatically and ethically inappropriate for this research topic [77]. It can therefore be argued that the GRADE method of scoring under-appreciates the importance of observational research in certain fields including substance abuse.

This review provides evidence for a statistically significant association between khat use and psychiatric symptoms in general, and more specifically symptoms of depression and psychological distress. It would be useful for further research within this field to investigate the causality of this association, most probably through the use of cohort studies. This review provides evidence for a statistically significant association between khat use and psychiatric symptoms. It would be useful for further research in this field to investigate the causality of this relationship, most probably through cohort studies. Many researchers hypothesise that khat use is the cause of psychiatric symptoms, with its active ingredients distorting the brain's cytoarchitecture and therefore increasing one's vulnerability to mental illness [78-80]. Contrastingly, other researchers suggest that those with mental illness are more likely to chew khat as an attempt to self-medicate their symptoms [81]. Long-term cohort studies would be able to assess which variable predisposes the other, monitor psychiatric symptoms that take time to manifest, and investigate how the prevalence of psychiatric symptoms changes as the duration of khat use increases.

CONCLUSIONS

This review combines 35 cross-sectional studies in the field of khat use, and using meta-analysis suggests that khat use is associated with a 122% increase in the prevalence of psychiatric symptoms, particularly psychiatric distress. The high heterogeneity of the meta-analysis suggests that variables not explored within this review also contribute to the differences between the studies explored; these variables could provide a good focus for future research. Furthermore, the evidence base is unclear about causality within this relationship, another important focus for future research.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr Keith Brain (University of Birmingham), who originally suggested the topic idea, and Dr Jesse Young (University of Melbourne) for his feedback and enthusiasm towards the project. The authors would also like to thank the library team at the University of Birmingham for their help with the literature search. Finally, the authors would like to thank the Leslie James Topham fund (University of Birmingham Medical School) for providing funding towards living costs whilst this research was conducted.

COMPETING INTERESTS

No competing interests.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

ETHICAL APPROVAL

This review did not require ethical approval as no primary data was collected.

CONTRIBUTORSHIP STATEMENT

BE planned the review and created the protocol. BE and NA completed the independent literature searches. BE created the summary of findings table, and completed the meta-analyses including sensitivity and subgroup analyses. BE and NA independently assessed the quality of the included studies using the Newcastle-Ottawa Scale, and BE completed the GRADE scoring. BE wrote the systematic review.

DATA SHARING STATEMENT

Raw data can be found within each primary research study using the references provided.

REFERENCES

1. European Monitoring Centre for Drugs and Drug Addiction. Khat drug profile (date unknown). https://www.emcdda.europa.eu/publications/drug-profiles/khat/de [Accessed 1 December 2020].
2. Wabe, NT. Chemistry, pharmacology, and toxicology of khat (Catha edulis forsk): a review. Addict Health (2011). 3(3): 137-149. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905534/
3. World Health Organisation. Khat chewing in Yemen: turning over a new leaf (2008). https://www.who.int/bulletin/volumes/86/10/08-011008/en/ [Accessed 1 December 2020].
4. Al-Juhaishi T, Al-Kindi S, Gehani A. Khat: a widely used drug of abuse in the horn of Africa and the Arabian Peninsula: review of literature. Qatar Med J (2013). 2012(2):1-6. Doi: 10.5339/qmj.2012.2.5
5. Cochrane L, O-Regan D. Legal harvest and illegal trade: trends, challenges, and options in khat production in Ethiopia. Int J Drug Policy (2016). 30(1): 27-34. Doi: 10.1016/j.drugpo.2016.02.009
6. Douglas H, Boyle M, Lintzeris N. The health impacts of khat: a qualitative study among Somali-Australians. Med J Aust (2011). 195(11): 666-669. Doi: 10.5694/mja11.10166
7. Widmann M, Warsame AH, Mikulica J, et al. Khat use, PTSD, and psychotic symptoms among Somali refugees in Nairobi – a pilot study. Front Public Health (2014). 2(1): 71. Doi: 10.3389/fpubh.2014.00071

8. Cox G, Rampes H. Adverse effects of khat: a review. Adv Psychiatr Treat (2003). 9(6): 456-463. Doi: doi:10.1192/apt.9.6.456
9. Hassan NAGM, Gunaid AA, Murray-Lyon IM. Khat (catha edulis): health aspects of khat chewing. East Mediterr Health J (2007). 13(3): 706-718. Available from: https://pubmed.ncbi.nlm.nih.gov/17687845/
10. Young JT, Butt J, Hersi A, et al. Khat dependence, use patterns, and health consequences in Australia: an exploratory study. J Stud Alcohol Drugs (2016). 77(2): 343-348. Doi: 10.15288/jsad.2016.77.343
11. Omar YS, Jenkins A, Altena MR, et al. Khat use: what is the problem and what can be done? Biomed Res Int (2015). Article ID: 472302. Doi: 10.1155/2015/472302
12. Pantelis C, Hindler CG, Taylor JC. Use and abuse of khat (catha edulis): a review of the distribution, pharmacology, side effects and a description of psychosis attributed to khat chewing. Psychol Med (1989). 19(3): 657-668. Doi: 10.1017/s0033291700024259
13. Edwards B, Atkins N. Exploring the association between khat use and psychiatric symptoms: a systematic review. (2021). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=224510
14. PRISMA. PRISMA checklist. (2021). http://www.prisma-statement.org/PRISMAStatement/Checklist [Accessed 3 May 2021].
15. Medical Subject Headings 2021. US National Library of Medicine (2021). https://meshb.nlm.nih.gov/search [Accessed 19 September].
16. Sanati A. Does suicide always indicate a mental illness? London J Prim Care (2009). 2(2): 93-94. Doi: 10.1080/17571472.2009.11493259
17. Newcastle-Ottawa Quality Assessment Scale. The Ottawa Hospital (2021). http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 19 September 2021].
18. Modesti P, Reboldi G, Cappuccio F, et al. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. PLoS One (2016). 11(1): e0147601. Doi: 10.1371/journal.pone.0147601
19. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al. (editors) Cochrane handbook for systematic reviews of interventions. Version 6.2. Cochrane, 2021. Available from: www.training.cochrane.org/handbook [Accessed 5 November 2021].
20. Sambunjak D, Cumpston M, Watts C. Module 6: analysing the data. In: Cochrane Interactive Learning: Conducting an intervention review. Cochrane, 2017. Available from: https://training.cochrane.org/interactivelearning/module-6-analysing-data [Accessed 5 November 2021].
21. Schünemann H, Brozek J, Guyaa G, et al. The GRADE handbook (2013). https://gdt.gradepro.org/app/handbook/handbook.html#h.svwngs6pm0f2 [Accessed 2 May 2021].
22. Nakajima M, Hoffman R, al-Absi M. Level of khat dependence, use patterns, and psychosocial correlates in Yemen: a cross-sectional investigation. East Mediterr Health J (2017). 23(3): 161-167. Doi: 10.26719/2017.23.3.161
23. al'Absi M, Khalil NS, Habori MA et al. Effects of chronic khat use on cardiovascular, adrenocortical, and psychological responses to stress in men and women. Am J Addict (2018). 22(2): 99-107. Doi: 10.1111/j.1521-0391.2013.00302.x
24. Boka A, Alemu M, Fantu A. Magnitude of substance induced psychosis among adolescents in amanuel mental specialised hospital Addis Ababa, Ethiopia. J Drug

Alcohol Res (2021). 10(6): 236126. Available from: https://www.ashdin.com/articles/magnitude-of-substance-induced-psychosis-among-adolescents-in-amanuel-mental-specialized-hospital-addis-ababa-ethiopia-81031.html

25. Hassen MT, Soboka M, Widmann et al. Khat use patterns, associated features, and psychological problems in a khat-treatment-seeking student sample of Jimma University, southwestern Ethiopia. Front Public Health (2021). 9(1):645980. Doi: 10.3389/fpubh.2021.645980
26. Bahhawi TA, Albasheer OB, Makeen AM et al. Depression, anxiety, and stress and their association with khat use: a cross-sectional study among Jazan University students, Saudi Arabia. Neurospcyhiatr Dis Treat (2018). 14(1): 2755-2761. Doi: 10.2147/NDT.S182744
27. Nakajima M, Jebena MG, Taha M et al. Correlates of khat use during pregnancy: a cross-sectional study. Addict Behav (2017). 73(1): 178-184. Doi: 10.1016/j.addbeh.2017.05.008
28. Mains D, Hadley C, Tessema F. Chewing over the future: khat consumption, anxiety, depression and time among young men in Jimma, Ethiopia. Cult Med Psychiatry (2012). 37(1): 111-130. Doi: 10.1007/s11013-012-9292-9
29. Bhui K, Warfa N. Trauma, khat and common psychotic symptoms among Somali immigrants: a quantitative study. J Ethnopharmacol (2010). 132(3): 549-553. Doi: 10.1016/j.jep.2010.07.027
30. Woods D. Mental health and wellbeing of Somalis in the United Kingdom. (2004). Available from: https://www.semanticscholar.org/paper/Mental-health-and-well-being-of-Somalis-in-the-Woods/2c4a853a72d029c785575880fcf8a0870d7d0b7c
31. Dawud B, Yeshigeta E, Negash A, et al. Substance use disorders and associated factors among adult psychiatric patients in Jimma Town, Southwest Ethiopia, 2017, community-based cross-sectional study. Clin Med Insights Psychiatry (2017). 12(1). Doi: 10.1177/1179557321989699
32. Alebachew W, Semahegn A, Ali T et al. Prevalence, associated factors and consequences of substance use among health and medical science students of Haramaya University, eastern Ethiopia, 2018: a cross-sectional study. BMC Psychiatry (2019). 19(1): 343. Doi: 10.1186/s12888-019-2340-z
33. Yitayih Y, Abera M, Tesfaye E, et al. Substance use disorder and associated factors among prisoners in a correctional institution in Jimma, Southwest Ethiopia: a cross-sectional study. BMC Psychiatry (2018). 18(1): 314. Doi: 10.1186/s12888-018-1901-x
34. Kroll J, Yusuf AI, Fujiwara K. Psychoses, PTSD, and depression in Somali refugees in Minnesota. Soc Psychiatry Psychiatr Epidemiol (2011). 6(1): 481-493. Doi: 10.1007/s00127-010-0216-0
35. Ahmed AG, Emad S. The khat users: a study of khat chewing in Liverpool's Somali men. Med Sci Law (1998). 38(2): 165-169. Doi: 10.1177/002580249803800215
36. Belew M. The magnitude of khat use and its association with health, nutrition and socioeconomic status. Ethiop Med J (2000). 38(1): 11-26. Available from: https://pubmed.ncbi.nlm.nih.gov/11144876/
37. Numan N. Exploration of adverse psychological symptoms in Yemeni khat users by the Symptoms Checklist-90 (SCL-90). Addiction (2004). 99(1): 61-65. Doi: 10.1111/j.1360-0443.2004.00570.x
38. Odenwald M, Neuner F, Schauer M, et al. Khat use as a risk factor for psychotic disorders: a cross-sectional and case-control study in Somalia. BMC Med (2005). 3:5. Doi: https://doi.org/10.1186/1741-7015-3-5

39. Deyessa N, Berhane Y, Alem A, et al. Depression among women in rural Ethiopia as related to socioeconomic factors: a community-based study on women in reproductive age groups. Scand J Public Health (2008). 36(6): 589-597. Doi: 10.1177/1403494808086976
40. Odenwald M, Hinkel H, Schauer E, et al. Use of khat and posttraumatic stress disorder as risk factors for psychotic symptoms: a study of Somali combatants. Soc Sci Med (2009). 69(7): 1040-1048. Doi: 10.1016/j.socscimed.2009.07.020
41. Damena T, Mossie A, Tesfaye M. Khat chewing and mental distress: a community based study, in Jimma City, Southwestern Ethiopia. Ethiop J Health Sci (2011). 21(1): 37-45. Doi: 10.4314/ejhs.v21i1.69042
42. Tulloch AD, Frayn E, Craig TKJ, et al. Khat use among Somali mental health service users in South London. Soc Psychiatry Psychiatr Epidemiol (2012). 47(1): 1649-1656. Doi: 10.1007/s00127-011-0471-8
43. Dessie Y, Ebrahim J, Awoke T. Mental distress among university students in Ethiopia: a cross sectional survey. Pan Afr Med J (2013). 15(1): 95. Doi: 10.11604/pamj.2013.15.95.2173
44. Fekadu W, Haregwoin M, Kibrom H, et al. Magnitude of mental illness and associated factors among holy water users at Entoto St Mary Church, Addis Ababa, Ethiopia, 2014. J Psychiatry (2014). 18(1): 285. Doi: 10.4172/2378-5756.1000285
45. Dachew B, Bifftu B, Tadesse B. Khat use and its determinants among university students in northwest Ethiopia: a multivariable analysis. Int J Med Sci Public Health (2014). 4(3): 1. Doi: 10.5455/ijmsph.2015.1809201460
46. Soboka M, Tesfaye M, Feyissa GT, et al. Khat use in people living with HIV: a facility-based cross-sectional survey from South West Ethiopia. BMC Psychiatry (2015). 15(1): 69. Doi: https://doi.org/10.1186/s12888-015-0446-5
47. Zenebe Y, Feyissa GT, Krahl W. Khat use in persons with mental illness in Southwest Ethiopia: a cross-sectional study. J Addict Res Ther (2015). 6(1): 3. Doi: 10.4172/2155-6105.1000242
48. El-Setouhy M, Alsanosy RM, Alsharqi A, et al. Khat dependency and psychophysical symptoms among chewers in Jazan Region, Kingdom of Saudi Arabia. BioMed Res Int (2016). 2016(1): 2642506. Doi: 10.1155/2016/2642506
49. Hersi L, Tesfay K, Gesesew H, et al. Mental distress and associated factors among undergraduate students at the University of Hargeisa, Somaliland: a cross-sectional study. Int J Ment Health Syst (2017). 11(1): 39. Doi: 10.1186/s13033-017-0146-2
50. Hunduma G, Girma M, Digaffe T, et al. Prevalence and determinants of common mental illness among adult residents of Harari Regional State, eastern Ethiopia. Pan Afr Med J (2017). 28(1): 262. Doi: 10.11604/pamj.2017.28.262.12508
51. Kerebih H, Ajaeb M, Hailesilassie H. Common mental disorders among medical students in Jimma University, Southwest Ethiopia. Afr Health Sci (2017). 17(3): 884-851. Doi: 10.4314/ahs.v17i3.27
52. Mossie A, Kindu D, Negash A. Prevalence and severity of depression and its association with substance use in Jimma Town, southwest Ethiopia. Depress Res Treat (2016). 2016(1): 3460462. Doi: 10.1155/2016/3460462
53. 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(1): 5. Doi: https://doi.org/10.1186/s13033-016-0108-0
54. Tariku G, Zerihun A, Bisrat Z, et al. Mental distress and its association factors among students of Mizam Aman Health Science College, Ethiopia. J Med Sci (2017). 17(2): 61-67. Doi: 10.3923/jms.2017.61.67

