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Prevalence of Depression in Vitiligo Patients- A Systematic Review and Meta-Analysis

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ABSTRACT

Background: the incidence of depression in vitiligo patients ranges from 10% to over 60%, depending on the outcome measures, sample size and study population. The purpose is to estimate the prevalence of depression among vitiligo patients by conducting a systematic review and metanalysis of published studies.

Methods: we conducted a literature search on Medline via PubMed, Scopus, web of science and Cochrane library.

Results: 35 studies finally met our inclusion criteria. Our findings showed that the overall prevalence of depression among patients with vitiligo was 35 % (26%-45). Moreover, we observed a variation in the prevalence based on the used tool. For example, the GHQ revealed 30% (20%-39%) and the HDRS revealed 50% (44% - 57%). Our analysis demonstrated no significant differences between vitiligo and healthy cases in terms of HDRS and DBI. Moreover, there was no significant differences between vitiligo and psoriasis in terms of GHQ and BDI scores.

Conclusion: in conclusion the current evidence suggests that patients with vitiligo have a high risk and prevalence of depression, different questionnaires have yielded variable prevalence due to the different domains and validation method.

Key Words: Vitiligo, Depression, Prevalence, Risk factors

INTRODUCTION

Depigmentation disorders such as vitiligo affect 0.5% to 2% of the worldwide people.[1] White patches or macules may appear on different regions of the body as a result of a lack of functional melanocytes.[2,3] Vitiligo is known to have substantial psychological effects because of its cosmetic disfigurement.[4] Patients who have vitiligo may have a substantial reduction in their quality of life because of its chronicity and visibility.[5] Additionally, vitiligo patients may suffer from embarrassment and stigmatization because of their appearance, which may lead to depression, social isolation, and low self-esteem.[6,7]

Depression and vitiligo have been linked in many epidemiological studies[8–10]; in contrast, several studies have not been able to demonstrate this link[11,12]. Although validated psychometric tools were used in most studies to assess depressive symptoms, a few studies identified depression clinically based on the criteria outlined in "Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)".[13] Studies have used a variety of depression screening questionnaires and rating scales, including Depression anxiety stress SCALE (DASS), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Emotional State Questionnaires (ES-Q), Hospital Anxiety and Depression Scale (HADS), and Centre for Epidemiologic Studies Depression Scale (CES-D). Even among investigations that utilized the same instrument, various cut-offs may be applied. Because of the variety of research designs, it's difficult to deter-

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mine if vitiligo is associated with depression. The incidence of depression in vitiligo patients ranges from 10% to over 60%, depending on the outcome measures, sample size, and study population.[14,15] Hence, this study aimed to estimate the prevalence of depression among vitiligo patients by conducting a systematic review and meta-analysis of published studies.

MATERIALS AND METHODS

We prepared this review with a careful following of the Cochrane Handbook for Systematic Reviews of Interventions. We also followed The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines during the design of our study.

Literature search: We performed a literature search via PubMed, Web of Science, Scopus, and Cochrane Library using the following keywords: *"Vitiligo", "Depression", "Depressive Disorder", " Antidepressant*. We combined these keywords with balloon operators OR, AND as following: *Vitiligo AND (Depression OR Depressive Disorder OR Antidepressant)*. We searched bibliographies of the identified papers for possible eligible studies. We searched for articles that were included in previous related systematic reviews. We used Endnote X8 software package (Thompson Reuter, USA) to retrieve the identified citations.

Eligibility criteria: We included studies in the English language that were conducted on patients with vitiligo to assess the prevalence or risk factors of depression. All primary studies were included, except case series with less than ten patients. We excluded animal studies, reviews, book chapters, thesis, editorial letters, and papers with an overlapped dataset. We screened the identified articles at two phases; title and abstract screening followed by full-text screening; each phase was performed in dependently by two authors. We removed the duplicated articles manually during screening or using the Endnote X8

program (Thompson Reuter, USA).

Data extraction: Two independent authors extracted data and revised by another two independent authors. The following study characteristics were extracted: name of the first author, year of publication, study country, study setting, types of vitiligo, duration of disease, and patient demographics such as age and gender of participants.

Statistical analysis: We pooled data as were pooled as mean difference (MD) and 95% confidence interval (in continuous data), or as odds ratio (OR) and 95% confidence interval (in categorical data). Open Meta-analyst software was used to pool studies. We used the I^2 square test to quantify the degree of heterogeneity across the studies. In certain outcomes, we used Revman 5.4 to pool outcomes.

