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

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Betsy Edwards^{1*}, Naomi Atkins²

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

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

*Correspondence: Betsy Edwards, <u>BHE701@student.bham.ac.uk</u>, 67 Peterborough Avenue Upminster RM14 3LL

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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 I² 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:

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"khat" OR "qat" OR "qaad" OR "catha" OR "miraa" OR "mairungi" AND
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"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 I² 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 I² 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, I² 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, I² 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 I² 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 I² 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 (I²=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 I² 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 underappreciates 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 metaanalysis suggests that khat use is associated with a 122% increase in the prevalence of psychiatric symptoms, particularly psychiatric distress. The high heterogeneity of the metaanalysis 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.

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COMPETING INTERESTS

No competing interests.

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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.

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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

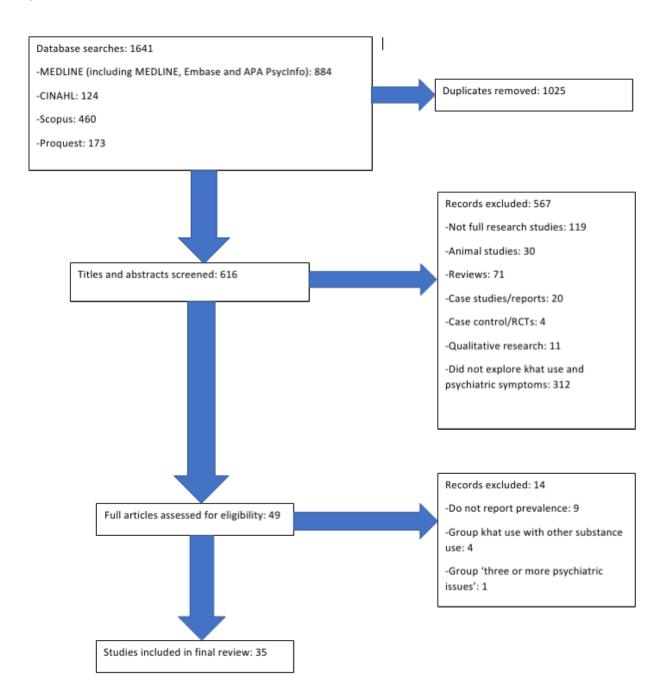
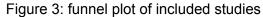
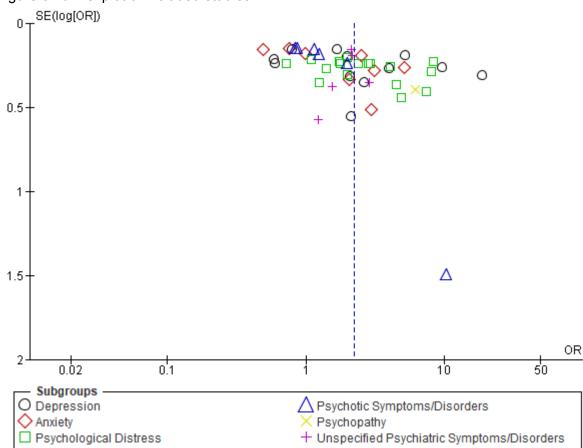