55. 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(1): 7427892. Doi: 10.1155/2017/7427892
56. Yeshaw Y, Mossie A. Depression, anxiety, stress, and their associated factors among Jimma University staff, Jimma, Southwest Ethiopia, 2016: a cross-sectional study. Neuropsychiatr Dis Treat (2017). 13(1): 2803-2812. Doi: 10.2147/NDT.S150444
57. Bedaso A, Kediro G, Yeneabat T. Factors associated with depression among prisoners in southern Ethiopia: a cross-sectional study. BMC Res Notes (2018). 11(1): 637. Doi: 10.1186/s13104-018-3745-3
58. Adraro W, Kerebih H, Tesema W, et al. Nearly three in every five prisoners experience common mental disorders (CMDs) in Jimma correctional institution: south-west Ethiopia. BMC Public Health (2019). 19(1): 1559. Doi: 10.1186/s12889-019-7879-6
59. Ongeri L, Kirui F, Muniu E, et al. Khat use and psychotic symptoms in a rural khat growing population in Kenya: a household survey. BMC Psychiatry (2019). 19(1): 137. Doi: 10.1186/s12888-019-2118-3
60. Atnafie SA, Muluneh NY, Getahun KA, et al. Depression, anxiety, stress, and associated factors among khat chewers in Amhara Region, Northwest Ethiopia. Depress Res and Treat (2020). 2020(1): 7934892. Doi: 10.1155/2020/7934892
61. Hajure M, Dibaba B, Shemsu S, et al. Psychological distress among health care workers in health facilities of Mettu Town during COVID-19 outbreak, southwest Ethiopia, 2020. Front Psychiatry (2021). 10(1): 740. Doi: 10.3389/fpsyt.2021.574671
62. Hambisa M, Derese A, Abdeta T. Depressive symptoms among Haramaya University students in Ethiopia: a cross-sectional study. Depress Res Treat (2020). 2020(1): 5027918. Doi: 10.1155/2020/5027918
63. Kelemu R, Kahsay A, Ahmed K. Prevalence of mental distress and associated factors among Samara University students, northeast Ethiopia. Depress Res Treat (2020). 2020(1): 7836296. Doi: 10.1155/2020/7836296
64. Mekuriaw B, Belayneh Z, Yitayih Y. Magnitude of khat use and associated factors among women attending antenatal care in Gedeo zone health centers, southern Ethiopia: a facility based cross sectional study. BMC Public Health (2020). 20(1): 110. Doi: https://doi.org/10.1186/s12889-019-8026-0
65. Yitiyah Y, Soboka M, Tesfaye E, et al. A cross-sectional study of psychopathy and khat abuse among prisoners in the correctional institution in Jimma, Ethiopia. PLoS One (2020). 15(1): e0227405. Doi: 10.1371/journal.pone.0227405
66. Haile K, Sahile A. Depressive symptoms in primary health care attendees in Sebeta Town, Ethiopia: prevalence, associated factors, and detection by health workers. Sci Prog (2021). 104(3): 1-15. Doi: 10.1177/00368504211034304
67. Hambisa S, Siraj J, Mesafint G, Yimam M. Assessment of psychological distress and associated factors among hospitalised patients during COVID-19 pandemic at selected hospitals in Southwest Ethiopia. Neuropsychiatr Dis Treat (2021). 2021(17): 885-892. Doi: 10.2147/NDT.S297460
68. Melaku L, Mossie A, Negash A. Stress among medical students and its association with substance use and academic performance. J Biomed Educ (2015). 2015(1): 149509. Doi: 10.1155/2015/149509
69. Mekuriaw B, Zegeye A, Molla A, et al. Prevalence of common mental disorder and its association with khat chewing among Ethiopian college students: a systematic review and meta-analysis. Psychiatry J (2020). 2020(1): 1462141. Doi: 10.1155/2020/1462141

70. Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: a tutorial. Clin Epidemiology Glob Health (2019). 7(2): 192-198. Doi: 10.1016/j.cegh.2018.05.005
71. World Health Organisation. Depression and other common mental disorders; global health estimates (2017). Available from: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf [Accessed 5 November 2021].
72. Bantjes J, Lochner C, Saal W, et al. Prevalence and sociodemographic correlates of common mental disorders among first-year university students in post-apartheid South Africa: implications for a public mental health approach to student wellness. BMC Public Health (2019). 19(1): 922. Doi: 10.1186/s12889-019-7218-y
73. Mental Health Foundation. Mental health statistics: refugees and asylum seekers (no date). Available from: https://www.mentalhealth.org.uk/statistics/mental-health-statistics-refugees-and-asylum-seekers [Accessed 5 November 2021].
74. Public Health England. Mental health: migrant health guide (2017). Available from: https://www.gov.uk/guidance/mental-health-migrant-health-guide [Accessed 5 November 2021].
75. Murthy RS, Lakshminarayana R. Mental health consequences of war: a brief review of research findings. World J Psychiatry (2006). 5(1): 25-30. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472271/ [Accessed 5 November 2021].
76. Durcan G, Zwemstra JC. Mental health in prison (no date). Available from: https://www.euro.who.int/__data/assets/pdf_file/0017/249200/Prisons-and-Health,-11-Mental-health-in-prison.pdf [Accessed 5 November 2021].
77. Price PC, Jhangiani R, Chiang IA, et al. Chapter 6: Nonexperimental research. In: Price PC, Jhangiani R, Chiang IA, Leighton DC, Cuttler C (editors). Research methods in psychology. 3rd ed. 2017. Available from: https://opentext.wsu.edu/carriecuttler/ [Accessed 5 November 2021].
78. Echoru I, Bukenya E, Masilili G, et al. Khat distorts the prefrontal cortex histology and function of adult wistar rats. Anat J Afr (2018). 7(1): 1121-1131. Doi: 10.4314/aja.v7i1.169485
79. Fluyau D, Mitra P, Lorthe K. Antipsychotics for amphetamine psychosis: a systematic review. Front Psychiatry (2019). 10(1): 740. Doi: 10.3389/fpsyt.2019.00740
80. Mullen J, Richards J, Crawford A. "Amphetamine related psychiatric disorders", In: Statpearls. Florida, USA: Statpearls Publishing (2021).
81. Odenwald M, al'Absi M. Khat use and related addiction, mental health and physical disorders: the need to address a growing risk. East Mediterr Health J (2017). 23(3): 236-244. Doi: 10.26719/2017.23.3.236

Legends:
Figure 1: PRISMA flow chart of included and excluded studies
Figure 2: Meta-analysis of included studies
Figure 3: funnel plot of included studies

Figure 1: PRISMA flow chart of included and excluded studies

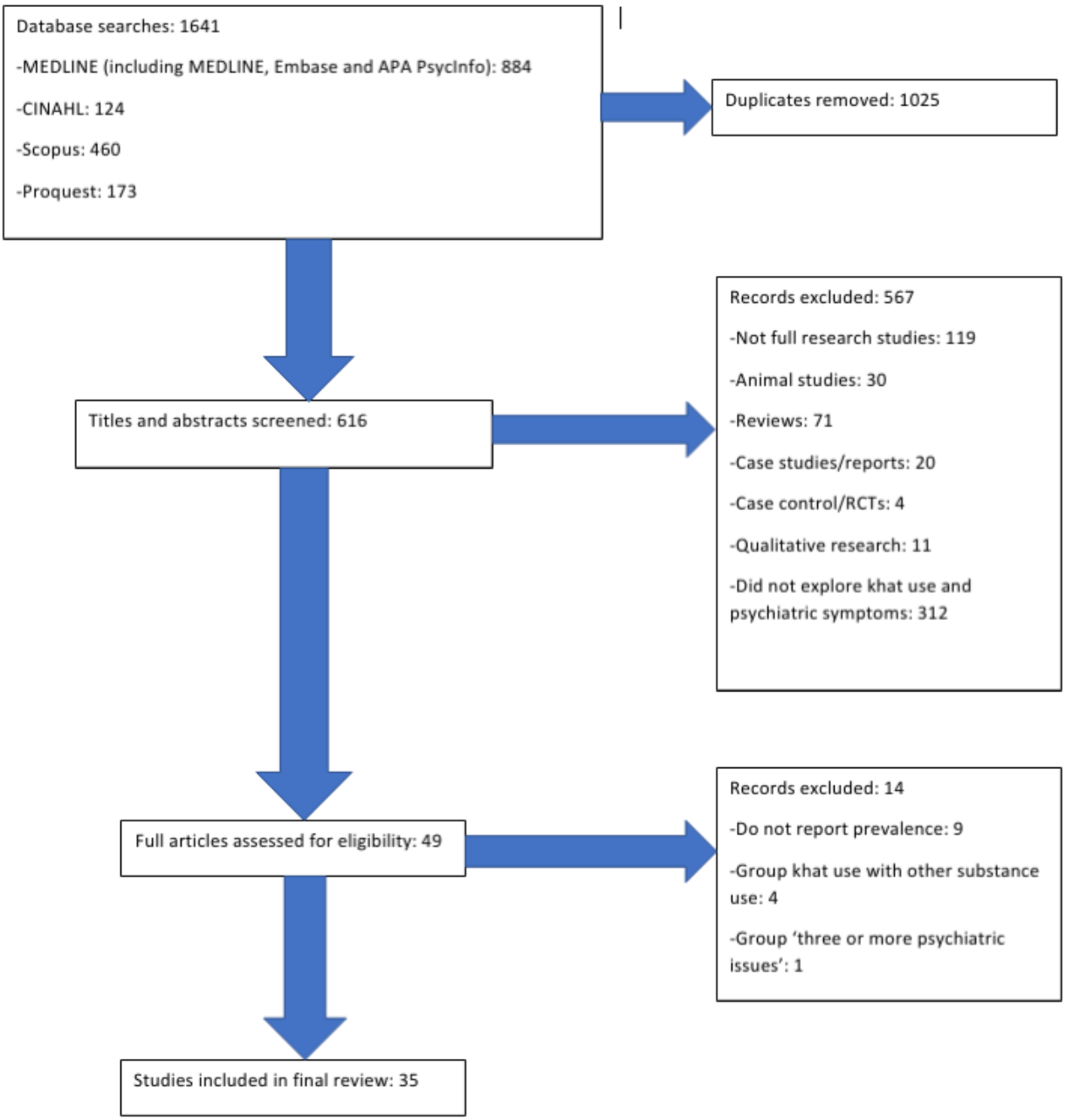


Figure 2: Meta-analysis of included studies

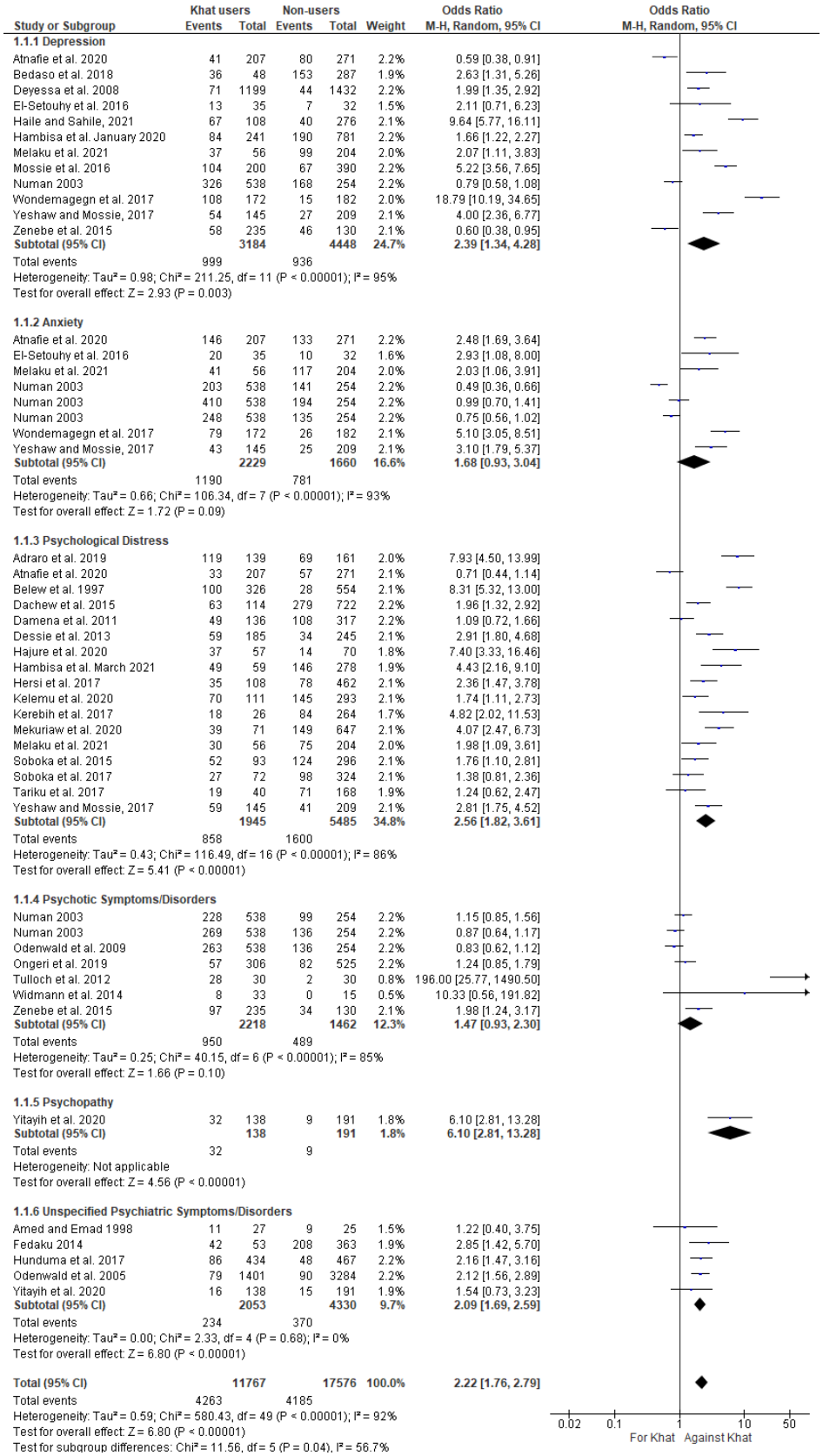
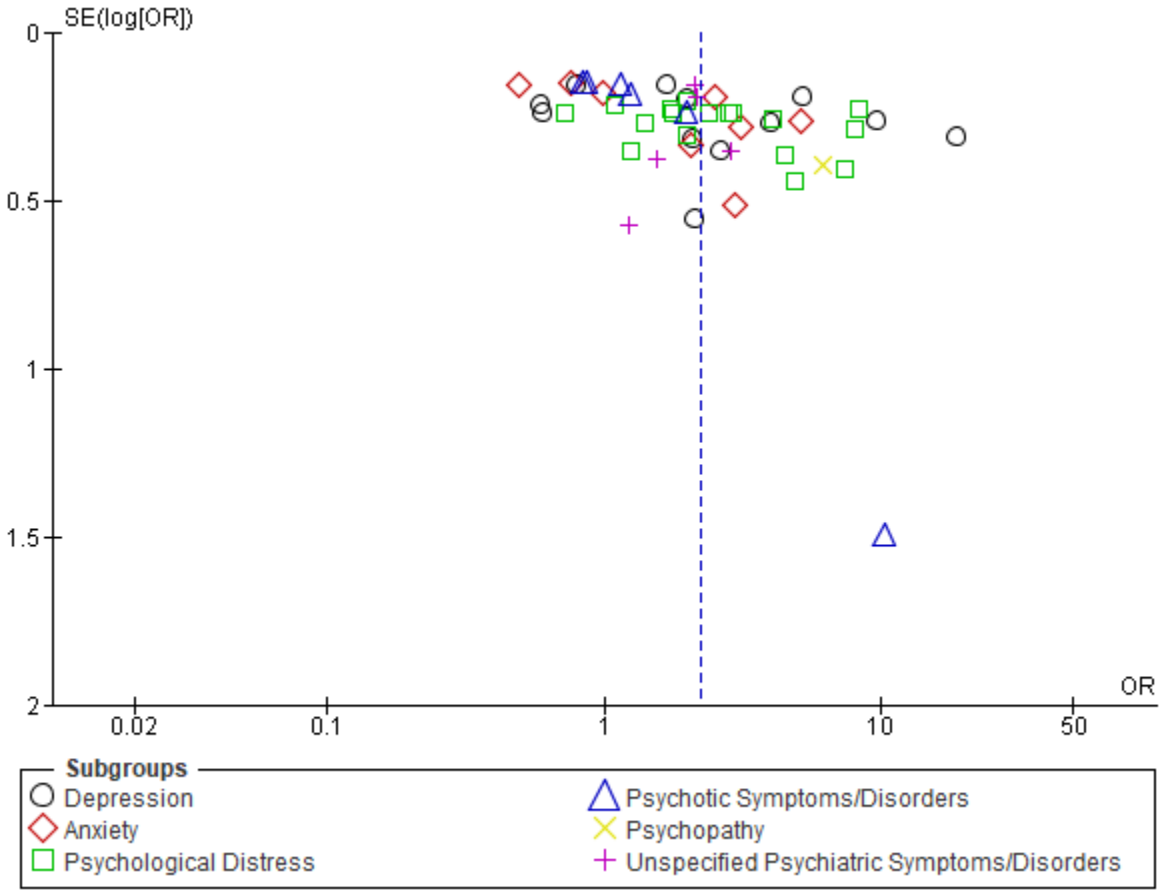