RESULTS

Result of literature search: We obtained articles from PubMed (n=145), Scopus (n=364), Cochrane library (n=3), and Web of Science (n=136). Duplicated articles (n=156) were removed using the Endnote X8 program, 492articles underwent title\abstract screening, and 186 articles underwent full-text review **(Figure1)**. Thirty-five studies were eligible to be included in our study.

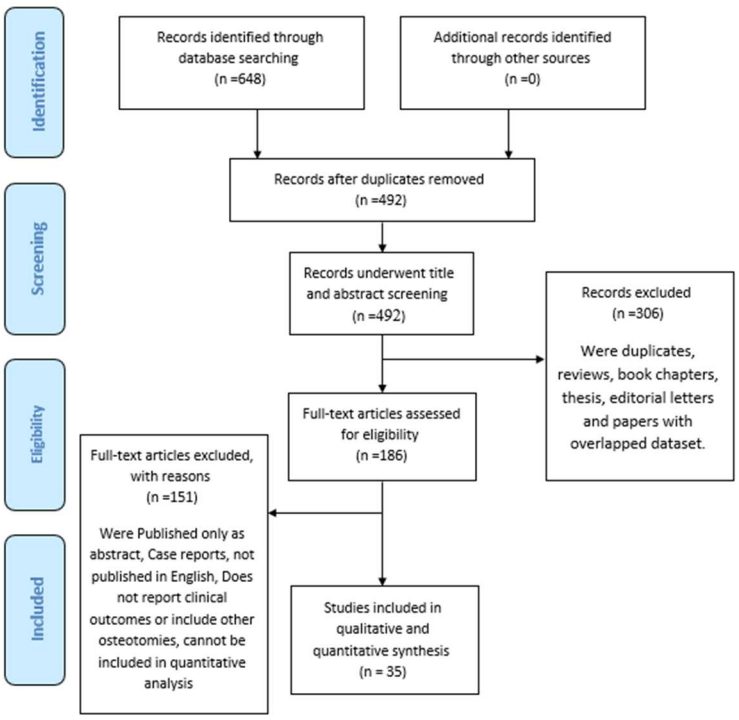

Figure 1: PRISMA flow diagram

Table 1: characteristics of included studies

Study ID	Type of study	Country	N	Age (years) mean (SD\range)	Scores used for depression	Females (N)	Males (N)	Location of vitiligo	Mean duration of vitiligo
Ahmed et al. (2007)	Cross sectional	Pakistan	100	24 6	GHQ-12 and ICD	62	38	NA	NA
Abdelmaguid et al. (2022)	Cross sectional	Egypt	100	(18 – 60)	HDRS	76	24	NA	NA
Ajose et al. (2014)	Case control	Nigeria	102	35.9 (13.65)	HADS	51	51	Segmental= 24 (24%), Non-segmental=61 (60%,) Mucosal=8 (8%), Genital= 9 (9%)	<6months=41 (40%), 6 months–2years =25 (25%), >2 years =36 (35%)
Arycan et al. (2008)	Cross sectional	Turkey	113	29.2 (2–71)	ICD	60	53	Upper limbs = 43(38.1%) Lower limbs= 15(13.3%) Trunk= 17(15%) Head and neck= 28(24.8%) Genital area= 10(8.8%)	<1 year = 23 (20.4%) <2 years = 51 (45.1%)
Balaban et al. (2011)	Case control	Turkey	42	39 7	DSM-IV and HADS	23	19	NA	NA
Baidya et al. (2021)	Cross sectional	India	80	NA	ICD	48	32	NA	NA
Chan et al. (2013)	Cross sectional	Singapore	222	48 4 (14.9)	CES-D	117	105	Generalized= 88 (39.6) Localized= 134 (60.4)	NA
Choi et al. (2010)	Cross sectional	Korea	57	15 4 (1.8)	CES-D	30	27	<1% of body surface area = 29 (50.9%) Involvement of face = 42 (73.7%)	3.9 ± 3.8 years
Esfandiar et al. (2003)	Cross sectional	Iran	120	38 4	HDRS	74	46	NA	NA
Erdoğan et al. (2020)	Case control	Turkey	30	13 (3.03)	BAI	13	16	Vulgaris=15 (51.7%) Focal = 13 (44.8%) Segmental = 1 (3 .4%)	31.4 (35.5) months
Ghajarzadeh et al. (2012)	Cross sectional	Iran	100	28 9 (11.5)	BDI	50	50	NA	NA
Karelson et al. (2013)	Case control	Estonia	54	36 6	ES-Q	32	22	Vulgar = 43 (79.6%), Focal = 4 (7.4%), acrofacial = 3 (5.6%), segmental = 3 (5.6%) universal = 1 (1.9%).	11.3 years
Kent and al-Abadie M (1996)	Cross sectional	UK	614	46 6	GHQ	NA	NA	NA	NA
Kruger & Schallreuter (2015)	Case control	Germany	96	41 7 (18–67)	BDI	NA	NA	NA	17.4 (1–51) years
Maleki et al. (2005)	Case control	Iran	52	NA	HDRS	NA	NA	NA	NA
Mattoo et al. (2001)	Case control	India	113	30 11 (12.49)	GHQ-12 and ICD	51	62	NA	9.01 (9.63) years
Nasser et al. (2020)	Case control	Egypt	50	34.69 (5.87)	DASS	NA	NA	Acral = 3 (6%) Focal = 12 (24%) Segmental = 12 (24%) Generalized = 22 (44%) Universal = 1 (2%)	NA