Figure 2: Meta-analysis of included studies

Figure 2: Meta-	Figure 2: Meta-analysis of included studies							
Study or Subgroup	Khat us Events		Non-u Events		Weight	Odds Ratio M-H, Random, 95% CI	Odds M-H, Rando	
1.1.1 Depression						,	,	
Atnafie et al. 2020	41	207	80	271	2.2%	0.59 [0.38, 0.91]		
Bedaso et al. 2018	36	48	153	287	1.9%	2.63 [1.31, 5.26]		
	71				2.2%			
Deyessa et al. 2008		1199	44	1432		1.99 [1.35, 2.92]		_
El-Setouhy et al. 2016	13	35	7	32	1.5%	2.11 [0.71, 6.23]	T	
Haile and Sahile, 2021	67	108	40	276	2.1%	9.64 [5.77, 16.11]		
Hambisa et al. January 2020	84	241	190	781	2.2%	1.66 [1.22, 2.27]		_
Melaku et al. 2021	37	56	99	204	2.0%	2.07 [1.11, 3.83]		
Mossie et al. 2016	104	200	67	390	2.2%	5.22 [3.56, 7.65]		
	326	538	168	254	2.2%			
Numan 2003						0.79 [0.58, 1.08]		
Wondemagegn et al. 2017	108	172	15	182	2.0%	18.79 [10.19, 34.65]		
Yeshaw and Mossie, 2017	54	145	27	209	2.1%	4.00 [2.36, 6.77]		
Zenebe et al. 2015	58	235	46	130	2.1%	0.60 [0.38, 0.95]		_
Subtotal (95% CI)		3184		4448	24.7%	2.39 [1.34, 4.28]		•
Total events	999		936					
Heterogeneity: Tau ² = 0.98; Ch	i ² = 211.25	i. df= 11	(P < 0.0)	0001): P	= 95%			
Test for overall effect: Z = 2.93			•					
		,						
1.1.2 Anxiety								
	4.40	207	400	074	0.000	2 40 14 00 2 04		
Atnafie et al. 2020	146	207	133	271	2.2%	2.48 [1.69, 3.64]		-
El-Setouhy et al. 2016	20	35	10	32	1.6%	2.93 [1.08, 8.00]		
Melaku et al. 2021	41	56	117	204	2.0%	2.03 [1.06, 3.91]	ŀ	
Numan 2003	203	538	141	254	2.2%	0.49 [0.36, 0.66]	-	
Numan 2003	410	538	194	254	2.2%	0.99 [0.70, 1.41]	-	_
Numan 2003	248	538	135	254	2.2%	0.75 [0.56, 1.02]	-	
Wondemagegn et al. 2017	79	172	26	182	2.1%	5.10 [3.05, 8.51]		
	43		25	209				
Yeshaw and Mossie, 2017	43	145	25		2.1% 16.6%	3.10 [1.79, 5.37]	1	
Subtotal (95% CI)		2229		1660	10.0%	1.68 [0.93, 3.04]	1	•
Total events	1190		781					
Heterogeneity: Tau ² = 0.66; Ch	$i^2 = 106.34$, df = 7 (P < 0.00	001); I*=	93%			
Test for overall effect: Z = 1.72								
	(,							
1.1.3 Psychological Distress								
Adraro et al. 2019	119	120	60	161	2.0%	7.02 (4.60, 12.00)		
		139	69	161		7.93 [4.50, 13.99]		_
Atnafie et al. 2020	33	207	57	271	2.1%	0.71 [0.44, 1.14]		
Belew et al. 1997	100	326	28	554	2.1%	8.31 [5.32, 13.00]		
Dachew et al. 2015	63	114	279	722	2.2%	1.96 [1.32, 2.92]		
Damena et al. 2011	49	136	108	317	2.2%	1.09 [0.72, 1.66]	-	_
Dessie et al. 2013	59	185	34	245	2.1%	2.91 [1.80, 4.68]		
Hajure et al. 2020	37	57	14	70	1.8%	7.40 [3.33, 16.46]		
Hambisa et al. March 2021	49	59	146	278	1.9%	4.43 [2.16, 9.10]		
Hersi et al. 2017	35	108	78	462	2.1%	2.36 [1.47, 3.78]		
	70			293				
Kelemu et al. 2020		111	145		2.1%	1.74 [1.11, 2.73]		-
Kerebih et al. 2017	18	26	84	264	1.7%	4.82 [2.02, 11.53]		
Mekuriaw et al. 2020	39	71	149	647	2.1%	4.07 [2.47, 6.73]		
Melaku et al. 2021	30	56	75	204	2.0%	1.98 [1.09, 3.61]		
Soboka et al. 2015	52	93	124	296	2.1%	1.76 [1.10, 2.81]		
Soboka et al. 2017	27	72	98	324	2.1%	1.38 [0.81, 2.36]	+	
Tariku et al. 2017	19	40	71	168	1.9%	1.24 [0.62, 2.47]	_	
	59	145	41	209	2.1%			
Yeshaw and Mossie, 2017	29	1945	41	5485	34.8%	2.81 [1.75, 4.52]		_
Subtotal (95% CI)		1945		3403	34.070	2.56 [1.82, 3.61]		•
Total events	858		1600					
Heterogeneity: Tau² = 0.43; Ch	i² = 116.49	i, df = 16	(P < 0.0	0001); l²	= 86%			
Test for overall effect: Z = 5.41	(P < 0.000)	01)						
1.1.4 Psychotic Symptoms/Dis	sorders							
Numan 2003	228	538	99	254	2.2%	1.15 [0.85, 1.56]	+	-
Numan 2003	269	538	136	254	2.2%	0.87 [0.64, 1.17]		_
Odenwald et al. 2009	263	538	136	254	2.2%			_
						0.83 [0.62, 1.12]		
Ongeri et al. 2019	57	306	82	525	2.2%	1.24 [0.85, 1.79]	T	_
Tulloch et al. 2012	28	30	2	30	0.8%	196.00 [25.77, 1490.50]		
Widmann et al. 2014	8	33	0	15	0.5%	10.33 [0.56, 191.82]		
Zenebe et al. 2015	97	235	34	130	2.1%	1.98 [1.24, 3.17]		
Subtotal (95% CI)		2218		1462	12.3%	1.47 [0.93, 2.30]	+	•
Total events	950		489					
Heterogeneity: Tau ² = 0.25; Ch		df = 6 / P		01\:I²=	85%			
Test for overall effect: Z = 1.66		ui – 0 (i	- 0.000	01),1 -	0370			
restroi overali ellect. Z = 1.00 i	(= 0.10)							
1.1.5 Developathy								
1.1.5 Psychopathy								
Yitayih et al. 2020	32	138	9	191	1.8%	6.10 [2.81, 13.28]		
Subtotal (95% CI)		138		191	1.8%	6.10 [2.81, 13.28]		-
Total events	32		9					
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.56	re « n nnn	01)						
. 551 for 646 full 611661. Z = 4.30 f		-17						
1 1 6 Unenocified Develoatric	Sumptom	e/Dieord	lore					
1.1.6 Unspecified Psychiatric						4 00 10 15 5 5		
Amed and Emad 1998	11	27	9	25	1.5%	1.22 [0.40, 3.75]		
Fedaku 2014	42	53	208	363	1.9%	2.85 [1.42, 5.70]		
Hunduma et al. 2017	86	434	48	467	2.2%	2.16 [1.47, 3.16]		
Odenwald et al. 2005	79	1401	90	3284	2.2%	2.12 [1.56, 2.89]		-
Yitayih et al. 2020	16	138	15	191	1.9%	1.54 [0.73, 3.23]		
Subtotal (95% CI)	10	2053	13	4330	9.7%	2.09 [1.69, 2.59]		•
		2033		+550	3.170	2.05 [1.05, 2.09]		*
Total events	234		370					
Heterogeneity: Tau² = 0.00; Ch			= 0.68); I	= 0%				
Test for overall effect: Z = 6.80	(P < 0.000	01)						
	_							
Total (95% CI)		11767		17576	100.0%	2.22 [1.76, 2.79]		♦
Total events	4263		4185			,		-
Heterogeneity: Tau ² = 0.59; Ch		df = 40		00043-12	- 02%			
			(F = 0.0	0001); l*	- 5∠70		0.02 0.1 1	10 50
Test for overall effect: Z = 6.80								Against Khat
Test for subgroup differences:	Chi ² = 11.	56, df = 5	5 (P = 0.0	(34), 2 = 6	6.7%			-







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1 2 3 4 5	pplementary Mater	cted by copyright, includin			
Study	Population	Sample	Criteria for 'Khat User'	Psychiatric Measure*	Results g on 25
Ahmed and 10 Emad 1998 12[35]	Somali immigrants living in Liverpool	Convenience sample of 52 Khat users = 27	Unspecified	GHQ-28	- 11/27 khat users (p=0.72)
14Belew et al. 152000 [36] 16 17 18 19	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 perienced mental distress, compared to 28/55# 60 - users (OR = 8.31, 5.20-13.31, p=0.00) - 89/294 long-term (OR = 8.31, 5.20-13.31) - 89/294 long-term (OR = 8.31, 5.20-13.31) - 89/294 long-term (OR = 8.31, 5.20-13.31) - 89/294 long-term (OR = 8.31, 5.20-13.31)
21Numan 2003 22[37] 23 24 25	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, symptoticism - Khat users had less phobic anxiety (37.7% vs 55.5%, p<0.05)
27Odenwald et 28al. 2005 [38] 29 30 31 32 33	'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 regative screened individuals (46.6% vs 29.9%, p<0.0015
3Deyessa et 36al. 2008 [39] 37 38 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)