Figure 3: funnel plot of included studies



Supplementary Material 1: Summary of Findings Table

Study	Population	Sample	Criteria for 'Khat User'	Psychiatric Measure*	Results
Ahmed and Emad 1998 [35]	Somali immigrants living in Liverpool	Convenience sample of 52 Khat users = 27	Unspecified	GHQ-28	- 11/27 khat users experienced psychiatric dysfunction, compared to 9/25 non-users (p=0.72)
Belew et al. 2000 [36]	Individuals aged 15+ from a specified community in Ethiopia	Random sample of 1200 participants Khat users = 326	Anyone who has chewed khat within the last 30 days	SRQ	- 100/326 khat-users experienced mental distress, compared to 28/554 non-users (OR = 8.31, 5.20-13.31, p=0.00) - 89/294 long-term users (over 2 years) experienced mental distress, compared to 28/554 never-users (OR = 8.14, 5.06-13.17, p=0.00)
Numan 2003 [37]	Yemeni population	Random sample of 800 participants Khat users = 67.9%	Frequent use – 4-6 days a week Heavy use – use everyday	SCL-90	- No significant differences (at p<0.05) in psychiatric symptoms: obsession-compulsion, depression, anxiety, paranoid ideation, psychoticism - Khat users had less phobic anxiety (37.7% vs 55.5%, p<0.05)
Odenwald et al. 2005 [38]	'General population' of Somalia	Random sample of 4854 Khat users = 78% of those with psychiatric issues, 4% of those without	Number of bundles in previous week recorded	CIDI, PANSS	- More positive screened individuals (mental problems severe enough to prevent employment or household tasks) chewed khat than negative screened individuals (46.6% vs 29.9%, p<0.001)
Deyessa et al. 2008 [39]	Women of reproductive age in rural Ethiopia	Random sample of 3200 Khat users = 40%	At least once per week	CIDI, ICD-10	- 5.9% of regular users had had a depressive episode in the last 12 months, compared to 3.1% of non-regular users (less than once per month) and 3.6% of non-users - AOR for regular vs non-users is 1.35 (0.92-1.99)

Odenwald et al. 2009 [40]	Armed combatants in Somali	8124 armed individuals (not random as still in conflict at time of study) Khat users = 36.4%	Anyone who has chewed khat within the last week	CIDI	- 8.9% of khat users experienced paranoid ideation compared to 2.6% of non-users
Damena et al. 2011 [41]	Adults in Jimma City, Ethiopia	Random sample of 1308 Khat users = 38%	Uses WHO-validated substance abuse questionnaire, but unsure what is classified as 'khat user'	SRQ-20	- 49/136 long-term khat chewers experienced mental distress, compared to 108/317 short-term khat chewers (less than two years), and 153/747 non-users
Tulloch et al. 2012 [42]	Adult Somali khat users living in South London	Secondary data based on 172 eligible Somali mental health patients Khat users = 47%	Anyone who has chewed khat within the last year	Diagnosis provided by service records	- 28/30 khat users experienced psychosis compared to 2/30 non-users ($p<0.001$)
Dessie et al. 2013 [43]	Students in Ethiopia	Random sample of 413 Khat users = 43%	Anyone who has ever used khat	SRQ-20	- 59/185 khat users experienced mental distress compared to 34/245 non-users (AOR = 2.23, 1.14-4.35, $p<0.05$)
Fekadu 2014 [44]	Holy water users from Entoto St Mary Church, Ethiopia	409 individuals selected using systematic random sampling Daily khat users = 12.7%	Khat use recorded as 'never' or 'daily', although no indication of the duration of daily usage	BPRS	- 42/53 daily khat-users experienced mental illness compared to 208/363 non-users (AOR = 2.85, 1.42-5.70)
Widmann et al. 2014 [7]	Male Somali refugees living in a disadvantaged	Convenience sample of 33 users and 15 comparable non-users	SDS	CIDI, MINI	- 24% of khat users had psychotic symptoms compared to 0% of non-chewers ($p=0.044$)

	urban settlement in Kenya	Khat users = 69%			
Dachew et al. 2015 [45]	Undergraduate students from Gondar University, Ethiopia	872 patients selected using stratified, random sampling Current khat users = 16%	Questionnaire identifying 'current use'	SRQ-20	- 63/114 current khat users had mental distress, compared to 279/722 non-users (OR=1.96, 1.32-2.92, p=0.02)
Soboka et al. 2015 [46]	HIV patients at a specified facility in South West Ethiopia	All eligible adults invited to participate Sample of 389 Khat users = 93	Anyone who has chewed khat within the last month	K-6	- 52/93 khat-users experienced psychological distress, compared to 124/296 non-users (OR = 1.76, 1.10-2.82)
Zenebe et al. 2015 [47]	Psychiatric outpatients in Ethiopia	365 adult psychiatric outpatients of a specified hospital within 2-week study period Khat use = 64.4%	Anyone who has used khat within the last 30 days	Psychiatric diagnosis from psychiatric records	- 58/235 khat users had a major depressive disorder compared to 46/130 non-users (AOR = 1.43, 0.74-2.77) - 97/235 khat users had schizophrenia compared to 34/130 non-users (AOR = 0.87, 0.45-1.68)
El-Setouhy et al. 2016 [48]	Jazan region of Saudi Arabia	Volunteer sample of 70 males Khat dependent = 52.2%	SDS	Q16	- 13/35 dependent users felt depressed compared to 7/32 non-dependent users (OR = 2.30, 0.7-6.8) - 20/35 dependent users felt anxious compared to 10/32 non-dependent users (OR = 3.50, 1.2-10.0)
Hersi et al. 2017 [49]	Students in Somaliland	Stratified random sample of 570 Khat users = 19%	Use in last 12 months	SRQ-20	- 32% of khat users experienced psychological distress, compared to 17% of non-users (AOR = 2.87, 1.26-6.56)
Hunduma et al. 2017 [50]	Adults in Ethiopia	Random sample of 968 Khat users = 48%	Khat use in last 3 months	SRQ-20	- 86/434 khat users had a common mental disorder, compared to 48/467 non-users (OR = 2.16, 1.47-3.16)

Kerebih et al. 2017 [51]	Medical students in Ethiopia	Stratified random sample of 305 Khat users = 9%	Anyone who has ever used khat	SRQ-20	- 18/26 khat users experienced mental distress compared to 84/264 non-users (AOR = 6.91, 1.88-25.42, p=0.004)
Mossie et al. 2016 [52]	Adults in Ethiopia	Random sample of 650 Khat users = 34%	Khat use within the last 30 days	BDI	- 104/200 khat users had depression compared to 67/390 non-users (AOR = 10.07, 5.56-18.25)
Soboka et al. 2017 [53]	Adults with hypertension at a specified clinic in South West Ethiopia	All eligible adults invited to participate Sample of 396 Khat users = 79	Anyone who has chewed khat within the last month	K-6	- 27/72 current khat-users experienced psychological distress, compared to 98/324 non-users
Tariku et al. 2017 [54]	Students at a health sciences college in Ethiopia	Stratified random sample of 317 Khat users = 13%	Anyone who has ever used khat	Not specified	- 19/40 khat users experienced mental distress compared to 71/168 non-users (AOR = 2.29, 1.04-5.04)
Wondemagegn et al. 2017 [55]	Adolescents and adults in Nekemte town, West Ethiopia	Random sample of 359 participants Khat users = 49%	Anyone who has chewed khat within the last 30 days	DSM-IV	- 108/172 users experienced depression compared to 15/182 non-users (AOR = 25.36, 12.13-53.05, p=0.000) - 79/172 users experienced anxiety compared to 26/182 non-users (AOR = 5.49, 3.04-9.96, p=0.000)
Yeshaw and Mossie 2017 [56]	Staff of Jimma University, Ethiopia	Random sample of 363 Khat users = 41%	Anyone who has ever used khat	DASS-21	- 54/145 khat users had depression compared to 27/209 non-users (AOR = 4.99, 2.57-9.69) - 43/145 khat users had anxiety compared to 25/209 non-users (AOR = 2.94, 1.52-5.66) - 59/145 khat users had psychological stress compared to 41/209 non-users (AOR = 2.78, 1.49-5.21)
Bedaso et al. 2018 [57]	Prisoners in Ethiopia	Random sample of 335 Khat users = 14%	Unspecified, but appears to be chewing khat before incarceration	PHQ-9	- 36/48 khat users had depression, compared to 153/287 non-users (AOR = 2.48, 1.05-5.86, p=0.039)
Adraro et al. 2019 [58]	Prisoners in Ethiopia	Random sample of 300 Khat users = 46%	Anyone who has ever used khat	SRQ-20	- 119/139 khat users experienced mental distress, compared to 69/161 non-users (AOR = 4.33, 2.02-9.27, p<0.001)

Ongeri et al. 2019 [59]	Khat-growing regions of Kenya	Random sample of 831 individuals aged 10+ Khat users = 36.8%	Unspecified	PSQ	- 18.6% of khat users experienced at least one psychotic symptom compared to 15.6% of non-users (p=0.26)
Atnafie et al. 2020 [60]	Khat chewers in Amhara region of Ethiopia	Convenience sample of 508 participants Khat dependent = 43%	SDS	DASS-21	- 33/207 khat-dependent users experienced stress compared to 57/271 non-dependent users (AOR = 1.70, 0.98-2.95) - 146/207 khat-dependent users experienced anxiety compared to 133/271 non-dependent users (AOR = 2.47, 1.57-3.81) - 41/207 khat-dependent users experienced depression compared to 80/271 non-users (AOR = 6.28, 1.67-23.61)
Hajure et al. 2020 [61]	Healthcare providers in Ethiopia	Convenience sample of 127 Khat users = 45%	Khat use in last three months	IES-R	- 37/57 khat users experienced psychological stress, compared to 14/70 non-users (AOR = 5.74, 1.83-18.1, p<0.001)
Hambisa et al. 2020 [62]	Students in Ethiopia	Random sample of 1022 Khat users = 24%	Khat use within last month	BDI	- 84/241 khat users had depressive symptoms compared to 190/781 non-users (OR = 1.60, 1.22-2.27)
Kelemu et al. 2020 [63]	Students in Ethiopia	Random sample of 404 Khat users = 27%	Anyone who has ever used khat	SRQ-20	- 70/111 khat users experienced mental distress, compared to 145/293 non-users (AOR = 3.09, 1.74-5.50)
Mekuriaw et al. 2020 [64]	Pregnant women in Ethiopia	Random sample of 845 Khat users = 11%	Investigates usage but unclear what quantifies a 'current khat user'	SRQ-20	- 39/71 khat users experienced mental distress, compared to 149/647 non-users (AOR = 3.57, 2.06-6.18, p=0.001)
Yitayih et al. 2020 [65]	Prisoners in a correctional	Random sample of 336 Khat users = 138	DAST-10	PCL:SV	- 32/138 khat users met the criteria for psychopathy, compared to 9/191 non-users

	institution in Jimma, Ethiopia				- 16/138 khat users had mental illness, compared to 15/191 non-users
Haile and Sahile, 2021 [66]	Adult primary healthcare attendees in Ethiopia	Stratified and systematic random sample of 384 Khat users = 39%	Unspecified	PHQ-9	- 67/108 khat users had depressive symptoms, compared to 40/276 non-users (AOR = 5.43, 2.55-11.56, p<0.01)
Hambisa et al. 2021 [67]	Hospitalised patients in Ethiopia	Systematic sample of 337 Khat users = 18%	Unspecified; discusses 'current khat use' and 'khat use in the previous three months'	K10	- 49/59 khat users experienced psychological distress, compared to 146/278 non-users (AOR = 4.16, 1.67-10.35)
Melaku et al. 2021 [68]	Medical students in Ethiopia	Systematic random sample of 260 Khat users = 22%	Anyone who has ever used khat	DASS-21	- 37/56 khat users had depression, compared to 99/204 non-users (OR = 2.07, 1.11-3.83) - 41/56 khat users had anxiety, compared to 117/204 non-users (OR = 2.03, 1.06-3.91) - 30/56 khat users had psychological stress, compared to 75/204 non-users (OR = 1.99, 1.09-3.61)

*List of abbreviated screening tools: GHQ-28 (General Health Questionnaire-28, for mental disorders), SRQ-20 (Self-Reporting Questionnaire - 20 items, for mental distress), SCL-90 (Symptom Checklist - 90 items, for psychological symptoms), CIDI (Composite International Diagnostic Interview - for psychiatric disorders), PANSS (Positive and Negative Syndrome Scale - for schizophrenia), ICD-10 (International Classification of Diseases, 10th revision), BPRS (Brief Psychiatric Rating Scale - for depression, anxiety and hallucinations), SDS (Severity of Dependence Scale), MINI (Mini International Psychiatric Review), K-6 (Kessler Psychological Distress Scale - 6 questions), Q16 (Questionnaire 16 for neurotoxic symptoms), BDI (Beck's Depression Inventory), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition), DASS-21 (The Depression, Anxiety and Stress Scale - 21 Items), PHQ-9 (Patient Health Questionnaire - 9 items, for depression), PSQ (Psychosis Screening Questionnaire), IES-R (Impacts of Events Scale - Revised), DAST-10 (Drug Abuse Screening Test-10), PCL:SV (Psychopathy Checklist: Screening Version), K10 (Kessler Psychological Distress Scale - 10 questions)

Supplementary Material 2: Quality of assessment of primary studies using Newcastle-Ottawa scale [16-17].

Study	Selection (/5)	Comparability (/2)	Outcome (/3)	Overall Score (/10)	Comments
Ahmed and Emad 1998 [21]	1	2	1	4	- Non-random sample - No justification of sample size - 100% response rate - Questionnaire described in insufficient detail no definition of khat use - No significant differences in baseline characteristics between khat users and non-users - Uses self-report - No details of statistical analysis and no confidence intervals provided
Belew et al. 2000 [22]	3	2	2	7	- Insufficient details of non-responders; no baseline characteristics provided - Questionnaire described in limited detail but methods do define current, past and never khat use
Numan 2003 [23]	3	1	1	5	- Sample size not justified - Eight non-respondents excluded because of incomplete data - Non-validated but described method of khat usage data collection - Only controlled variable seems to be Yemeni nationality - No confidence intervals included
Odenwald et al. 2005 [24]	3	2	2	7	- Sample size not justified - No details of non-responders - Non-validated but described method of khat usage data collection - Uses clinical interviews - No confidence intervals included

Deyessa et al. 2008 [25]	3	2	3	8	- Providers reasons for non-responders but not characteristics - Non-validated but described method of khat usage data collection - Clinical interview
Odenwald et al. 2009 [26]	2	2	2	6	- Sample size not justified - No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Damena et al. 2011 [27]	4	1	1	6	- Providers reasons for non-responders but not characteristics - Uses WHO-validated khat use measurement tool despite definition of 'khat user' being unclear within the study - Only controlled variable seems to be region (Jimma City) - Uses self-report - No confidence intervals included
Tulloch et al. 2012 [28]	4	2	2	8	- Entire eligible sample used - Missing information discussed - Non-validated but described method of khat usage data collection - No confidence intervals included
Dessie et al. 2013 [29]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self report
Fekadu 2014 [30]	2	2	2	6	- No details of non-responders - Khat usage data collection described insufficiently: 'daily' or 'never' - Uses self-report
Widmann et al. 2014 [7]	2	2	3	7	- Opportunity sample - Sample size not justified - No details of non-responders - Clinical interview

Dachew et al. 2015 [31]	2	2	2	6	- Justification of sample size unsatisfactory - No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Soboka et al. 2015 [32]	3	2	2	7	- All eligible participants invited to participate - Limited description of non-responders (gender only) - Non-validated but described method of khat usage data collection - Uses self-report
Zenebe et al. 2015 [33]	3	2	3	8	- No details of non-responders - Non-validated but described method of khat usage data collection - Medical records used
El-Setouhy et al. 2016 [34]	4	2	2	8	- Volunteer sample; no non-responders - Uses self-report
Hersi et al. 2017 [35]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Hunduma et al. 2017 [36]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Kerebih et al. 2017 [37]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Mossie et al. 2016 [38]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Soboka et al. 2017 [39]	2	2	2	6	- Invited all eligible participants

					- Does not discuss whether sample size is large enough for conclusions to be drawn - No details of non-responders - Non-validated but described method of khat usage data collection - Unclear if all variables are self-reported
Tariku et al. 2017 [40]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self report
Wondemagegn et al. 2017 [41]	3	1	3	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Only one community studied but no other controlled variables
Yeshaw and Mossie 2017 [42]	2	2	2	6	- Sample size not justified - No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Bedaso et al. 2018 [43]	3	2	2	8	- 100% response rate - Limited description of khat usage data collection - Uses self-report
Adraro et al. 2019 [44]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Ongeri et al. 2019 [45]	2	2	2	6	- No details of non-responders - No description of what quantifies a ‘current khat user’ - Uses self-report
Atnafie et al. 2020 [46]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection

					- Uses self-report
Hajure et al. 2020 [47]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Hambisa et al. 2020 [48]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Kelemu et al. 2020 [49]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Mekuriaw et al. 2020 [50]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Yitayih et al. 2020 [51]	4	2	2	8	- Provides reasons for non-responders but not characteristics - Uses DAST-10 for khat abuse -Uses self-report
Haile and Sahile, 2021 [52]	3	2	2	7	- 100% response rate - No description of what quantifies a ‘current khat user’ - Uses self-report
Hambisa et al. 2021 [53]	2	2	2	6	- Providers reasons for non-responders but not characteristics - No description of what quantifies a ‘current khat user’ - Uses self-report
Melaku et al. 2021 [54]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report

Supplementary Material 3: Sensitivity Analysis

Study Excluded	Odds Ratio	95% CIs	I^2 Value (%)	P-Value
Depression				
Atnafie et al. 2020	2.28	1.81-2.87	91	<0.00001
Bedaso et al. 2018	2.21	1.75-2.79	92	<0.00001
Deyessa et al. 2008	2.23	1.76-2.82	92	<0.00001
El-Setouhy et al. 2016	2.22	1.76-2.80	92	<0.00001
Haile and Sahile 2021	2.14	1.71-2.69	91	<0.00001
Hambisa et al 2020	2.24	1.77-2.84	92	<0.00001
Melaku et al. 2021	2.22	1.76-2.81	92	<0.00001
Mossie et al. 2016	2.17	1.73-2.73	91	<0.00001
Numan 2003	2.27	1.80-2.87	91	<0.00001
Wondemagegn et al. 2017	2.11	1.69-2.64	91	<0.00001
Yeshaw and Mossie 2017	2.19	1.74-2.76	92	<0.00001
Zenebe et al. 2015	2.28	1.81-2.87	91	<0.00001
Anxiety				
Atnafie et al. 2020	2.22	1.75-2.80	92	<0.00001
El-Setouhy et al. 2016	2.21	1.75-2.79	92	<0.00001
Melaku et al. 2021	2.22	1.76-2.81	92	<0.00001
Numan 2003	2.29	1.83-2.86	91	<0.00001
Numan 2003	2.26	1.79-2.86	92	<0.00001
Numan 2003	2.27	1.80-2.87	91	<0.00001
Wondemagegn et al. 2017	2.18	1.73-2.74	91	<0.00001
Yeshaw and Mossie 2017	2.20	1.75-2.78	92	<0.00001
Psychological Distress				
Adraro et al. 2019	2.16	1.72-2.71	91	<0.00001

Atnafie et al. 2020	2.27	1.80-2.87	92	<0.00001
Belew et al. 2000	2.15	1.72-2.69	91	<0.00001
Dachew et al. 2015	2.23	1.76-2.82	92	<0.00001
Damena et al. 2011	2.26	1.78-2.85	92	<0.00001
Dessie et al. 2013	2.21	1.75-2.79	92	<0.00001
Hajure et al. 2020	2.17	1.72-2.73	92	<0.00001
Hambisa et al. 2021	2.19	1.74-2.76	92	<0.00001
Hersi et al. 2017	2.22	1.75-2.80	92	<0.00001
Kelemu et al. 2020	2.23	1.77-2.82	92	<0.00001
Kerebih et al. 2017	2.19	1.74-2.76	92	<0.00001
Mekuriaw et al. 2020	2.19	1.74-2.76	92	<0.00001
Melaku et al. 2021	2.23	1.76-2.81	92	<0.00001
Soboka et al. 2015	2.23	1.77-2.82	92	<0.00001
Soboka et al. 2017	2.24	1.78-2.83	92	<0.00001
Tariku et al. 2017	2.25	1.78-2.84	92	<0.00001
Yeshaw and Mossie et al. 2017	2.21	1.75-2.79	92	<0.00001
Psychotic symptoms/disorders				
Numan 2003	2.26	1.78-2.86	92	<0.00001
Numan 2003	2.27	1.80-2.87	91	<0.00001
Odenwald et al. 2009	2.27	1.80-2.87	91	<0.00001
Ongeri et al. 2019	2.25	1.78-2.85	92	<0.00001
Tulloch et al. 2012	2.14	1.70-2.68	91	<0.00001
Widmann et al. 2014	2.20	1.75-2.77	92	<0.00001
Zenebe et al. 2015	2.23	1.76-2.82	92	<0.00001
Psychopathy				
Yitayih et al. 2020	2.18	1.73-2.74	92	<0.00001
Unspecified psychiatric symptoms/disorders				

Ahmed and Emad 1998	2.24	1.78-2.83	92	<0.00001
Fedaku et al. 2014	2.21	1.75-2.79	92	<0.00001
Hunduma et al. 2017	2.22	1.76-2.81	92	<0.00001
Odenwald et al. 2005	2.23	1.76-2.82	92	<0.00001
Yitayih et al. 2020	2.24	1.77-2.82	92	<0.00001

BMJ Open

EXPLORING THE ASSOCIATION BETWEEN KHAT USE AND PSYCHIATRIC SYMPTOMS: A SYSTEMATIC REVIEW

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061865.R1
Article Type:	Original research
Date Submitted by the Author:	10-Jun-2022
Complete List of Authors:	Edwards, Betsy; University of Birmingham, Atkins, Naomi; University of Birmingham
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Global health, Mental health, Public health
Keywords:	PSYCHIATRY, MENTAL HEALTH, Substance misuse < PSYCHIATRY, PUBLIC HEALTH, Adult psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

EXPLORING THE ASSOCIATION BETWEEN KHAT USE AND PSYCHIATRIC SYMPTOMS: A SYSTEMATIC REVIEW

Betsy Edwards[1*], Naomi Atkins[2]

[1] College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[2]College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[*]Correspondence: Betsy Edwards, BHE701@student.bham.ac.uk , 67 Peterborough Avenue Upminster RM14 3LL

Keywords: khat, psychiatric symptoms, mental health, review, meta-analysis

Word count (excluding title page, references, figures and tables): 3284

Abstract

Objectives: Consumption of the drug khat is high across East Africa and the South-Western Arabian Peninsula despite evidence for its adverse psychiatric effects. This systematic review aims to explore cross-sectional research in the field to determine the strength of the association between khat use and psychiatric symptoms

Methods: Six databases were searched in October 2021 - Ovid Medline, Embase, APA PsycInfo, CINAHL, Scopus and Proquest - using the following search terms: "khat" OR "qat" OR "qaad" OR "catha" OR "miraa" OR "mairungi" AND "depression" OR "anxiety" OR "mania" OR "psych*" OR "schiz*" OR "mental" OR "hallucinations" OR "delusions" OR "bipolar". Eligible studies were cross-sectional studies of any population or setting comparing the prevalence of psychiatric symptoms in long-term or dependent khat users with non-users. The quality of each study was appraised by the Newcastle-Ottawa scale. A meta-analysis was planned using a random effects model to produce an odds ratio with 95% confidence intervals - using the Mantel-Haenszel method - alongside an I^2 statistic to represent heterogeneity. The quality of this meta-analysis was appraised using the GRADE scoring system.

Results: 35 studies were eligible for inclusion (total participants = 31893), spanning 5 countries (Ethiopia, Somalia, Kenya, Saudi Arabia, UK). Meta-analysis suggests that khat use is associated with an 122% increased prevalence of psychiatric symptoms (OR = 2.22, 95% CIs 1.76-2.79, p<0.00001, GRADE score: 'very low').

Conclusions: The high heterogeneity of the meta-analysis is likely due to the wide variation between the studies within the evidence base. To perform a more accurate systematic review, further primary studies are needed with standardised measurements of variables, particularly khat consumption.

Strengths and Limitations of this Review

- Follows all guidelines listed in the PRISMA 2020 Checklist for systematic reviews
- Searches published and unpublished literature using search terms that include all commonly-used variations of 'khat' from around the world
- Includes both dependent and non-dependent khat use due to poor definitions of khat usage in primary research studies
- Includes both psychiatric symptoms and psychiatric disorders

INTRODUCTION

The stimulant drug khat consists of the buds and leaves of the plant *Catha edulis*, an evergreen shrub highly prevalent in East Africa and the South-Western Arabian Peninsula [1-2]. Ethiopia is the world's largest exporter of khat, however its consumption is highest in Yemen where up to 90% of adult males and 50% of adult females chew khat for three to four hours per day [3-5]. Within its local regions, khat chewing has been a cultural tradition for many generations and is thought to increase sociability, concentration, energy and spirituality [2, 6-7].

Psychiatric symptoms have been recognised as a consequence of khat use for several decades [8-9]. Milder psychological consequences related to its use include anxiety, restlessness,

insomnia and dysphoric mood, all of which can reduce quality of life [2, 8-11]. More severe psychological harms associated with its use include psychosis and depression, which in some cases have resulted in acts of suicide and homocide [8-11]. Users most at risk of these sequelae are those abusing larger amounts of khat - some studies have provided evidence for a dose-dependent relationship - and those with pre-existing psychiatric disorders [8-10].

The evidence base exploring the association between khat use and psychiatric symptoms - which consists mostly of cross-sectional studies - is currently small and insufficient [12]. Studies often vary in terms of populations and regions studied, measurement of khat use, symptoms explored and quality of methodology. Hence, results can be inconsistent, making it difficult for academics, policy makers and the public to understand the psychiatric risks of khat consumption. This systematic review aims to investigate the strength of the association between khat use and psychiatric symptoms by collating the evidence we have so far, in order to guide further research in the field and to evaluate the need for any potential interventions for khat users, e.g. increased education about potential psychiatric side effects.

METHODS

The protocol for this systematic review can be found on Prospero, with registration number CRD42020224510 [13]. Originally, this systematic review had two objectives; to investigate the strength of the association between khat use and psychiatric symptoms, and secondly to investigate the role of trauma within this relationship. Due to the vast amount of literature in the field, the second objective was removed from the protocol to ensure that the findings would be suitable for one single review. It is recommended that a follow-up review should be conducted to explore the role of trauma.

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines at all times [14]. Ethical approval was not necessary as only secondary data was used.

Patient and Public Involvement

No members of the public or patients were involved in the design of this systematic review.

Literature Search

A literature search was carried out independently by authors BE and NA in October 2021 using the following search terms:

“khat” OR “qat” OR “qaad” OR “catha” OR “miraa” OR “mairungi”
AND
“depression” OR “anxiety” OR “mania” OR “psych*” OR “schiz*” OR “mental” OR “hallucinations” OR “delusions” OR “bipolar”

These search terms encompassed all previously reported psychiatric symptoms associated with khat, and included all predominant cultural variations of the term ‘khat’ as identified by the Medical Subject Headings Thesaurus (MeSH) [15]. Advice was provided by the library team at the University of Birmingham. Note that studies surrounding suicidality were

excluded, as suicidality is often but not always associated with psychiatric dysfunction [16]. Disagreements between the authors were discussed in person. Removal of duplicates was automated for the databases Ovid MEDLINE, Embase and APA PsycInfo, and was performed manually for the remaining databases.

Six electronic databases were searched. Five of these were databases of published literature: Ovid MEDLINE, Embase, APA PsycInfo, CINAHL and Scopus. Additionally, Proquest was searched to obtain any relevant grey or unpublished literature. The full search strategy for each database can be found in Supplementary Material 1.

Study Eligibility

The literature search used the following inclusion criteria:

- Population: adults (aged 18+)
- Exposure: long-term or dependent khat use
- Comparator: no khat use or non-dependent khat use*
- Outcome: prevalence of psychiatric symptoms in khat users and prevalence of psychiatric symptoms in non-users
- Study design: cross-sectional studies; note that mixed-method studies are considered eligible but only the cross-sectional data will be considered for the review
- Language: all
- Publication type: must be a complete study but no restriction on publication status
- Setting: all
- Date of publication: all

Each potentially eligible study was compared to a checklist of the above criteria to determine whether or not it should be included within the review.

*Note that non-dependent khat use was only considered a suitable comparator for studies where the exposure group were dependent khat-users, where both dependence and non-dependence were validated by a recognised tool such as the Severity of Dependence Scale (SDS).

The literature search used the following exclusion criteria:

- Population: children, animals
- Exposure: substance abuse other than khat
- Comparator: ‘substance users’ where khat use is not specifically described
- Outcome: neurobehavioural processes, withdrawal symptoms, suicide, substance use disorders
- Study design: any study design other than cross-sectional, e.g. case control, randomised controlled trial, case report, review
- Language: no exclusion criteria
- Publication type: unfinished studies including abstract only, conference abstracts, letters, retracted articles, book chapters
- Setting: no exclusion criteria

Data Collection and Quality Assessment

A summary of findings table - see Supplementary Material 2 - was created to present the following study features: population, sample, criteria for 'khat user', psychiatric measure, effect estimate. In addition, the quality of each primary study (e.g. risk of bias due to inadequate reporting methods or missing data) was assessed using the Newcastle-Ottawa Scale (see Supplementary Material 3) [17-18]. Data was collected manually by both authors independently, with any disagreements between the independent assessments resolved by discussion.

Synthesis of Findings

The prevalence of khat-users and non-users with psychiatric symptoms from each study was entered into a meta-analysis using the software Revman, provided by the Cochrane organisation. After inputting all dichotomous values, this software created a forest plot of odds ratios, each with 95% confidence intervals, using the Mantel-Haenszel method [19]. A random effects model was used as this assumes that the outcome is normally distributed rather than always the same, hence attributing the differences between studies to both chance and genuine variation [19]. An I^2 statistic was given to indicate variability between studies, as this is again recommended by the Cochrane organisation [20].

A subgroup analysis was also included, grouping studies investigating similar symptoms. An odds ratio and I^2 statistic was provided for each subgroup, as well as a chi-squared test and p-value for overall subgroup differences.

A sensitivity analysis was conducted to look for any studies that are prominent outliers. Each study was removed from the meta-analysis one at a time, and the odds ratio, 95% confidence intervals, I^2 value and p-value reported within a table.

The quality of the meta-analysis was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework [21].

RESULTS

Included and Excluded Studies

The PRISMA flow chart in Figure 1 shows the number of studies included and excluded at each stage of the literature search [14]. When searching the relevant databases, 1641 results were found that included the relevant terms within their title or abstract. After removing duplicates, this number was reduced to 616.

Each title and abstract were screened, and 567 results were removed for the following reasons:

- 119 were not research studies, e.g. these included conference abstracts, letters, and newspaper/magazine articles
- 30 were animal studies
- 71 were reviews, including systematic reviews and meta-analyses
- 20 were case studies or case reports
- 4 were case control studies or randomised controlled trials
- 11 were qualitative studies
- 312 did not explore the relationship between khat use and psychiatric symptoms

49 studies were read in full in order to determine their eligibility. Of these, 14 were excluded for the following reasons:

- 9 explored both khat use and psychiatric symptoms but not their prevalence [22-30]
- 4 did not report khat-use alone, and instead reported substance use or equivalent [31-34]
- 1 only reported the prevalence of khat use alongside 'three or more psychiatric issues'[10]

35 studies were included in the final review [7, 35-68].

Summary of Included Studies

The summary of findings table – Supplementary Material 2 – contains the effect estimates of each individual study, alongside each study's characteristics (i.e., target population, sample, and methods of measuring khat use and psychiatric symptoms).

A subsequent table - Supplementary Material 3 - provides information regarding the quality of each primary study, assessed using the Newcastle-Ottawa Scale [17-18]. According to Mekuriaw et al. 2020, a score of 5/10 indicates a medium-quality study whilst a score of 6/10 indicates a high-quality study [69]. In this systematic review, the average quality score was 6.8 , with a range of 4-8. No issues due to missing data arose.