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Odenwald et al. 2009 [40]	Armed combatants in Somali	8124 armed individuals (not random as still in conflict at time of study)	Anyone who has chewed khat within the last week	CIDI	- 8.9% of khat users experienced paranoid ideation compared to 2.6% of mon-users on 25 on 25 users
10 Damena et	Adults in Jimma City, Ethiopia	Khat users = 36.4% Random sample of 1308	Uses WHO-validated substance abuse	SRQ-20	- 49/136 long-term
13 ^{41, 2011} [41] 14 15 16 17	Спу, Ешпоріа	Khat users = 38%	questionnaire, but unsure what is classified as 'khat user'		chewers (less than two years), and 153/747 non-users
8 Tulloch et 9 Tulloch et 2012 [42] 21 22 23 24	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 (p< (p< (p) (b) (b) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c
Dessie et al. 272013 [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)
29Fekadu 2014 30[44] 31 32 33 34	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-sisers experienced mental illness compared to 208/383 non-users (AOR = 2.85, 1.42-5.70)
36Widmann et 37al. 2014 [7] 38 39	Male Somali refugees living in a disadvantaged	Convenience sample of 33 users and 15 comparable non-users	SDS	CIDI, MINI	- 24% of khat users har psychotic symptoms compared to 0% of non-chewers (p-0.044)
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4	urban settlement in Kenya	Khat users = 69%			2-0618 t, incli			
Dachew et 7 al. 2015 [45] 8 9 10 11	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-susers (OR=1.96, 1.32-2.92, p=0.02)			
3Soboka et al. 142015 [46] 15 16	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 compared to 1247.96 non-users (OR = 1.76, 1.10-2.82)			
⁸ Zenebe et al. 202015 [47] 21 22 23 24	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 46/13 man-users (AOR = 1.43, 0.74-2.77) - 97/235 khat users had schizophrenia compared to 34/130 non-users (AOB = 0.87, 0.45-1.68)			
El-Setouhy 28t al. 2016 29[48]	Jazan region of Saudi Arabia	Volunteer sample of 70 males Khat dependent = 52.2%	SDS	Q16	- 13/35 dependent sees felt depressed compared to 7/32 non-dependent uses (QR = 2.30, 0.7-6.8) - 20/35 dependent sees felt anxious compared to 10/32 non-dependent uses (QR = 3.50, 1.2-10.0)			
³¹ Hersi et al. ³² 2017 [49]	Students in Somaliland	Stratified random sample of 570 Khat users = 19%	Use in last 12 months	SRQ-20	- 32% of khat user serienced psychological distress, compared to 1 % non-users (AOR = 2.87, 1.26-6.56)			
35Hunduma et 36al. 2017 [50] 37 38	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 48/469 non-users (OR = 2.16, 1.47-3.16)			
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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-esers (AOR = 6.91, 1.88-25.42, p=0.004)
Mossie et al. 8 2016 [52]	Adults in Ethiopia	Random sample of 650 Khat users = 34%	Khat use within the last 30 days	BDI	- 104/200 khat uses had depression compared to 67/390 non-users (AOR = 20.07, 5.56-18.25)
Soboka et al. 12017 [53] 13 14 15	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 khaz Bers experienced psychological distress, compared of the
¹⁶ Tariku et al. ¹⁷ 2017 [54] 18 19	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 a eienced mental distress compared to 71/168 non-assers (AOR = 2.29, 1.04-5.04)
21Wondemage 22gn et al. 232017 [55] 24	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 = 3.42, 3.04-9.96, p=0.000)
Yeshaw and Mossie 2017	Staff of Jimma University,	Random sample of 363	Anyone who has ever used khat	DASS-21	- 54/145 khat users had depression compared to 27/209 non-users (AOk = 2.99, 2.57-9.69)

used khat

2018 [57]

³2019 [58]

45 46 47

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Ethiopia

Ethiopia

300

Khat users = 41%

Khat users = 46%

non-users (AO $\mathbf{K} = 2.94, 1.52-5.66$) - 59/145 khat users phad psychological stress compared to 41/209 non-use (AOR = 2.78, 1.49-5.21)Bedaso et al. Unspecified, but PHQ-9 - 36/48 khat users ad gepression, compared to 153/287 Prisoners in Random sample of non-users (AO $\mathbf{R} = 2.48, 1.05-5.86, p=0.039$) Ethiopia 335 appears to be chewing Khat users = 14%khat before incarceration ⁷Adraro et al. Prisoners in Random sample of Anyone who has ever SRQ-20 - 119/139 khat users experienced mental distress,

> compared to 69/16 non-users (AOR = 4.33, 2.02-9.27, p<0.00 lg

- 43/145 khat users hage anxiety compared to 25/209

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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 5.6% of non-users (p=0.26)
Atnafie et al. 102020 [60] 11 12 13 14 15 16 17	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 57/27 and and dependent users (AOR = 1.70, 0.98-2.95) - 146/207 khat-dependent users experienced anxiety compared to 133/26 from dependent users (AOR = 2.47, 1.57-3.81) - 41/207 khat-dependent users experienced depression compared to 80/27 from users (AOR = 6.28, 1.67-23.61)
18 Hajure et al. 19 Hajure et al. 20 [61] 21 22	Healthcare providers in Ethiopia	Convenience sample of 127 Khat users = 45%	Khat use in last three months	IES-R	- 37/57 khat users exactionced psychological stress, compared to 145 below on-users (AOR = 5.74, 1.83-18.1, p<0.001)
²³ Hambisa et ²⁴ al. 2020 [62] ²⁵ ²⁶	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 susers (OR = 1.60, 1.22-2.27)
28Kelemu et 29al. 2020 [63] 30 31 32	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 none (AOR = 3.09, 1.74-5.50)
33 34 Mekuriaw et 35al. 2020 [64] 36 37	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-uses (AOR = 3.57, 2.06-6.18, p=0.001)
⁸ Yitayih et al. ³⁹ 2020 [65]	Prisoners in a correctional	Random sample of 336 Khat users = 138	DAST-10	PCL:SV	- 32/138 khat users me the criteria for psychopathy, compared to 9/191 ion-users
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3	institution in Jimma, Ethiopia				- 16/138 khat users had mental illness, compared to
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 3al. 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 rienced psychological distress, compared to 1452 8 non-users (AOR = 4.16, 1.67-10.35)
⁶ Melaku et al. ⁷ 2021 [68] 19 20 21	Medical students in Ethiopia	Systematic random sample of 260 Khat users = 22%	Anyone who has ever used khat	DASS-21	- 37/56 khat users Rad Repression, compared to 99/204 non-users (OR 37, 1.11-3.83) - 41/56 khat users Rad Repression, compared to 99/204 non-users (OR 37, 1.11-3.83) - 30/56 khat users Rad Repression, compared to 117/204 non-users (OR 37, 1.06-3.91) - 30/56 khat users Rad Repression, compared to 117/204 non-users (OR 37, 1.11-3.83)
23 *1	ist of abbreviated so	creening tools: GHO-	28 (General Health Quest	tionnaire-28 for	mental disorders), SRO20 (Self-Reporting

*List of abbreviated screening tools: GHQ-28 (General Health Questionnaire-28, for mental disorders), RQ20 (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 Rauge Scale - for depression, anxiety and hallucinations), SDS (Severity of Dependence Scale), MINI (Mini International Esychiatric 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 Debression, 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 (Psychographics) (Psychographics), K10 (Kessler Psychological Distress Scale - 10 questions)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Stress Scale - 21 Items), PHQ-9 (Patient Health Questionnaire - 9 items, for depression), PSQ (Psychosis screening Questionnaire),

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

Study	Selection (/5)	Comparabilit y (/2)	Outcome (/3)	Overall Score (/10)	On 25 July 19 Comments
Ahmed and Emad 1998 [21]	1	2	1	4	- Non-random sample region response rate to many response rate to
Belew et al. 2000 [22]	3	2	2	7	- Insufficient details of bondesponders; no baseline characteristics provided - Questionnaire described in limited detail but methods do define current, past and never that guestions are considered to the contract of the c
Numan 2003 [23]	3	1	1	5	- Sample size not justified 2 - Eight non-respondents ex guded 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 of a non-responders - No details of non-responders - Non-validated but described method of khat usage data collection - Uses clinical interviews - No confidence intervals in luded

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2	8
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Deyessa et al. 2008 [25]	3	2	3	8	- Providers reasons for Fon Sesponders but not characteristics - Non-validated but deseribed 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-responding to the Non-validated but desagged method of khat usage data collection - Uses self-report
Damena et al. 2011 [27]	4	1	1	6	- Providers reasons for consequence of the conseque
Tulloch et al. 2012 [28]	4	2	2	8	- Entire eligible sample rect Missing information 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 desembled 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 bi - No details of non-responders - Clinical interview

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Dachew et al. 2015 [31]	2	2	2	6	- Justification of samplesized unsatisfactory - No details of non-respenders - Non-validated but deserbed method of khat usage data collection - Uses self-report
Soboka et al. 2015 [32]	3	2	2	7	- All eligible participants in the ligible participants in
Zenebe et al. 2015 [33]	3	2	3	8	- No details of non-responding of the Non-validated but desart and method of khat usage data collection - Medical records used and collection
El-Setouhy et al. 2016 [34]	4	2	2	8	- Volunteer sample; no responders - Uses self-report
Hersi et al. 2017 [35]	3	2	2	7	- No details of non-respenders - Non-validated but deseribed 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 deseribed 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 desertibed 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

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					136/bmjopen-2022
					- Uses self-report
Hajure et al. 2020 [47]	3	2	2	7	- No details of non-responders - Non-validated but deserbed 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 desembled method of khat usage data collection - Uses self-report
Kelemu et al. 2020 [49]	3	2	2	7	- No details of non-respectives Non-validated but deserbed 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-sesponders but not characteristics - Uses DAST-10 for khazi alguse -Uses self-report
Haile and Sahile, 2021 [52]	3	2	2	7	- 100% response rate
Hambisa et al. 2021 [53]	2	2	2	6	- Providers reasons for converse 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	l² Value (%)	P-Value
Depression		•	<u> </u>	
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 <0.00001 <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 5
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 <0.00001 <0.00001 <0.00001 <0.00001 <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				ģ
Numan 2003	2.26	1.78-2.86	92	<0.00001 colored color
Numan 2003	2.27	1.80-2.87	91	
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	
Widmann et al. 2014	2.20	1.75-2.77	92	<0.00001 colored <0.000
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
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EXPLORING THE ASSOCIATION BETWEEN KHAT USE AND PSYCHIATRIC SYMPTOMS: A SYSTEMATIC REVIEW

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Betsy Edwards^{1*}, Naomi Atkins²

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

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

*Correspondence: Betsy Edwards, <u>BHE701@student.bham.ac.uk</u>, 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 I² 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 I² 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 I² 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, I² 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, I² 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 I² 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 I² 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 (I²=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.

 This review combines 35 cross-sectional studies in the field of khat use, and using metaanalysis suggests that khat use is associated with a 122% increase in the prevalence of psychiatric symptoms, particularly psychiatric distress. The high heterogeneity of the metaanalysis 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.

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COMPETING INTERESTS

No competing interests.

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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.

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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

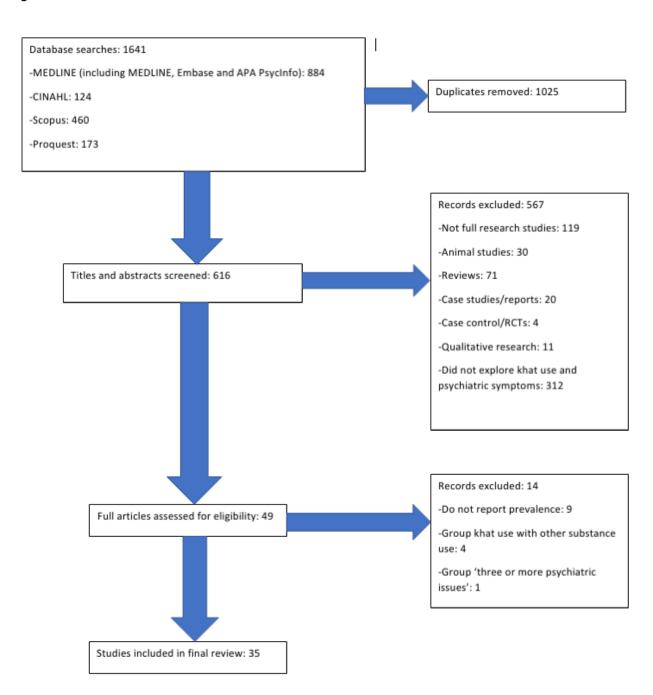
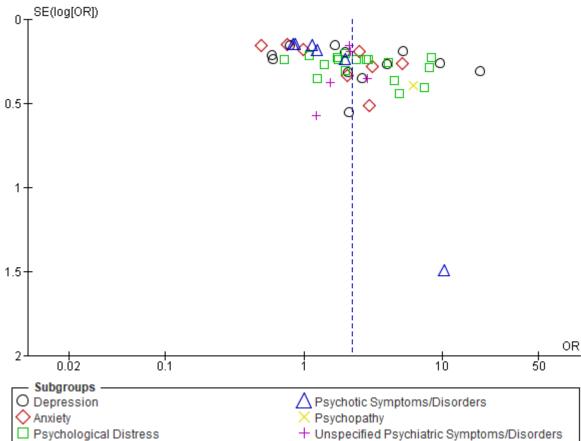