Symptoms Explored within Included Studies

The included studies explored a range of symptoms in association with khat usage. These have been grouped into the following subgroups:

- 12 studies explored symptoms of 'depression'; this subgroup includes 'depressive symptoms', 'feeling depressed', diagnoses of depression, and the presence of 'depressive episodes' within the last month
- 6 studies explored symptoms of' anxiety'; this subgroup includes 'feeling anxious', 'obsession-compulsion', 'phobic anxiety' and diagnoses of anxiety disorders
- 16 studies explored symptoms of 'psychological distress'; this subgroup includes 'psychological stress', 'psychological distress', 'mental distress', and 'stress'
- 6 studies explored symptoms of psychotic disorders; this subgroup includes 'psychotic symptoms', 'psychosis', 'paranoid ideation', 'psychoticism', and diagnoses of 'schizophrenia'
- 1 study explored psychopathy
- 5 studies explored unspecified psychiatric symptoms and disorders; this subgroup includes common mental disorders', 'psychiatric dysfunction', 'mental illness' and 'mental problems that prevent employment or household tasks'
- No studies explored bipolar disorder or mania

Meta-Analysis

The meta-analysis of the 35 included studies can be seen in Figure 2. This meta-analysis suggests that khat use is associated with an 122% increased prevalence of psychiatric symptoms (OR = 2.22, 95% CIs 1.76-2.79, $p<0.00001$). All but one of the 35 studies were scored as at least medium or high-quality when assessed using the Newcastle-Ottawa Scale; the remaining study scored 4/10 - where 5/10 is medium-quality - and had a very small weighting within the meta-analysis of 1.5%. The heterogeneity of this meta-analysis is 92%, which is classified as high [20-21].

Subgroup Analysis

The accompanying subgroup analysis - grouping studies investigating similar symptoms - shows that there is a statistically significant subgroup effect of p=0.04; usually, a p-value of less than 0.1 is regarded as a statistically significant subgroup effect [70]. This means that khat use has a varying association with the symptoms investigated.

The largest association found is between khat use and symptoms of psychological distress (OR = 2.56, 95% CIs 1.82-3.61, p<0.00001). A higher odds ratio can be found in the psychopathology category (OR = 6.10, 95% CIs 2.81-13.28), but as this is only comprised of one single study this has not been considered as a subgroup.

The two subgroups of symptoms with the lowest odds ratios are anxiety (OR = 1.68, 95% CIs 0.93-3.04) and psychotic symptoms/disorders (OR = 1.47, 95% CIs 0.93-2.30). As the confidence intervals cross the null value in both of these subgroups, this meta-analysis suggests that neither anxiety nor psychotic symptoms are associated with khat use.

Every subgroup has at least five studies to support it, a reasonable amount of supporting evidence. Most of these subgroups have a high level of heterogeneity, apart from the subgroup of unspecified psychiatric symptoms/disorders, which has a heterogeneity of 0%. Note that whilst psychopathology has been listed as a separate symptom, it is not to be considered as a subgroup as only one study investigated this.

Sensitivity Analysis

A sensitivity analysis of the meta-analysis data was conducted and can be seen in Supplementary Material 4. Each study was removed in turn and the odds ratio, confidence intervals, I^2 value and p-value recorded. Removing the depression data from Wondemagegn et al. 2017 caused the largest change in odds ratio, from 2.22 to 2.11. The I^2 value for heterogeneity remained at 91% or 92% regardless of which study was removed, and the p-value was always <0.00001.

GRADE Analysis

The meta-analysis shown in Figure 2 received a GRADE score of 'very low' [21]. As per guidance in the GRADE handbook, the score automatically starts as 'low', because the meta-analysis focuses on observational studies [21]. The score was then downgraded for the following two reasons: 'inconsistency of results' demonstrated by the high I^2 statistic, and 'indirectness of evidence' due to the differences between studies including populations investigated and methods of measuring khat use [21]. The score was not downgraded for publication bias, as despite occasional outliers, overall the funnel plot for the included studies was fairly symmetrical (see Figure 3).

DISCUSSION

Our findings suggest that khat use is associated with a 122% increased prevalence in overall psychiatric symptoms (OR = 2.22, 95% CIs 1.76-2.79, p<0.00001). When subgrouped into groups of similar symptoms, the strongest relationship is between khat use and psychological distress (OR = 2.56, 95% CIs 1.82-3.61, p<0.00001). The subgroup analyses also found that the associations between khat use and anxiety, and khat use and psychotic

symptoms/disorders is statistically insignificant (OR = 1.68, 95% CIs 0.93-3.04 and OR = 1.47, 95% CIs 0.93-2.30 respectively).

The overall prevalence of psychiatric symptoms and disorders within this systematic review is 29%. Most of the included studies were conducted in Africa, which the WHO estimates has a 5.5% prevalence of common mental disorders [71]. The prevalence of symptoms is higher in this review than expected, as many of the studies focus on populations with an increased risk of mental illness, e.g. students, migrants, combatants, refugees, prisoners and psychiatric outpatients [72-76].

This review has a strong, high-quality methodology, following all of the PRISMA guidelines for systematic reviews [14]. However, it can be argued that the evidence base surrounding khat use and psychiatric symptoms is too small to merit the pooling of data. This is reflected in the high heterogeneity of the meta-analysis conducted (I^2=92%), which suggests that the studies analysed may be too different to meaningfully compare [20]; these differences are likely to include the wide variety of populations and regions studies, the differences in khat consumption measurement, and the differences in psychiatric symptom explored. It is also reflected in the low GRADE score of the meta-analysis, however this scoring system favours experimental rather than observational data, which would be both pragmatically and ethically inappropriate when investigating substance use [77].

Despite these concerns, this review is important as it is currently the largest systematic review of khat usage and psychiatric symptoms. A 122% estimated increased prevalence of psychiatric symptoms - in khat users - is easy for laypersons to understand, eliminating their need to evaluate various studies of varying quality against each other. Furthermore, the issues highlighted by this review are important for guiding further research. Whilst the results provided by this review are unlikely to be entirely accurate, they can provide a valid estimate until the evidence base expands enough to provide a systematic review with much lower heterogeneity.

One issue in particular is the variation in measuring khat consumption between studies. This review is limited as it has included both non-dependent and dependent khat use, which are likely to have varying association with psychiatric symptoms. Many studies simply described khat users as those who had chewed within the previous week or previous month, hence it was often difficult to distinguish between current users, long-term users and dependent users. This likely contributes to the high heterogeneity of the meta-analysis of this review, and should be considered in future primary and secondary research within this field.

Another limitation of this review is that it includes both psychiatric symptoms and psychiatric disorders under the term ‘psychiatric symptoms’. Out of the 35 included studies, 28 measured psychiatric symptoms using screening tools, 5 measured psychiatric disorders using diagnostic tools, and 2 used a mixture of both screening and diagnostic tools. This may also have contributed to the high heterogeneity of the meta-analysis.

One final limitation of this review is that it cannot demonstrate causation between the two variables. It would be useful for future research to include cohort studies Many researchers hypothesise that khat use is the cause of psychiatric symptoms, with its active ingredients distorting the brain’s cytoarchitecture and therefore increasing one’s vulnerability to mental illness [78-80]. Contrastingly, other researchers suggest that those with mental illness are more likely to chew khat as an attempt to self-medicate their symptoms [81]. Long-term cohort studies would be able to assess which variable predisposes the other, monitor psychiatric symptoms that take time to manifest, and investigate how the prevalence of psychiatric symptoms changes as the duration of khat use increases.

CONCLUSIONS

This review combines 35 cross-sectional studies in the field of khat use, and using meta-analysis suggests that khat use is associated with a 122% increase in the prevalence of psychiatric symptoms, particularly psychiatric distress. The high heterogeneity of the meta-analysis is likely due to the wide variation between the studies within the evidence base. To perform a more accurate systematic review, further primary studies are needed with standardised measurements of variables, particularly khat consumption. Furthermore, the evidence base is unclear about causality within this relationship, another important focus for future research.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr Keith Brain (University of Birmingham), who originally suggested the topic idea, and Dr Jesse Young (University of Melbourne) for his feedback and enthusiasm towards the project. The authors would also like to thank the library team at the University of Birmingham for their help with the literature search. Finally, the authors would like to thank the Leslie James Topham fund (University of Birmingham Medical School) for providing funding towards living costs whilst this research was conducted.

COMPETING INTERESTS

No competing interests.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

ETHICAL APPROVAL

This review did not require ethical approval as no primary data was collected.

CONTRIBUTORSHIP STATEMENT

BE planned the review and created the protocol. BE and NA completed the independent literature searches. BE created the summary of findings table, and completed the meta-analyses including sensitivity and subgroup analyses. BE and NA independently assessed the quality of the included studies using the Newcastle-Ottawa Scale, and BE completed the GRADE scoring. BE wrote the systematic review.

DATA SHARING STATEMENT

Raw data can be found within each primary research study using the references provided.

REFERENCES

1. European Monitoring Centre for Drugs and Drug Addiction. Khat drug profile (date unknown). https://www.emcdda.europa.eu/publications/drug-profiles/khat/de [Accessed 1 December 2020].
2. Wabe, NT. Chemistry, pharmacology, and toxicology of khat (Catha edulis forsk): a review. Addict Health (2011). 3(3): 137-149. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905534/
3. World Health Organisation. Khat chewing in Yemen: turning over a new leaf (2008). https://www.who.int/bulletin/volumes/86/10/08-011008/en/ [Accessed 1 December 2020].
4. Al-Juhaishi T, Al-Kindi S, Gehani A. Khat: a widely used drug of abuse in the horn of Africa and the Arabian Peninsula: review of literature. Qatar Med J (2013). 2012(2):1-6. Doi: 10.5339/qmj.2012.2.5
5. Cochrane L, O-Regan D. Legal harvest and illegal trade: trends, challenges, and options in khat production in Ethiopia. Int J Drug Policy (2016). 30(1): 27-34. Doi: 10.1016/j.drugpo.2016.02.009
6. Douglas H, Boyle M, Lintzeris N. The health impacts of khat: a qualitative study among Somali-Australians. Med J Aust (2011). 195(11): 666-669. Doi: 10.5694/mja11.10166
7. Widmann M, Warsame AH, Mikulica J, et al. Khat use, PTSD, and psychotic symptoms among Somali refugees in Nairobi – a pilot study. Front Public Health (2014). 2(1): 71. Doi: 10.3389/fpubh.2014.00071
8. Cox G, Rampes H. Adverse effects of khat: a review. Adv Psychiatr Treat (2003). 9(6): 456-463. Doi: doi:10.1192/apt.9.6.456
9. Hassan NAGM, Gunaid AA, Murray-Lyon IM. Khat (catha edulis): health aspects of khat chewing. East Mediterr Health J (2007). 13(3): 706-718. Available from: https://pubmed.ncbi.nlm.nih.gov/17687845/
10. Young JT, Butt J, Hersi A, et al. Khat dependence, use patterns, and health consequences in Australia: an exploratory study. J Stud Alcohol Drugs (2016). 77(2): 343-348. Doi: 10.15288/jsad.2016.77.343
11. Omar YS, Jenkins A, Altena MR, et al. Khat use: what is the problem and what can be done? Biomed Res Int (2015). Article ID: 472302. Doi: 10.1155/2015/472302
12. Anderson DM, Carrier NCM. Khat: social harms and legislation. (2011). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/116260/occ95.pdf
13. Edwards B, Atkins N. Exploring the association between khat use and psychiatric symptoms: a systematic review. (2021). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=224510
14. PRISMA. PRISMA checklist. (2021). http://www.prisma-statement.org/PRISMAStatement/Checklist [Accessed 3 May 2021].
15. Medical Subject Headings 2021. US National Library of Medicine (2021). https://meshb.nlm.nih.gov/search [Accessed 19 September].

16. Sanati A. Does suicide always indicate a mental illness? London J Prim Care (2009). 2(2): 93-94. Doi: 10.1080/17571472.2009.11493259
17. Newcastle-Ottawa Quality Assessment Scale. The Ottawa Hospital (2021). http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 19 September 2021].
18. Modesti P, Reboldi G, Cappuccio F, et al. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. PLoS One (2016). 11(1): e0147601. Doi: 10.1371/journal.pone.0147601
19. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al. (editors) Cochrane handbook for systematic reviews of interventions. Version 6.2. Cochrane, 2021. Available from: www.training.cochrane.org/handbook [Accessed 5 November 2021].
20. Sambunjak D, Cumpston M, Watts C. Module 6: analysing the data. In: Cochrane Interactive Learning: Conducting an intervention review. Cochrane, 2017. Available from: https://training.cochrane.org/interactivelearning/module-6-analysing-data [Accessed 5 November 2021].
21. Schünemann H, Brozek J, Guyaa G, et al. The GRADE handbook (2013). https://gdt.gradepro.org/app/handbook/handbook.html#h.svwngs6pm0f2 [Accessed 2 May 2021].
22. Nakajima M, Hoffman R, al-Absi M. Level of khat dependence, use patterns, and psychosocial correlates in Yemen: a cross-sectional investigation. East Mediterr Health J (2017). 23(3): 161-167. Doi: 10.26719/2017.23.3.161
23. al'Absi M, Khalil NS, Habori MA et al. Effects of chronic khat use on cardiovascular, adrenocortical, and psychological responses to stress in men and women. Am J Addict (2018). 22(2): 99-107. Doi: 10.1111/j.1521-0391.2013.00302.x
24. Boka A, Alemu M, Fantu A. Magnitude of substance induced psychosis among adolescents in amanuel mental specialised hospital Addis Ababa, Ethiopia. J Drug Alcohol Res (2021). 10(6): 236126. Available from: https://www.ashdin.com/articles/magnitude-of-substance-induced-psychosis-among-adolescents-in-amanuel-mental-specialized-hospital-addis-ababa-ethiopia-81031.html
25. Hassen MT, Soboka M, Widmann et al. Khat use patterns, associated features, and psychological problems in a khat-treatment-seeking student sample of Jimma University, southwestern Ethiopia. Front Public Health (2021). 9(1):645980. Doi: 10.3389/fpubh.2021.645980
26. Bahhawi TA, Albasheer OB, Makeen AM et al. Depression, anxiety, and stress and their association with khat use: a cross-sectional study among Jazan University students, Saudi Arabia. Neurospcyhiatr Dis Treat (2018). 14(1): 2755-2761. Doi: 10.2147/NDT.S182744
27. Nakajima M, Jebena MG, Taha M et al. Correlates of khat use during pregnancy: a cross-sectional study. Addict Behav (2017). 73(1): 178-184. Doi: 10.1016/j.addbeh.2017.05.008
28. Mains D, Hadley C, Tessema F. Chewing over the future: khat consumption, anxiety, depression and time among young men in Jimma, Ethiopia. Cult Med Psychiatry (2012). 37(1): 111-130. Doi: 10.1007/s11013-012-9292-9
29. Bhui K, Warfa N. Trauma, khat and common psychotic symptoms among Somali immigrants: a quantitative study. J Ethnopharmacol (2010). 132(3): 549-553. Doi: 10.1016/j.jep.2010.07.027