Figure 2: Meta-a	analy	/sis	of in	cluc	ded s	studies	
Study or Subgroup	Khat us Events	sers Total	Non-us Events		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
1.1.1 Depression Atnafie et al. 2020 Bedaso et al. 2018 Deyessa et al. 2008 El-Setouhy et al. 2016 Haile and Sahile, 2021 Hambisa et al. January 2020 Melaku et al. 2021 Mossie et al. 2016 Numan 2003 Wondemagegn et al. 2017 Yeshaw and Mossie, 2017 Zenebe et al. 2015 Subtotal (95% Cl) Total events Heterogeneity: Tau² = 0.98; Chi Test for overall effect Z = 2.93			80 153 44 7 40 190 99 67 168 15 27 46 936 (P < 0.0	271 287 1432 32 276 781 204 390 254 182 209 130 4448	2.2% 1.9% 2.2% 1.5% 2.1% 2.2% 2.0% 2.2% 2.0% 2.1% 24.7% = 95%	0.59 [0.38, 0.91] 2.63 [1.31, 5.26] 1.99 [1.35, 2.92] 2.11 [0.71, 6.23] 9.64 [5.77, 16.11] 1.66 [1.22, 2.27] 2.07 [1.11, 3.83] 5.22 [3.56, 7.65] 0.79 [0.58, 1.08] 18.79 [10.19, 3.465] 4.00 [2.36, 6.77] 0.60 [0.38, 0.95] 2.39 [1.34, 4.28]	
Atnafie et al. 2020 El-Setouhy et al. 2016 Melaku et al. 2021 Numan 2003 Numan 2003 Numan 2003 Wondemagegn et al. 2017 Yeshaw and Mossie, 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau² = 0.66; Chi Test for overall effect: Z = 1.72 (207 35 56 538 538 538 172 145 2229	133 10 117 141 194 135 26 25 781 (P < 0.00	271 32 204 254 254 254 182 209 1660	2.2% 1.6% 2.0% 2.2% 2.2% 2.1% 2.1% 16.6%	2.48 [1.69, 3.64] 2.93 [1.08, 8.00] 2.03 [1.06, 3.91] 0.49 [0.36, 0.66] 0.99 [0.70, 1.41] 0.75 [0.56, 1.02] 5.10 [3.05, 8.51] 3.10 [1.79, 5.37] 1.68 [0.93, 3.04]	
1.1.3 Psychological Distress Adraro et al. 2019 Athafie et al. 2020 Belew et al. 1997 Dachew et al. 2015 Damena et al. 2011 Dessie et al. 2011 Dessie et al. 2013 Hajure et al. 2020 Hambisa et al. March 2021 Hersi et al. 2017 Kelemu et al. 2020 Kerebih et al. 2017 Mekuriaw et al. 2020 Melaku et al. 2021 Soboka et al. 2017 Tariku et al. 2017 Yeshaw and Mossie, 2017 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.43; Chi	119 33 100 63 49 59 37 49 35 70 18 39 30 52 27 19 59 858 *= 116.49	139 207 326 114 136 185 57 59 108 111 26 71 56 93 72 40 145 1945	69 57 28 279 108 34 14 146 78 145 84 149 75 124 98 71 41	161 271 554 722 317 245 70 278 462 293 264 647 204 296 324 168 209 5485	2.0% 2.1% 2.1% 2.2% 2.1% 1.8% 1.9% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1	7.93 [4.50, 13.99] 0.71 [0.44, 1.14] 8.31 [5.32, 13.00] 1.96 [1.32, 2.92] 1.09 [0.72, 1.66] 2.91 [1.80, 4.68] 7.40 [3.33, 16.46] 4.43 [2.16, 9.10] 2.36 [1.47, 3.78] 1.74 [1.11, 2.73] 4.82 [2.02, 11.53] 4.07 [2.47, 6.73] 1.98 [1.09, 3.61] 1.76 [1.10, 2.81] 1.38 [0.81, 2.36] 1.24 [0.62, 2.47] 2.81 [1.75, 4.52] 2.56 [1.82, 3.61]	
Test for overall effect: Z = 5.41 (1.1.4 Psychotic Symptoms/Dis Numan 2003 Numan 2003 Odenwald et al. 2009 Ongeri et al. 2019 Tulloch et al. 2012 Widmann et al. 2014 Zenebe et al. 2015 Subtotal (95% Ct) Total events Heterogeneity: Tau² = 0.25; Chi Test for overall effect: Z = 1.66 (228 269 263 57 28 8 97 950 == 40.15,	538 538 538 306 30 33 235 2218	99 136 136 82 2 0 34 489	254 254 254 525 30 15 130 1462	2.2% 2.2% 2.2% 2.2% 0.8% 0.5% 2.1% 12.3%	1.15 [0.85, 1.56] 0.87 [0.64, 1.17] 0.83 [0.62, 1.12] 1.24 [0.85, 1.79] 196.00 [25.77, 1490.50] 10.33 [0.56, 191.82] 1.98 [1.24, 3.17] 1.47 [0.93, 2.30]	
1.1.5 Psychopathy Yitayih et al. 2020 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 4.56 (32 32 P < 0.000	138 138 01)	9	191 191	1.8% 1.8%	6.10 [2.81, 13.28] 6.10 [2.81, 13.28]	•
1.1.6 Unspecified Psychiatric Amed and Emad 1998 Fedaku 2014 Hunduma et al. 2017 Odenwald et al. 2005 Yitayih et al. 2020 Subtotal (95% Cl) Total events Heterogeneity: Tau² = 0.00; Chi Test for overall effect Z = 8.80 (11 42 86 79 16 234 *= 2.33, d	27 53 434 1401 138 2053 If = 4 (P :	9 208 48 90 15	25 363 467 3284 191 4330 == 0%	1.5% 1.9% 2.2% 2.2% 1.9% 9.7%	1.22 [0.40, 3.75] 2.85 [1.42, 5.70] 2.16 [1.47, 3.16] 2.12 [1.56, 2.89] 1.54 [0.73, 3.23] 2.09 [1.69, 2.59]	
Total (95% CI) Total events Heterogeneity: Tau ² = 0.59; Chi Test for overall effect Z = 6.80 (Test for subgroup differences:	P < 0.000	01)		0001); l²		2.22 [1.76, 2.79]	0.02 0.1 10 50 For Khat Against Khat

Figure 3: funnel plot of included studies SE(log[OR])



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)

45 46 47 Supplementary Material 2: Summary of Findings Table

Study	Population	Sample	Criteria for 'Khat User'	Psychiatric Measure*	Results G S 25
Ahmed and Emad 1998 2[35]	Somali immigrants living in Liverpool	Convenience sample of 52 Khat users = 27	Unspecified	GHQ-28	- 11/27 khat users (p=0.72)
4Belew et al. 52000 [36] 6 7 8 9	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
1Numan 2003 [2]37] 3 4 5	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, symptoticism - Khat users had less phobic anxiety (37.7% vs 55.5%, p<0.05)
7Odenwald et 8al. 2005 [38] 9 0 1 2	'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 regartive screened individuals (46.6% vs 29.9%, p<0.001) 10, 2025
Deyessa et 6al. 2008 [39] 7 8 9	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)

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Odenwald et	Armed	8124 armed	Anyone who has	CIDI	- 8.9% of khat users experienced paranoid ideation
al. 2009 [40]	combatants in	individuals (not	chewed khat within the		compared to 2.6% of non-users
6	Somali	random as still in	last week		ding
7		conflict at time of			yn 2
8		study)			on 25 July Ens
10		Khat users =			ing.
15	A 1 1/ ' T'	36.4%	H WHO 1:1 / 1	CD 0 20	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Damena et	Adults in Jimma	Random sample of 1308	Uses WHO-validated substance abuse	SRQ-20	- 49/136 long-term
al. 2011 [41]	City, Ethiopia	Khat users = 38%	questionnaire, but		distress, compatible of 108/317 short-term khat chewers (less that we years), and 153/747 non-users
14 15		Kiiai useis – 30%	unsure what is		See
16			classified as 'khat		ade peri
17			user'		d dr deur
Fulloch et	Adult Somali	Secondary data	Anyone who has	Diagnosis	- 28/30 khat users Experienced psychosis compared to
al. 2012 [42]	khat users living	based on 172	chewed khat within the	provided by	2/30 non-users (p< 2/20)
21	in South London	eligible Somali	last year	service	ng.
22		mental health	-	records	AI 1
23		patients			pen
24		Khat users = 47%			nin g
Dessie et al.	Students in	Random sample of	Anyone who has ever	SRQ-20	- 59/185 khat users experienced mental distress compared
¹ / ₂ 2013 [43]	Ethiopia	413	used khat		to $34/245$ non- $\frac{1}{6}$ sers (AOR = 2.23, 1.14-4.35, p<0.05)
28	TT 1	Khat users = 43%	771 . 1 1	DDD G	<u> </u>
29Fekadu 2014	Holy water users	409 individuals	Khat use recorded as	BPRS	- 42/53 daily khat-sers experienced symptoms of mental
30[44] 31	from Entoto St	selected using	'never' or 'daily',		illness comparæt tæ $208/363$ non-users (AOR = 2.85,
32	Mary Church,	systematic random	although no indication of the duration of daily		1.42-5.70)
33	Ethiopia	sampling Daily khat users =	usage		1.42-5.70) hnologies
34		12.7%	usage		es. at
35 36Widmann et	Male Somali	Convenience	SDS	CIDI, MINI	- 24% of khat users had psychotic symptoms compared to
37al. 2014 [7]	refugees living	sample of 33 users	~-~	, , , , , , , , , ,	0% of non-chewers (p\(\frac{1}{2}\)0.044)
38	in a	and 15			
39	disadvantaged	comparable			yli og
40 41	-	non-users			уга
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2					igh 202
3	urban settlement in Kenya	Khat users = 69%			2-0618 t, inclu
Dachew et al. 2015 [45] 8 10	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 nonsusers (OR=1.96, 1.32-2.92, p=0.02)
Soboka et al. 42015 [46] 5 6	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 compared to 1247 6 non-users (OR = 1.76, 1.10-2.82)
Zenebe et al. 202015 [47] 21 22 23 24	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 46/13 man-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 set al. 2016 29[48]	Jazan region of Saudi Arabia	Volunteer sample of 70 males Khat dependent = 52.2%	SDS	Q16	- 13/35 dependent sers felt depressed compared to 7/32 non-dependent users (QR = 2.30, 0.7-6.8) - 20/35 dependent sers felt anxious compared to 10/32 non-dependent users (QR = 3.50, 1.2-10.0)
¹ Hersi et al. ² 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 1 26% of non-users (AOR = 2.87, 1.26-6.56)
Hunduma et 6al. 2017 [50] 7 8	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 48/469 non-users (OR = 2.16, 1.47-3.16)
39 40 41 42 43 44		For peer n	eview only - http://bmjopen.k	omi.com/site/abou	ut/quidelines.xhtml

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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-esers (AOR = 6.91, 1.88-25.42, p=0.004)
Mossie et al. 8 2016 [52]	Adults in Ethiopia	Random sample of 650 Khat users = 34%	Khat use within the last 30 days	BDI	- 104/200 khat use had depression compared to 67/390 non-users (AOR = 20.07, 5.56-18.25)
Soboka et al. 2017 [53] 13 14 15	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 khaz-Beers experienced psychological distress, compared of the
⁶ Tariku et al. ¹⁷ 2017 [54] 18 19	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 are ienced mental distress compared to 71/168 non-ascrif (AOR = 2.29, 1.04-5.04)
21Wondemage 22gn et al. 232017 [55] 24	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 = 3.42, 3.04-9.96, p=0.000)
25Yeshaw and 27Mossie 2017 28[56] 29 30	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 = 1.99, 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)
33Bedaso et al. 342018 [57] 35 36	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 ad Sepression, compared to 153/287 non-users (AO) = 2.48, 1.05-5.86, p=0.039)
³ Adraro et al. ³⁸ 2019 [58] ³⁹	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 69/16 non-users (AOR = 4.33, 2.02-9.27, p<0.001
41 42 43 44 45		For peer ro	eview only - http://bmjopen.b	omj.com/site/about	raphique de l'applique de l'ap

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1 2					7	open-zuz	
Ongeri et al. 2019 [59]	Khat-growing regions of Kenya	Random sample of 831 individuals aged 10+ Khat users = 36.8%	Unspecified	PSQ			sperienced at least one psychotic 5.6% of non-users (p=0.26)
Atnafie et al. 102020 [60] 11 12 13 14 15 16 17	Khat chewers in Amhara region of Ethiopia	Convenience sample of 508 participants Khat dependent = 43%	SDS	DASS-21	compared to 57/27 0.98-2.95) - 146/207 khat-dep compared to 133/2 1.57-3.81) - 41/207 khat-depe	Settinement Superes	t users experienced stress h-dependent users (AOR = 1.70, Int users experienced anxiety bn-dependent users (AOR = 2.47, t users experienced depression h-users (AOR = 6.28, 1.67-23.61)
¹⁸ Hajure et al. 20 ² 020 [61] 21 22	Healthcare providers in Ethiopia	Convenience sample of 127 Khat users = 45%	Khat use in last three months	IES-R	- 37/57 khat users		rienced psychological stress, non-users (AOR = 5.74, 1.83-18.1,
² 3Hambisa et ²⁴ al. 2020 [62] ²⁵ ²⁶	Students in Ethiopia	Random sample of 1022 Khat users = 24%	Khat use within last month	BDI			depressive symptoms compared s (OR = 1.60, 1.22-2.27)
28Kelemu et 29al. 2020 [63] 30 31	Students in Ethiopia	Random sample of 404 Khat users = 27%	Anyone who has ever used khat	SRQ-20	to 145/293 non	ilar technolo	erienced mental distress, compared es (AOR = 3.09, 1.74-5.50)
34Mekuriaw et 35al. 2020 [64] 36 37	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 to 149/647 non p=0.001)	axparagence	rienced mental distress, compared is (AOR = 3.57, 2.06-6.18,
³⁸ Yitayih et al. ³⁹ 2020 [65]	Prisoners in a correctional	Random sample of 336 Khat users = 138	DAST-10	PCL:SV	- 32/138 khat users compared to 9/	_	the criteria for psychopathy, non-users
42 43 44 45		For peer r	eview only - http://bmjopen.l	bmj.com/site/abo	out/guidelines.xhtml	inique de i	