30. Woods D. Mental health and wellbeing of Somalis in the United Kingdom. (2004). Available from: https://www.semanticscholar.org/paper/Mental-health-and-well-being-of-Somalis-in-the-Woods/2c4a853a72d029c785575880fcf8a0870d7d0b7c
31. Dawud B, Yeshigeta E, Negash A, et al. Substance use disorders and associated factors among adult psychiatric patients in Jimma Town, Southwest Ethiopia, 2017, community-based cross-sectional study. Clin Med Insights Psychiatry (2017). 12(1). Doi: 10.1177/1179557321989699
32. Alebachew W, Semahegn A, Ali T et al. Prevalence, associated factors and consequences of substance use among health and medical science students of Haramaya University, eastern Ethiopia, 2018: a cross-sectional study. BMC Psychiatry (2019). 19(1): 343. Doi: 10.1186/s12888-019-2340-z
33. Yitayih Y, Abera M, Tesfaye E, et al. Substance use disorder and associated factors among prisoners in a correctional institution in Jimma, Southwest Ethiopia: a cross-sectional study. BMC Psychiatry (2018). 18(1): 314. Doi: 10.1186/s12888-018-1901-x
34. Kroll J, Yusuf AI, Fujiwara K. Psychoses, PTSD, and depression in Somali refugees in Minnesota. Soc Psychiatry Psychiatr Epidemiol (2011). 6(1): 481-493. Doi: 10.1007/s00127-010-0216-0
35. Ahmed AG, Emad S. The khat users: a study of khat chewing in Liverpool's Somali men. Med Sci Law (1998). 38(2): 165-169. Doi: 10.1177/002580249803800215
36. Belew M. The magnitude of khat use and its association with health, nutrition and socioeconomic status. Ethiop Med J (2000). 38(1): 11-26. Available from: https://pubmed.ncbi.nlm.nih.gov/11144876/
37. Numan N. Exploration of adverse psychological symptoms in Yemeni khat users by the Symptoms Checklist-90 (SCL-90). Addiction (2004). 99(1): 61-65. Doi: 10.1111/j.1360-0443.2004.00570.x
38. Odenwald M, Neuner F, Schauer M, et al. Khat use as a risk factor for psychotic disorders: a cross-sectional and case-control study in Somalia. BMC Med (2005). 3:5. Doi: https://doi.org/10.1186/1741-7015-3-5
39. Deyessa N, Berhane Y, Alem A, et al. Depression among women in rural Ethiopia as related to socioeconomic factors: a community-based study on women in reproductive age groups. Scand J Public Health (2008). 36(6): 589-597. Doi: 10.1177/1403494808086976
40. Odenwald M, Hinkel H, Schauer E, et al. Use of khat and posttraumatic stress disorder as risk factors for psychotic symptoms: a study of Somali combatants. Soc Sci Med (2009). 69(7): 1040-1048. Doi: 10.1016/j.socscimed.2009.07.020
41. Damena T, Mossie A, Tesfaye M. Khat chewing and mental distress: a community based study, in Jimma City, Southwestern Ethiopia. Ethiop J Health Sci (2011). 21(1): 37-45. Doi: 10.4314/ejhs.v21i1.69042
42. Tulloch AD, Frayn E, Craig TKJ, et al. Khat use among Somali mental health service users in South London. Soc Psychiatry Psychiatr Epidemiol (2012). 47(1): 1649-1656. Doi: 10.1007/s00127-011-0471-8
43. Dessie Y, Ebrahim J, Awoke T. Mental distress among university students in Ethiopia: a cross sectional survey. Pan Afr Med J (2013). 15(1): 95. Doi: 10.11604/pamj.2013.15.95.2173
44. Fekadu W, Haregwoin M, Kibrom H, et al. Magnitude of mental illness and associated factors among holy water users at Entoto St Mary Church, Addis Ababa, Ethiopia, 2014. J Psychiatry (2014). 18(1): 285. Doi: 10.4172/2378-5756.1000285

45. Dachew B, Bifftu B, Tadesse B. Khat use and its determinants among university students in northwest Ethiopia: a multivariable analysis. Int J Med Sci Public Health (2014). 4(3): 1. Doi: 10.5455/ijmsph.2015.1809201460
46. Soboka M, Tesfaye M, Feyissa GT, et al. Khat use in people living with HIV: a facility-based cross-sectional survey from South West Ethiopia. BMC Psychiatry (2015). 15(1): 69. Doi: https://doi.org/10.1186/s12888-015-0446-5
47. Zenebe Y, Feyissa GT, Krahl W. Khat use in persons with mental illness in Southwest Ethiopia: a cross-sectional study. J Addict Res Ther (2015). 6(1): 3. Doi: 10.4172/2155-6105.1000242
48. El-Setouhy M, Alsanosy RM, Alsharqi A, et al. Khat dependency and psychophysical symptoms among chewers in Jazan Region, Kingdom of Saudi Arabia. BioMed Res Int (2016). 2016(1): 2642506. Doi: 10.1155/2016/2642506
49. Hersi L, Tesfay K, Gesesew H, et al. Mental distress and associated factors among undergraduate students at the University of Hargeisa, Somaliland: a cross-sectional study. Int J Ment Health Syst (2017). 11(1): 39. Doi: 10.1186/s13033-017-0146-2
50. Hunduma G, Girma M, Digaffe T, et al. Prevalence and determinants of common mental illness among adult residents of Harari Regional State, eastern Ethiopia. Pan Afr Med J (2017). 28(1): 262. Doi: 10.11604/pamj.2017.28.262.12508
51. Kerebih H, Ajaeb M, Hailesilassie H. Common mental disorders among medical students in Jimma University, Southwest Ethiopia. Afr Health Sci (2017). 17(3): 884-851. Doi: 10.4314/ahs.v17i3.27
52. Mossie A, Kindu D, Negash A. Prevalence and severity of depression and its association with substance use in Jimma Town, southwest Ethiopia. Depress Res Treat (2016). 2016(1): 3460462. Doi: 10.1155/2016/3460462
53. 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(1): 5. Doi: https://doi.org/10.1186/s13033-016-0108-0
54. Tariku G, Zerihun A, Bisrat Z, et al. Mental distress and its association factors among students of Mizam Aman Health Science College, Ethiopia. J Med Sci (2017). 17(2): 61-67. Doi: 10.3923/jms.2017.61.67
55. 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(1): 7427892. Doi: 10.1155/2017/7427892
56. Yeshaw Y, Mossie A. Depression, anxiety, stress, and their associated factors among Jimma University staff, Jimma, Southwest Ethiopia, 2016: a cross-sectional study. Neuropsychiatr Dis Treat (2017). 13(1): 2803-2812. Doi: 10.2147/NDT.S150444
57. Bedaso A, Kediro G, Yeneabat T. Factors associated with depression among prisoners in southern Ethiopia: a cross-sectional study. BMC Res Notes (2018). 11(1): 637. Doi: 10.1186/s13104-018-3745-3
58. Adraro W, Kerebih H, Tesema W, et al. Nearly three in every five prisoners experience common mental disorders (CMDs) in Jimma correctional institution: south-west Ethiopia. BMC Public Health (2019). 19(1): 1559. Doi: 10.1186/s12889-019-7879-6
59. Ongeri L, Kirui F, Muniu E, et al. Khat use and psychotic symptoms in a rural khat growing population in Kenya: a household survey. BMC Psychiatry (2019). 19(1): 137. Doi: 10.1186/s12888-019-2118-3

60. Atnafie SA, Muluneh NY, Getahun KA, et al. Depression, anxiety, stress, and associated factors among khat chewers in Amhara Region, Northwest Ethiopia. Depress Res and Treat (2020). 2020(1): 7934892. Doi: 10.1155/2020/7934892
61. Hajure M, Dibaba B, Shemsu S, et al. Psychological distress among health care workers in health facilities of Mettu Town during COVID-19 outbreak, southwest Ethiopia, 2020. Front Psychiatry (2021). 10(1): 740. Doi: 10.3389/fpsyt.2021.574671
62. Hambisa M, Derese A, Abdeta T. Depressive symptoms among Haramaya University students in Ethiopia: a cross-sectional study. Depress Res Treat (2020). 2020(1): 5027918. Doi: 10.1155/2020/5027918
63. Kelemu R, Kahsay A, Ahmed K. Prevalence of mental distress and associated factors among Samara University students, northeast Ethiopia. Depress Res Treat (2020). 2020(1): 7836296. Doi: 10.1155/2020/7836296
64. Mekuriaw B, Belayneh Z, Yitayih Y. Magnitude of khat use and associated factors among women attending antenatal care in Gedeo zone health centers, southern Ethiopia: a facility based cross sectional study. BMC Public Health (2020). 20(1): 110. Doi: https://doi.org/10.1186/s12889-019-8026-0
65. Yitiyah Y, Soboka M, Tesfaye E, et al. A cross-sectional study of psychopathy and khat abuse among prisoners in the correctional institution in Jimma, Ethiopia. PLoS One (2020). 15(1): e0227405. Doi: 10.1371/journal.pone.0227405
66. Haile K, Sahile A. Depressive symptoms in primary health care attendees in Sebeta Town, Ethiopia: prevalence, associated factors, and detection by health workers. Sci Prog (2021). 104(3): 1-15. Doi: 10.1177/00368504211034304
67. Hambisa S, Siraj J, Mesafint G, Yimam M. Assessment of psychological distress and associated factors among hospitalised patients during COVID-19 pandemic at selected hospitals in Southwest Ethiopia. Neuropsychiatr Dis Treat (2021). 2021(17): 885-892. Doi: 10.2147/NDT.S297460
68. Melaku L, Mossie A, Negash A. Stress among medical students and its association with substance use and academic performance. J Biomed Educ (2015). 2015(1): 149509. Doi: 10.1155/2015/149509
69. Mekuriaw B, Zegeye A, Molla A, et al. Prevalence of common mental disorder and its association with khat chewing among Ethiopian college students: a systematic review and meta-analysis. Psychiatry J (2020). 2020(1): 1462141. Doi: 10.1155/2020/1462141
70. Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: a tutorial. Clin Epidemiology Glob Health (2019). 7(2): 192-198. Doi: 10.1016/j.cegh.2018.05.005
71. World Health Organisation. Depression and other common mental disorders; global health estimates (2017). Available from: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf [Accessed 5 November 2021].
72. Bantjes J, Lochner C, Saal W, et al. Prevalence and sociodemographic correlates of common mental disorders among first-year university students in post-apartheid South Africa: implications for a public mental health approach to student wellness. BMC Public Health (2019). 19(1): 922. Doi: 10.1186/s12889-019-7218-y
73. Mental Health Foundation. Mental health statistics: refugees and asylum seekers (no date). Available from: https://www.mentalhealth.org.uk/statistics/mental-health-statistics-refugees-and-asylum-seekers [Accessed 5 November 2021].
74. Public Health England. Mental health: migrant health guide (2017). Available from: https://www.gov.uk/guidance/mental-health-migrant-health-guide [Accessed 5 November 2021].

75. Murthy RS, Lakshminarayana R. Mental health consequences of war: a brief review of research findings. World J Psychiatry (2006). 5(1): 25-30. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472271/ [Accessed 5 November 2021].
76. Durcan G, Zwemstra JC. Mental health in prison (no date). Available from: https://www.euro.who.int/__data/assets/pdf_file/0017/249200/Prisons-and-Health,-11-Mental-health-in-prison.pdf [Accessed 5 November 2021].
77. Price PC, Jhangiani R, Chiang IA, et al. Chapter 6: Nonexperimental research. In: Price PC, Jhangiani R, Chiang IA, Leighton DC, Cuttler C (editors). Research methods in psychology. 3rd ed. 2017. Available from: https://opentext.wsu.edu/carriecuttler/ [Accessed 5 November 2021].
78. Echoru I, Bukenya E, Masilili G, et al. Khat distorts the prefrontal cortex histology and function of adult wistar rats. Anat J Afr (2018). 7(1): 1121-1131. Doi: 10.4314/aja.v7i1.169485
79. Fluyau D, Mitra P, Lorthe K. Antipsychotics for amphetamine psychosis: a systematic review. Front Psychiatry (2019). 10(1): 740. Doi: 10.3389/fpsyt.2019.00740
80. Mullen J, Richards J, Crawford A. "Amphetamine related psychiatric disorders", In: Statpearls. Florida, USA: Statpearls Publishing (2021).
81. Odenwald M, al'Absi M. Khat use and related addiction, mental health and physical disorders: the need to address a growing risk. East Mediterr Health J (2017). 23(3): 236-244. Doi: 10.26719/2017.23.3.236

Legends:

Figure 1: PRISMA flow chart of included and excluded studies

Figure 2: Meta-analysis of included studies

Figure 3: funnel plot of included studies

Figure 1: PRISMA flow chart of included and excluded studies

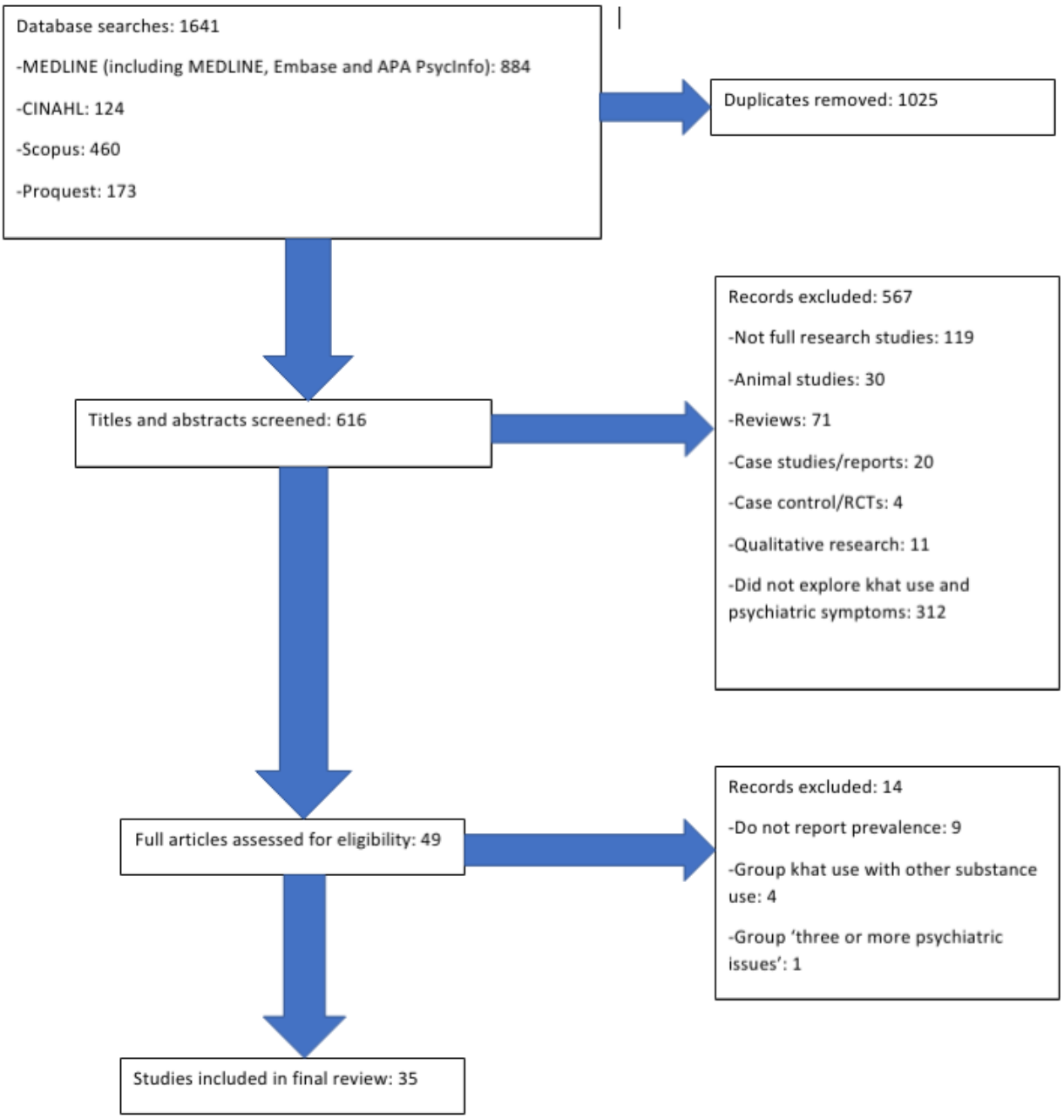


Figure 2: Meta-analysis of included studies

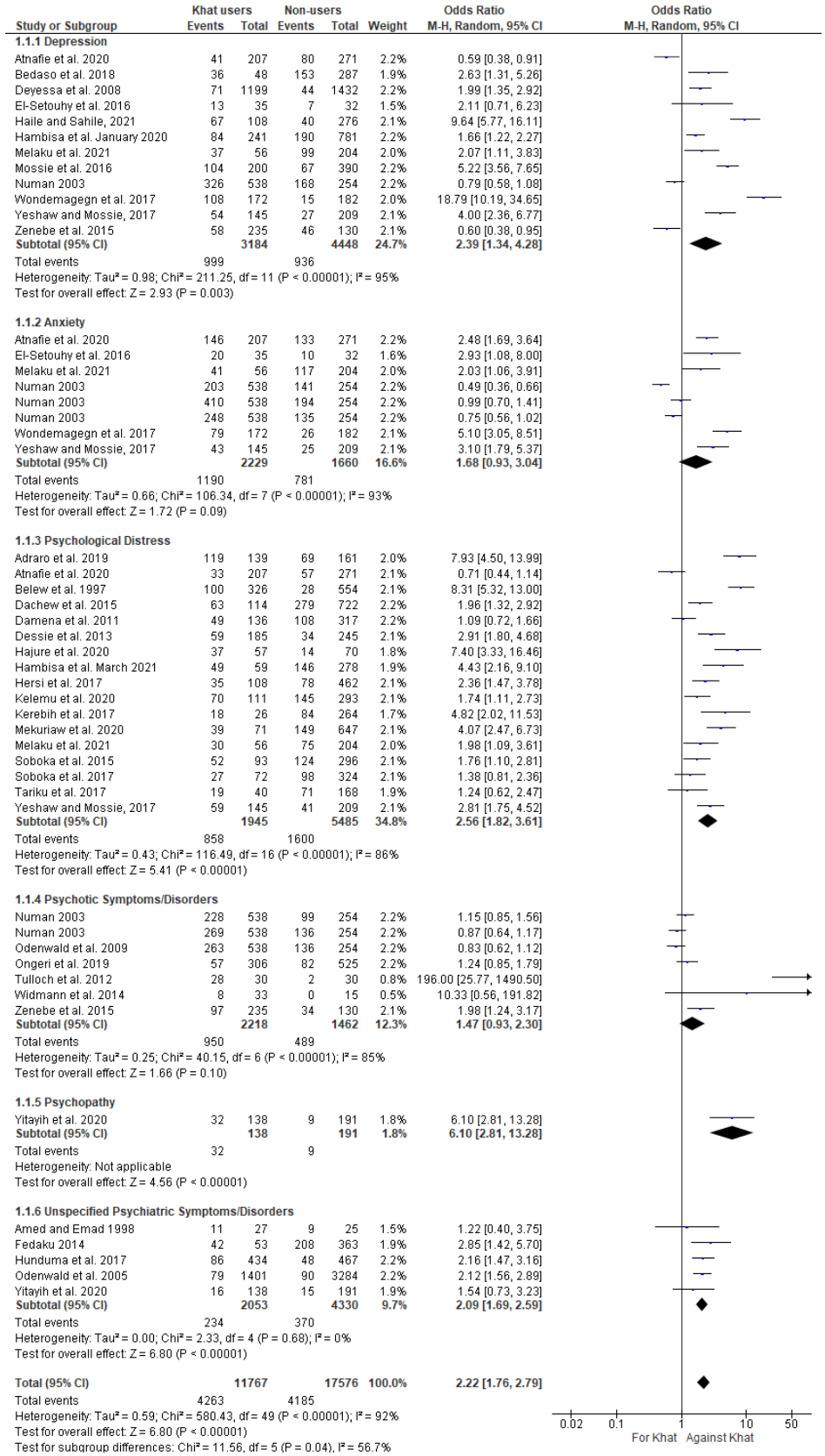
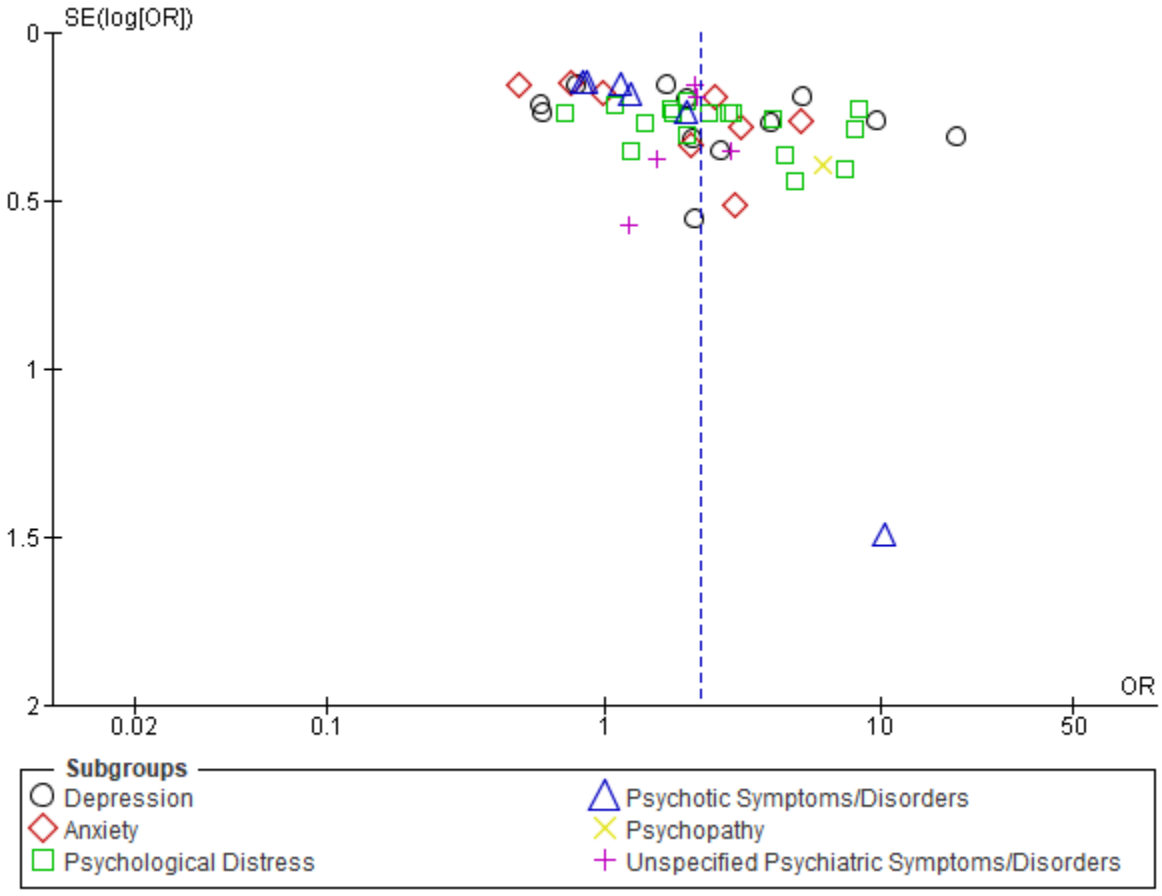


Figure 3: funnel plot of included studies



Supplementary Material 1: Search strategies

Ovid MEDLINE, Embase and APA PsycInfo	**Search Strategy**
#1	Khat.ab or khat.ti or qat.ab or qat.ti or qaad.ab or qaad.ti or catha.ab or catha.ti or miraa.ab or miraa.ti or mairungi.ab or mairungi.ti
#2	Depression.ab or depression.ti or anxiety.ab or anxiety.ti or bipolar.ab or bipolar.ti or mania.ab or mania.ti or psych*.ab or psych*.ti or schiz*.ab or schiz*.ti or mental.ab or mental.ti or hallucinations.ab or hallucinations.ti or delusions.ab or delusions.ti
#3	1 and 2
CINAHL	
#1	TI khat OR AB khat OR TI qat OR AB qat OR TI qaad OR AB qaad OR TI catha OR AB catha OR TI miraa OR AB miraa OR TI mairungi OR AB mairungi
#2	TI depression OR AB depression OR TI anxiety OR AB anxiety OR TI bipolar OR AB bipolar OR TI mania OR AB mania OR TI psych* OR AB psych* OR TI schiz* OR AB schiz*
#3	TI mental OR AB mental OR TI hallucinations OR AB hallucinations OR TI delusions OR AB delusions
#4	2 OR 3
#5	1 AND 4
Scopus	
#1	(TITLE (khat) OR ABS (khat) OR TITLE (qat) OR ABS (qat) OR TITLE (qaad) OR ABS (qaad) OR TITLE (catha) OR ABS (catha) OR TITLE (miraa) OR ABS (miraa) OR TITLE (mairungi) OR ABS (mairungi))
#2	(TITLE (depression) OR ABS (depression) OR TITLE (anxiety) OR ABS (anxiety) OR TITLE (bipolar) OR ABS (bipolar) OR TITLE (mania) OR ABS (mania) OR TITLE (psych*) OR ABS (psych*) OR TITLE (schiz*) OR ABS (schiz*) OR TITLE (mental) OR ABS (mental) OR TITLE (hallucinations) OR ABS (hallucinations) OR TITLE (delusions) OR ABS (delusions))

#3	1 AND 2
Proquest	
#1	ab(khat) OR ti(khat) OR ab(qat) OR ti(qat) OR ab(qaad) OR ti(qaad) OR ab(catha) OR ti(catha) OR ab(miraa) OR ti(miraa)
#2	ab(mairungi) OR ti(mairungi)
#3	ab(depression) OR ti(depression) OR ab(anxiety) OR ti(anxiety) OR ab(bipolar) OR ti(bipolar) OR ab(mania) OR ti(mania) OR ab(psych*) OR ti(psych*)
#4	ab(schiz*) OR ti(schiz*) OR ab(mental) OR ti(mental) OR ab(hallucinations) OR ti(hallucinations) OR ab(delusions) OR ti(delusions)
#5	1 OR 2
#6	3 OR 4
#7	5 AND 6 (limit: full texts only)

Supplementary Material 2: Summary of Findings Table

Study	Population	Sample	Criteria for 'Khat User'	Psychiatric Measure*	Results
Ahmed and Emad 1998 [35]	Somali immigrants living in Liverpool	Convenience sample of 52 Khat users = 27	Unspecified	GHQ-28	- 11/27 khat users experienced psychiatric dysfunction, compared to 9/25 non-users (p=0.72)
Belew et al. 2000 [36]	Individuals aged 15+ from a specified community in Ethiopia	Random sample of 1200 participants Khat users = 326	Anyone who has chewed khat within the last 30 days	SRQ	- 100/326 khat-users experienced mental distress, compared to 28/554 non-users (OR = 8.31, 5.20-13.31, p=0.00) - 89/294 long-term users (over 2 years) experienced mental distress, compared to 28/554 never-users (OR = 8.14, 5.06-13.17, p=0.00)
Numan 2003 [37]	Yemeni population	Random sample of 800 participants Khat users = 67.9%	Frequent use – 4-6 days a week Heavy use – use everyday	SCL-90	- No significant differences (at p<0.05) in psychiatric symptoms: obsession-compulsion, depression, anxiety, paranoid ideation, psychoticism - Khat users had less phobic anxiety (37.7% vs 55.5%, p<0.05)
Odenwald et al. 2005 [38]	'General population' of Somalia	Random sample of 4854 Khat users = 78% of those with psychiatric issues, 4% of those without	Number of bundles in previous week recorded	CIDI, PANSS	- More positive screened individuals (mental problems severe enough to prevent employment or household tasks) chewed khat than negative screened individuals (46.6% vs 29.9%, p<0.001)
Deyessa et al. 2008 [39]	Women of reproductive age in rural Ethiopia	Random sample of 3200 Khat users = 40%	At least once per week	CIDI, ICD-10	- 5.9% of regular users had had a depressive episode in the last 12 months, compared to 3.1% of non-regular users (less than once per month) and 3.6% of non-users - AOR for regular vs non-users is 1.35 (0.92-1.99)

Odenwald et al. 2009 [40]	Armed combatants in Somali	8124 armed individuals (not random as still in conflict at time of study) Khat users = 36.4%	Anyone who has chewed khat within the last week	CIDI	- 8.9% of khat users experienced paranoid ideation compared to 2.6% of non-users
Damena et al. 2011 [41]	Adults in Jimma City, Ethiopia	Random sample of 1308 Khat users = 38%	Uses WHO-validated substance abuse questionnaire, but unsure what is classified as 'khat user'	SRQ-20	- 49/136 long-term khat chewers experienced mental distress, compared to 108/317 short-term khat chewers (less than two years), and 153/747 non-users
Tulloch et al. 2012 [42]	Adult Somali khat users living in South London	Secondary data based on 172 eligible Somali mental health patients Khat users = 47%	Anyone who has chewed khat within the last year	Diagnosis provided by service records	- 28/30 khat users experienced psychosis compared to 2/30 non-users ($p<0.001$)
Dessie et al. 2013 [43]	Students in Ethiopia	Random sample of 413 Khat users = 43%	Anyone who has ever used khat	SRQ-20	- 59/185 khat users experienced mental distress compared to 34/245 non-users (AOR = 2.23, 1.14-4.35, $p<0.05$)
Fekadu 2014 [44]	Holy water users from Entoto St Mary Church, Ethiopia	409 individuals selected using systematic random sampling Daily khat users = 12.7%	Khat use recorded as 'never' or 'daily', although no indication of the duration of daily usage	BPRS	- 42/53 daily khat-users experienced symptoms of mental illness compared to 208/363 non-users (AOR = 2.85, 1.42-5.70)
Widmann et al. 2014 [7]	Male Somali refugees living in a disadvantaged	Convenience sample of 33 users and 15 comparable non-users	SDS	CIDI, MINI	- 24% of khat users had psychotic symptoms compared to 0% of non-chewers ($p=0.044$)

	urban settlement in Kenya	Khat users = 69%			
Dachew et al. 2015 [45]	Undergraduate students from Gondar University, Ethiopia	872 patients selected using stratified, random sampling Current khat users = 16%	Questionnaire identifying 'current use'	SRQ-20	- 63/114 current khat users had mental distress, compared to 279/722 non-users (OR=1.96, 1.32-2.92, p=0.02)
Soboka et al. 2015 [46]	HIV patients at a specified facility in South West Ethiopia	All eligible adults invited to participate Sample of 389 Khat users = 93	Anyone who has chewed khat within the last month	K-6	- 52/93 khat-users experienced psychological distress, compared to 124/296 non-users (OR = 1.76, 1.10-2.82)
Zenebe et al. 2015 [47]	Psychiatric outpatients in Ethiopia	365 adult psychiatric outpatients of a specified hospital within 2-week study period Khat use = 64.4%	Anyone who has used khat within the last 30 days	Psychiatric diagnosis from psychiatric records	- 58/235 khat users had a major depressive disorder compared to 46/130 non-users (AOR = 1.43, 0.74-2.77) - 97/235 khat users had schizophrenia compared to 34/130 non-users (AOR = 0.87, 0.45-1.68)
El-Setouhy et al. 2016 [48]	Jazan region of Saudi Arabia	Volunteer sample of 70 males Khat dependent = 52.2%	SDS	Q16	- 13/35 dependent users felt depressed compared to 7/32 non-dependent users (OR = 2.30, 0.7-6.8) - 20/35 dependent users felt anxious compared to 10/32 non-dependent users (OR = 3.50, 1.2-10.0)
Hersi et al. 2017 [49]	Students in Somaliland	Stratified random sample of 570 Khat users = 19%	Use in last 12 months	SRQ-20	- 32% of khat users experienced psychological distress, compared to 17% of non-users (AOR = 2.87, 1.26-6.56)
Hunduma et al. 2017 [50]	Adults in Ethiopia	Random sample of 968 Khat users = 48%	Khat use in last 3 months	SRQ-20	- 86/434 khat users had a common mental disorder, compared to 48/467 non-users (OR = 2.16, 1.47-3.16)