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]	institution in				- 16/138 khat users had mental illness, compared to
4	Jimma, Ethiopia				15/191 non-us ∉ s 8
Haile and	Adult primary	Stratified and	Unspecified	PHQ-9	- 67/108 khat users har depressive symptoms, compared
3 Sahile, 2021	healthcare	systematic random	_		to $40/276$ non-users (AOR = 5.43, 2.55-11.56,
8 [66]	attendees in	sample of 384			p<0.01)
9	Ethiopia	Khat users = 39%			Is en
10	_				seig seig
Hambisa et	Hospitalised	Systematic sample	Unspecified; discusses	K10	- 49/59 khat users ienced psychological distress,
al. 2021 [67]	patients in	of 337	'current khat use' and		compared to 1452 non-users (AOR = 4.16,
14	Ethiopia	Khat users = 18%	'khat use in the		1.67-10.35)
15			previous three months'		oac upe xt a
Melaku et al.	Medical students	Systematic	Anyone who has ever	DASS-21	- 37/56 khat users Lag 2 epression, compared to 99/204
⁷ 2021 [68]	in Ethiopia	random sample of	used khat		non-users (OR \(\frac{1}{2} \) \(\frac{1} \) \(\frac{1} \) \(\frac{1}{2} \) \(\frac{1}{2} \) \(\
10		260			- 41/56 khat users anxiety, compared to 117/204
20		Khat users = 22%			non-users (OR 33, 1.06-3.91)
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1					- 30/56 khat users and sychological stress, compared to
22					75/204 non-uses (R = 1.99, 1.09-3.61)
23 *T	ist of abbreviated so	creening tools: GHO-	28 (General Health Quest	tionnaire-28 for	mental disorders). SRO 20 (Self-Reporting

*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 Rauge Scale - for depression, anxiety and hallucinations), SDS (Severity of Dependence Scale), MINI (Mini International Esychiatric 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 Debression, 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 (Psychografied Checklist: Screening Version), K10 (Kessler Psychological Distress Scale - 10 questions)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Stress Scale - 21 Items), PHO-9 (Patient Health Questionnaire - 9 items, for depression), PSO (Psychosis screening Questionnaire),

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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 of 25
Ahmed and Emad 1998 [21]	1	2	1	4	- Non-random sample regions size - No justification of sample size - 100% response rate - Questionnaire described on the property insufficient detail no definition of khat use - No significant difference on baseline characteristics between khat users and appropriate the property of
Belew et al. 2000 [22]	3	2	2	7	- Insufficient details of bondesponders; no baseline characteristics provided - Questionnaire described in limited detail but methods do define current, past and bever khat use
Numan 2003 [23]	3	1	1	5	- Sample size not justified - Eight non-respondents expuded 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 in luded
Odenwald et al. 2005 [24]	3	2	2	7	- Sample size not justified

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					collection 5 6 - Uses clinical interviews 5 included
Deyessa et al. 2008 [25]	3	2	3	8	- Providers reasons for Ron-Tesponders but not characteristics - Non-validated but deserged method of khat usage data collection - Clinical interview
Odenwald et al. 2009 [26]	2	2	2	6	- Sample size not justified a - No details of non-respectives Non-validated but desembled method of khat usage data collection - Uses self-report
Damena et al. 2011 [27]	4	1	1	6	- Providers reasons for non-gesponders but not characteristics - Uses WHO-validated that 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 seed - Missing information descussed - Non-validated but deseribed 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

				BMJ Open	Page 3 Page by copyrigh
	Τ				- Uses self report inc 61
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 and a second sec
Dachew et al. 2015 [31]	2	2	2	6	- Justification of samples to unsatisfactory - No details of non-respective of method of khat usage data collection - Uses self-report
Soboka et al. 2015 [32]	3	2	2	7	- All eligible participants in vited to participate - Limited description of responders (gender only) - Non-validated but des ribed method of khat usage data collection - Uses self-report
Zenebe et al. 2015 [33]	3	2	3	8	- No details of non-respenders - Non-validated but deserbed method of khat usage data collection - Medical records used in the collection at the collection
El-Setouhy et al. 2016 [34]	4	2	2	8	- Volunteer sample; no non gesponders - 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

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					collection in the collection of the collection o
Hunduma et al. 2017 [36]	3	2	2	7	- No details of non-responders - Non-validated but desembled 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 deserbed method of khat usage data collection - Uses self-report
Mossie et al. 2016 [38]	3	2	2	7	- No details of non-respectives Non-validated but desembled 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 drawing in the conclusions and conclusions in the conclusions are conclusions. - 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-respenders - Non-validated but deserbed 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

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					- Only one community studed 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 deserged method of khat usage data collection - Uses self-report
Bedaso et al. 2018 [43]	3	2	2	8	- 100% response rate - Limited description of the
Adraro et al. 2019 [44]	3	2	2	7	- No details of non-respectivers - Non-validated but deseribed method of khat usage data collection - Uses self-report
Ongeri et al. 2019 [45]	2	2	2	6	- No details of non-respectives 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-respenders - Non-validated but deseribed 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

3 of 38				BMJ Open	136/bmjopen-202
					- Non-validated but des ribed method of khat usage data collection - Uses self-report of
Kelemu et al. 2020 [49]	3	2	2	7	- No details of non-responders - Non-validated but deserbled method of khat usage data collection - Uses self-report
Mekuriaw et al. 2020 [50]	3	2	2	7	- No details of non-respectives - Non-validated but deserted method of khat usage data collection - Uses self-report
Yitayih et al. 2020 [51]	4	2	2	8	- Provides reasons for new provides reasons fo
Haile and Sahile, 2021 [52]	3	2	2	7	- 100% response rate
Hambisa et al. 2021 [53]	2	2	2	6	- Providers reasons for Fon Fesponders 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	l² 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