Kerebih et al. 2017 [51]	Medical students in Ethiopia	Stratified random sample of 305 Khat users = 9%	Anyone who has ever used khat	SRQ-20	- 18/26 khat users experienced mental distress compared to 84/264 non-users (AOR = 6.91, 1.88-25.42, p=0.004)
Mossie et al. 2016 [52]	Adults in Ethiopia	Random sample of 650 Khat users = 34%	Khat use within the last 30 days	BDI	- 104/200 khat users had depression compared to 67/390 non-users (AOR = 10.07, 5.56-18.25)
Soboka et al. 2017 [53]	Adults with hypertension at a specified clinic in South West Ethiopia	All eligible adults invited to participate Sample of 396 Khat users = 79	Anyone who has chewed khat within the last month	K-6	- 27/72 current khat-users experienced psychological distress, compared to 98/324 non-users
Tariku et al. 2017 [54]	Students at a health sciences college in Ethiopia	Stratified random sample of 317 Khat users = 13%	Anyone who has ever used khat	Not specified	- 19/40 khat users experienced mental distress compared to 71/168 non-users (AOR = 2.29, 1.04-5.04)
Wondemagegn et al. 2017 [55]	Adolescents and adults in Nekemte town, West Ethiopia	Random sample of 359 participants Khat users = 49%	Anyone who has chewed khat within the last 30 days	DSM-IV	- 108/172 users experienced depression compared to 15/182 non-users (AOR = 25.36, 12.13-53.05, p=0.000) - 79/172 users experienced anxiety compared to 26/182 non-users (AOR = 5.49, 3.04-9.96, p=0.000)
Yeshaw and Mossie 2017 [56]	Staff of Jimma University, Ethiopia	Random sample of 363 Khat users = 41%	Anyone who has ever used khat	DASS-21	- 54/145 khat users had depression compared to 27/209 non-users (AOR = 4.99, 2.57-9.69) - 43/145 khat users had anxiety compared to 25/209 non-users (AOR = 2.94, 1.52-5.66) - 59/145 khat users had psychological stress compared to 41/209 non-users (AOR = 2.78, 1.49-5.21)
Bedaso et al. 2018 [57]	Prisoners in Ethiopia	Random sample of 335 Khat users = 14%	Unspecified, but appears to be chewing khat before incarceration	PHQ-9	- 36/48 khat users had depression, compared to 153/287 non-users (AOR = 2.48, 1.05-5.86, p=0.039)
Adraro et al. 2019 [58]	Prisoners in Ethiopia	Random sample of 300 Khat users = 46%	Anyone who has ever used khat	SRQ-20	- 119/139 khat users experienced mental distress, compared to 69/161 non-users (AOR = 4.33, 2.02-9.27, p<0.001)

Ongeri et al. 2019 [59]	Khat-growing regions of Kenya	Random sample of 831 individuals aged 10+ Khat users = 36.8%	Unspecified	PSQ	- 18.6% of khat users experienced at least one psychotic symptom compared to 15.6% of non-users (p=0.26)
Atnafie et al. 2020 [60]	Khat chewers in Amhara region of Ethiopia	Convenience sample of 508 participants Khat dependent = 43%	SDS	DASS-21	- 33/207 khat-dependent users experienced stress compared to 57/271 non-dependent users (AOR = 1.70, 0.98-2.95) - 146/207 khat-dependent users experienced anxiety compared to 133/271 non-dependent users (AOR = 2.47, 1.57-3.81) - 41/207 khat-dependent users experienced depression compared to 80/271 non-users (AOR = 6.28, 1.67-23.61)
Hajure et al. 2020 [61]	Healthcare providers in Ethiopia	Convenience sample of 127 Khat users = 45%	Khat use in last three months	IES-R	- 37/57 khat users experienced psychological stress, compared to 14/70 non-users (AOR = 5.74, 1.83-18.1, p<0.001)
Hambisa et al. 2020 [62]	Students in Ethiopia	Random sample of 1022 Khat users = 24%	Khat use within last month	BDI	- 84/241 khat users had depressive symptoms compared to 190/781 non-users (OR = 1.60, 1.22-2.27)
Kelemu et al. 2020 [63]	Students in Ethiopia	Random sample of 404 Khat users = 27%	Anyone who has ever used khat	SRQ-20	- 70/111 khat users experienced mental distress, compared to 145/293 non-users (AOR = 3.09, 1.74-5.50)
Mekuriaw et al. 2020 [64]	Pregnant women in Ethiopia	Random sample of 845 Khat users = 11%	Investigates usage but unclear what quantifies a 'current khat user'	SRQ-20	- 39/71 khat users experienced mental distress, compared to 149/647 non-users (AOR = 3.57, 2.06-6.18, p=0.001)
Yitayih et al. 2020 [65]	Prisoners in a correctional	Random sample of 336 Khat users = 138	DAST-10	PCL:SV	- 32/138 khat users met the criteria for psychopathy, compared to 9/191 non-users

	institution in Jimma, Ethiopia				- 16/138 khat users had mental illness, compared to 15/191 non-users
Haile and Sahile, 2021 [66]	Adult primary healthcare attendees in Ethiopia	Stratified and systematic random sample of 384 Khat users = 39%	Unspecified	PHQ-9	- 67/108 khat users had depressive symptoms, compared to 40/276 non-users (AOR = 5.43, 2.55-11.56, p<0.01)
Hambisa et al. 2021 [67]	Hospitalised patients in Ethiopia	Systematic sample of 337 Khat users = 18%	Unspecified; discusses 'current khat use' and 'khat use in the previous three months'	K10	- 49/59 khat users experienced psychological distress, compared to 146/278 non-users (AOR = 4.16, 1.67-10.35)
Melaku et al. 2021 [68]	Medical students in Ethiopia	Systematic random sample of 260 Khat users = 22%	Anyone who has ever used khat	DASS-21	- 37/56 khat users had depression, compared to 99/204 non-users (OR = 2.07, 1.11-3.83) - 41/56 khat users had anxiety, compared to 117/204 non-users (OR = 2.03, 1.06-3.91) - 30/56 khat users had psychological stress, compared to 75/204 non-users (OR = 1.99, 1.09-3.61)

*List of abbreviated screening tools: GHQ-28 (General Health Questionnaire-28, for mental disorders), SRQ-20 (Self-Reporting Questionnaire - 20 items, for mental distress), SCL-90 (Symptom Checklist - 90 items, for psychological symptoms), CIDI (Composite International Diagnostic Interview - for psychiatric disorders), PANSS (Positive and Negative Syndrome Scale - for schizophrenia), ICD-10 (International Classification of Diseases, 10th revision), BPRS (Brief Psychiatric Rating Scale - for depression, anxiety and hallucinations), SDS (Severity of Dependence Scale), MINI (Mini International Psychiatric Review), K-6 (Kessler Psychological Distress Scale - 6 questions), Q16 (Questionnaire 16 for neurotoxic symptoms), BDI (Beck's Depression Inventory), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition), DASS-21 (The Depression, Anxiety and Stress Scale - 21 Items), PHQ-9 (Patient Health Questionnaire - 9 items, for depression), PSQ (Psychosis Screening Questionnaire), IES-R (Impacts of Events Scale - Revised), DAST-10 (Drug Abuse Screening Test-10), PCL:SV (Psychopathy Checklist: Screening Version), K10 (Kessler Psychological Distress Scale - 10 questions)

Supplementary Material 3: Quality of assessment of primary studies using Newcastle-Ottawa scale [17-18].

Study	Selection (/5)	Comparability (/2)	Outcome (/3)	Overall Score (/10)	Comments
Ahmed and Emad 1998 [21]	1	2	1	4	- Non-random sample - No justification of sample size - 100% response rate - Questionnaire described in insufficient detail no definition of khat use - No significant differences in baseline characteristics between khat users and non-users - Uses self-report - No details of statistical analysis and no confidence intervals provided
Belew et al. 2000 [22]	3	2	2	7	- Insufficient details of non-responders; no baseline characteristics provided - Questionnaire described in limited detail but methods do define current, past and never khat use
Numan 2003 [23]	3	1	1	5	- Sample size not justified - Eight non-respondents excluded because of incomplete data - Non-validated but described method of khat usage data collection - Only controlled variable seems to be Yemeni nationality - No confidence intervals included
Odenwald et al. 2005 [24]	3	2	2	7	- Sample size not justified - No details of non-responders - Non-validated but described method of khat usage data

					collection - Uses clinical interviews - No confidence intervals included
Deyessa et al. 2008 [25]	3	2	3	8	- Providers reasons for non-responders but not characteristics - Non-validated but described method of khat usage data collection - Clinical interview
Odenwald et al. 2009 [26]	2	2	2	6	- Sample size not justified - No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Damena et al. 2011 [27]	4	1	1	6	- Providers reasons for non-responders but not characteristics - Uses WHO-validated khat use measurement tool despite definition of 'khat user' being unclear within the study - Only controlled variable seems to be region (Jimma City) - Uses self-report - No confidence intervals included
Tulloch et al. 2012 [28]	4	2	2	8	- Entire eligible sample used - Missing information discussed - Non-validated but described method of khat usage data collection - No confidence intervals included
Dessie et al. 2013 [29]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection

					- Uses self report
Fekadu 2014 [30]	2	2	2	6	- No details of non-responders - Khat usage data collection described insufficiently: 'daily' or 'never' - Uses self-report
Widmann et al. 2014 [7]	2	2	3	7	- Opportunity sample - Sample size not justified - No details of non-responders - Clinical interview
Dachew et al. 2015 [31]	2	2	2	6	- Justification of sample size unsatisfactory - No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Soboka et al. 2015 [32]	3	2	2	7	- All eligible participants invited to participate - Limited description of non-responders (gender only) - Non-validated but described method of khat usage data collection - Uses self-report
Zenebe et al. 2015 [33]	3	2	3	8	- No details of non-responders - Non-validated but described method of khat usage data collection - Medical records used
El-Setouhy et al. 2016 [34]	4	2	2	8	- Volunteer sample; no non-responders - Uses self-report
Hersi et al. 2017 [35]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data

					collection - Uses self-report
Hunduma et al. 2017 [36]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Kerebih et al. 2017 [37]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Mossie et al. 2016 [38]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Soboka et al. 2017 [39]	2	2	2	6	- Invited all eligible participants - Does not discuss whether sample size is large enough for conclusions to be drawn - No details of non-responders - Non-validated but described method of khat usage data collection - Unclear if all variables are self-reported
Tariku et al. 2017 [40]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self report
Wondemagegn et al. 2017 [41]	3	1	3	7	- No details of non-responders - Non-validated but described method of khat usage data collection

					- Only one community studied but no other controlled variables
Yeshaw and Mossie 2017 [42]	2	2	2	6	- Sample size not justified - No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Bedaso et al. 2018 [43]	3	2	2	8	- 100% response rate - Limited description of khat usage data collection - Uses self-report
Adraro et al. 2019 [44]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Ongeri et al. 2019 [45]	2	2	2	6	- No details of non-responders - No description of what quantifies a ‘current khat user’ - Uses self-report
Atnafie et al. 2020 [46]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Hajure et al. 2020 [47]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Hambisa et al. 2020 [48]	3	2	2	7	- No details of non-responders

					- Non-validated but described method of khat usage data collection - Uses self-report
Kelemu et al. 2020 [49]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Mekuriaw et al. 2020 [50]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report
Yitayih et al. 2020 [51]	4	2	2	8	- Provides reasons for non-responders but not characteristics - Uses DAST-10 for khat abuse -Uses self-report
Haile and Sahile, 2021 [52]	3	2	2	7	- 100% response rate - No description of what quantifies a ‘current khat user’ - Uses self-report
Hambisa et al. 2021 [53]	2	2	2	6	- Providers reasons for non-responders but not characteristics - No description of what quantifies a ‘current khat user’ - Uses self-report
Melaku et al. 2021 [54]	3	2	2	7	- No details of non-responders - Non-validated but described method of khat usage data collection - Uses self-report

Supplementary Material 4: Sensitivity Analysis

Study Excluded	Odds Ratio	95% CIs	I^2 Value (%)	P-Value
Depression				
Atnafie et al. 2020	2.28	1.81-2.87	91	<0.00001
Bedaso et al. 2018	2.21	1.75-2.79	92	<0.00001
Deyessa et al. 2008	2.23	1.76-2.82	92	<0.00001
El-Setouhy et al. 2016	2.22	1.76-2.80	92	<0.00001
Haile and Sahile 2021	2.14	1.71-2.69	91	<0.00001
Hambisa et al 2020	2.24	1.77-2.84	92	<0.00001
Melaku et al. 2021	2.22	1.76-2.81	92	<0.00001
Mossie et al. 2016	2.17	1.73-2.73	91	<0.00001
Numan 2003	2.27	1.80-2.87	91	<0.00001
Wondemagegn et al. 2017	2.11	1.69-2.64	91	<0.00001
Yeshaw and Mossie 2017	2.19	1.74-2.76	92	<0.00001
Zenebe et al. 2015	2.28	1.81-2.87	91	<0.00001
Anxiety				
Atnafie et al. 2020	2.22	1.75-2.80	92	<0.00001
El-Setouhy et al. 2016	2.21	1.75-2.79	92	<0.00001
Melaku et al. 2021	2.22	1.76-2.81	92	<0.00001
Numan 2003	2.29	1.83-2.86	91	<0.00001
Numan 2003	2.26	1.79-2.86	92	<0.00001
Numan 2003	2.27	1.80-2.87	91	<0.00001
Wondemagegn et al. 2017	2.18	1.73-2.74	91	<0.00001
Yeshaw and Mossie 2017	2.20	1.75-2.78	92	<0.00001
Psychological Distress				
Adraro et al. 2019	2.16	1.72-2.71	91	<0.00001

Atnafie et al. 2020	2.27	1.80-2.87	92	<0.00001
Belew et al. 2000	2.15	1.72-2.69	91	<0.00001
Dachew et al. 2015	2.23	1.76-2.82	92	<0.00001
Damena et al. 2011	2.26	1.78-2.85	92	<0.00001
Dessie et al. 2013	2.21	1.75-2.79	92	<0.00001
Hajure et al. 2020	2.17	1.72-2.73	92	<0.00001
Hambisa et al. 2021	2.19	1.74-2.76	92	<0.00001
Hersi et al. 2017	2.22	1.75-2.80	92	<0.00001
Kelemu et al. 2020	2.23	1.77-2.82	92	<0.00001
Kerebih et al. 2017	2.19	1.74-2.76	92	<0.00001
Mekuriaw et al. 2020	2.19	1.74-2.76	92	<0.00001
Melaku et al. 2021	2.23	1.76-2.81	92	<0.00001
Soboka et al. 2015	2.23	1.77-2.82	92	<0.00001
Soboka et al. 2017	2.24	1.78-2.83	92	<0.00001
Tariku et al. 2017	2.25	1.78-2.84	92	<0.00001
Yeshaw and Mossie et al. 2017	2.21	1.75-2.79	92	<0.00001
Psychotic symptoms/disorders				
Numan 2003	2.26	1.78-2.86	92	<0.00001
Numan 2003	2.27	1.80-2.87	91	<0.00001
Odenwald et al. 2009	2.27	1.80-2.87	91	<0.00001
Ongeri et al. 2019	2.25	1.78-2.85	92	<0.00001
Tulloch et al. 2012	2.14	1.70-2.68	91	<0.00001
Widmann et al. 2014	2.20	1.75-2.77	92	<0.00001
Zenebe et al. 2015	2.23	1.76-2.82	92	<0.00001
Psychopathy				
Yitayih et al. 2020	2.18	1.73-2.74	92	<0.00001
Unspecified psychiatric symptoms/disorders				

Ahmed and Emad 1998	2.24	1.78-2.83	92	<0.00001
Fedaku et al. 2014	2.21	1.75-2.79	92	<0.00001
Hunduma et al. 2017	2.22	1.76-2.81	92	<0.00001
Odenwald et al. 2005	2.23	1.76-2.82	92	<0.00001
Yitayih et al. 2020	2.24	1.77-2.82	92	<0.00001

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction, pages 2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Inclusion/exclusion: methods (study eligibility) page 4 Grouping for synthesis: results (symptoms explored within included studies): page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods (literature search), page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods (literature search), page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods (literature search), page 3-4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods (data collection and quality assessment), page 4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
Synthesis	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention	Methods (study eligibility),

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
methods		characteristics and comparing against the planned groups for each synthesis (item #5)).	page 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods (synthesis of findings), page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods (synthesis of findings), page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods (synthesis of findings), page 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods (synthesis of findings), page 5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results (included and excluded studies) pages 5-6, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results (included and excluded studies), pages 5-6
Study characteristics	17	Cite each included study and present its characteristics.	Results (summary of included studies) pages 5-6, Supplementary material 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results (summary of included studies) pages 5-6, Supplementary material 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results (summary of included studies) pages 5-6, Supplementary material 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results (GRADE analysis) page 7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results (meta-analysis) page 6, Figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results (subgroup) page 6-7, Figure 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results (sensitivity analysis)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			page 7, supplementary material 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results (summary of included studies) pages 5-6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results (meta-analysis) page 6, Figure 2, results (GRADE Analysis) page 7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion, pages 7-8
	23b	Discuss any limitations of the evidence included in the review.	Discussion, pages 7-8
	23c	Discuss any limitations of the review processes used.	Discussion, pages 7-8
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion, pages 7-8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods page 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods, page 3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements pages 8-9, and funding page 9
Competing interests	26	Declare any competing interests of review authors.	Competing interests, page 8
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	References pages 9-14

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/