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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 Protected <0.00001 by
Hajure et al. 2020	2.17	1.72-2.73	92	<0.00001 g
Hambisa et al. 2021	2.19	1.74-2.76	92	<0.00001 copyright,
Hersi et al. 2017	2.22	1.75-2.80	92	<0.00001 th
Kelemu et al. 2020	2.23	1.77-2.82	92	<0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001 <0.00001
Kerebih et al. 2017	2.19	1.74-2.76	92	<0.00001 fg
Mekuriaw et al. 2020	2.19	1.74-2.76	92	<0.00001 se
Melaku et al. 2021	2.23	1.76-2.81	92	<pre><0.00001</pre>
Soboka et al. 2015	2.23	1.77-2.82	92	<0.00001 to
Soboka et al. 2017	2.24	1.78-2.83	92	<0.00001 ts Supe
Tariku et al. 2017	2.25	1.78-2.84	92	<0.00001 nd da
Yeshaw and Mossie et al. 2017	2.21	1.75-2.79	92	<0.00001 ta min
Psychotic symptoms/disorders	•		•	<0.00001 m m m m m m m m m m m m m m m m m
Numan 2003	2.26	1.78-2.86	92	<0.00001 tr
Numan 2003	2.27	1.80-2.87	91	<0.00001 g
Odenwald et al. 2009	2.27	1.80-2.87	91	<0.00001 and s
Ongeri et al. 2019	2.25	1.78-2.85	92	<0.00001 milar
Tulloch et al. 2012	2.14	1.70-2.68	91	<0.00001 tech
Widmann et al. 2014	2.20	1.75-2.77	92	<0.00001 technolog
Zenebe et al. 2015	2.23	1.76-2.82	92	<0.00001 ⁸
Psychopathy	•	•	•	•
Yitayih et al. 2020	2.18	1.73-2.74	92	<0.00001 similar technologies. <0.00001 co.00001 co.00001 co.00001 <0.00001 co.00001 <0.00001
Unspecified psychiatric symptoms/	/disorders	•	•	•

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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
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PRISMA 2020 Checklist

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Section andTopic	Ite m#	Checklist item	06186	Location where item is reported
6 TITLE		<u></u>	5 c	
7 Title	1	Identify the report as a systematic review.	n 2	Title, page 1
8 ABSTRACT		Louis PRIOM 2000 C. A. J.	5	
9 Abstract	2	See the PRISMA 2020 for Abstracts checklist.	<u> </u>	Abstract page 2
10 INTRODUCTION	2	,	207	Introduction pages 2.2
1 Rationale	3	Describe the rationale for the review in the context of existing knowledge.	22	Introduction, pages 2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	D	Introduction, page 3
15 METHODS 14 Eligibility criteria 15 16 17 18	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. Superior A mi.	nloaded from ht	Inclusion/exclusion: methods (study eligibility) page 4 Grouping for synthesis: results (symptoms explored within included studies): page 6
20 Information 21 sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted studies. Specify the date when each source was last searched or consulted.	Mentify P	Methods (literature search), page 3
22 Search strategy 23	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	njope	Methods (literature search), page 3
24 Selection process 25 26	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how mangered screened each record and each report retrieved, whether they worked independently, and if applicable, details at tools used in the process.		Methods (literature search), page 3-4
27 Data collection 28 process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable automation tools used in the process.		Methods (data collection and quality assessment), page 4-5
30 Data items 31 32	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to results to collect.	utcome cide which 0, 20	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
33 34 35 36	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding Describe any assumptions made about any missing or unclear information.	Sources).	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
3 Study risk of bias 38 assessment 39 40	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how mare reviewers assessed each study and whether they worked independently, and if applicable, details of automation too the process.		Methods (data collection and quality assessment), page 4-5 and supplementary material 1
4 Effect measures 42 43	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation results.	aghique de	Methods (data collection and quality assessment), page 4-5 and supplementary material 1
45 Synthesis	13a	Describe the processes used to decide which studies where bigible for jeach synthesis (e.g., tablitating the study inte	r ∨e ntion	Methods (study eligibility),
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PRISMA 2020 Checklist

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Section and Topic	Ite m#	Checklist item	Location where item is reported
methods	111 #	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 semments statistics, or data conversions.	NA
φ	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 parallels.	Methods (synthesis of findings), page 5
4 4	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
† 6 7	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 best and	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		<u>2i </u>	
f Study selection 5 6	16a	Describe the results of the search and selection process, from the number of records identified in the search to be removed in the review, ideally using a flow diagram.	Results (included and excluded studies) pages 5-6, Figure 1
7 8	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. ar techr 10	Results (summary of included studies) pages 5-6, Supplementary material 1
Pisk of bias in studies	18	Present assessments of risk of bias for each included study. Ogeographics 2025 at	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
ф 1 2	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, described direction of the effect.	Results (meta-analysis) page 6, Figure 2
1 3 4	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 a sessite to business of the synthesized results all	Results (sensitivity analysis)



PRISMA 2020 Checklist

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Page 39 of 38 PRISMA 2020 Checklist 1 2							
3 Section and 4 Topic	Ite m#	Checklist item)22-06 ht, in	Location where item is reported			
5			1865 . Sludin	page 7, supplementary material 3			
7 Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis a	25 or	Results (summary of included studies) pages 5-6			
9 Certainty of 10 evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	July 20 Enseig	Results (meta-analysis) page 6, Figure 2, results (GRADE Analysis) page 7			
DISCUSSION			22. I				
13 Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	1 to	Discussion, pages 7-8			
14	23b	Discuss any limitations of the evidence included in the review.	22. Downle	Discussion, pages 7-8			
1\$	23c	Discuss any limitations of the review processes used.	ੇ 5 a	Discussion, pages 7-8			
16	23d	Discuss implications of the results for practice, policy, and future research.	a erie	Discussion, pages 7-8			
17 OTHER INFORMA 18 Registration and	TION 24a	Provide registration information for the review, including register name and registration number, or state that the	<u>g ⊊ ₹</u> he s fe≆i g w was not	Methods page 3			
19 protocol		registered.	<u>⋾</u> .₩ <u>₹</u>				
20	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	ning S)	Methods page 3			
2]	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3 b	Methods, page 3			
2f Support 23	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in	n the review.	Acknowledgements pages 8-9, and funding page 9			
² Competing ² interests	26	Declare any competing interests of review authors.	. <mark>bmj.</mark> ıing, a	Competing interests, page 8			
26 Availability of 27 data, code and 28 other materials	27	Report which of the following are publicly available and where they can be found: template data collection for from included studies; data used for all analyses; analytic code; any other materials used in the review.	msedation extracted similar	References pages 9-14			
29 30 <i>From:</i> Page MJ, M 31 10.1136/bmj.n71	1cKenzie	JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for	-	reviews. BMJ 2021;372:n71. doi:			
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