Continue……

Study ID	Type of study	Country	N	Age (years) mean (SD\range)	Scores used for depression	Females (N)	Males (N)	Location of vitiligo	Mean duration of vitiligo
Noh et al. (2013)	Case control	Korea	60	35 1 (9.8)	BDI	29	31	Segmental = 4 (7.3%) Vulgaris = 34 (61.8%) Focal = 13 (23.6%) Acrofacial= 4 (7.3%)	6.76 (7.05) years
Osman et al. (2009)	Cross sectional	Sudan	111	NA	GHQ	NA	NA	NA	NA
Picardi et al. (2000)	Cross sectional	Italy	32	NA	GHQ	NA	NA	NA	NA
Ramakrishna and Rajni (2014)	Cross sectional	India	53	NA	HDRS	NA	NA	NA	NA
RahulKrishna et al. (2020)	Case control	India	150	NA	clinically	83	67	NA	NA
Saleki and Yazdanfar (2015)	Case control	Iran	110	43 8	HDRS	60	50	Generalized (49.2%), Localized (31.8%) Universal (19.1%).	NA
Sampogna et al. (2008)	Cross sectional	Italy	181	35	GHQ	124	57	Generalized (64%), Focal (13%), Acrofacial (9%), Segmental (5%), Acral (2%), Symmetrical (1%)	9.2 (0–52) years
Sangma et al. (2015)	Case control	India	100	29 7	HDRS	59	41	NA	NA
Shah et al. (2014)	Cross sectional	U.K.	24	NA	HADS	NA	NA	NA	NA
Sharma et al. (2001)	Cross sectional	India	30	NR	GHQ-H and DSM-IV	NA	NA	Localized= 8 (26.7%) Generalized=14 (46.7%) Acrofacial = 7 (23.3%) Segmental = 1 (3.3%) Universal= 0(0%)	
Yamamoto et al. (2011)	Cross sectional	Japan	54	NR	CES-D	NA	NA	NA	NA
Yanik et al. (2014)	Case control	Turkey	57	43 63 (13.48)	BDI (10)	32	26	NA	NA
Salman et al. (2016)	Cross sectional	Turkey	37	31.8 (9.7)	HADS	20	17	NA	6.2 (6.5) years
Önen et al. (2018)	Case control	Turkey	41	10.71 (2.21)	BDI	22	19	NA	NA
Sawant et al. (2019)	Case control	India	100	NA	BDI	44	56	NA	NA
Yamamoto et al. (2011)	Cross sectional	Saudi Arabia	308	NA	BDI	NA	NA	Head and face= 28 (9.1%) Hands and feet= 144 (46.8%) Generalized= 136 (44.2%)	<4 years= 168 (54.5%) ≥4 years= 140 (45.5%)
Hamidizadeh et al. (2020)	Case control	Iran	100	34.5 (12.2)	BDI	69	31	NA	Female = 22.9(14.3) years Male = 25.6(12.3) years
Yamamoto et al. (2011)	Cross sectional	Thailand	104	41.55 (15.92)	PHQ-9	NA	NA	Segmental = 24 (23.1%) Non-segmental=80 (76.9%)	8 (10.05) years

NA: not available

Characteristics of included studies: We identified 35 studies that evaluated depression in vitiligo patients (n= 3631). The mean age of patients across the studies ranged between 24years and 36 years. A high majority of included cases were females**.** Data were collected mostly from outpatient dermatology clinics. Several scores were used to estimate depression among groups, including the Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) and. The study design of included studies was cross-sectional or case-control studies (**Table 1).**

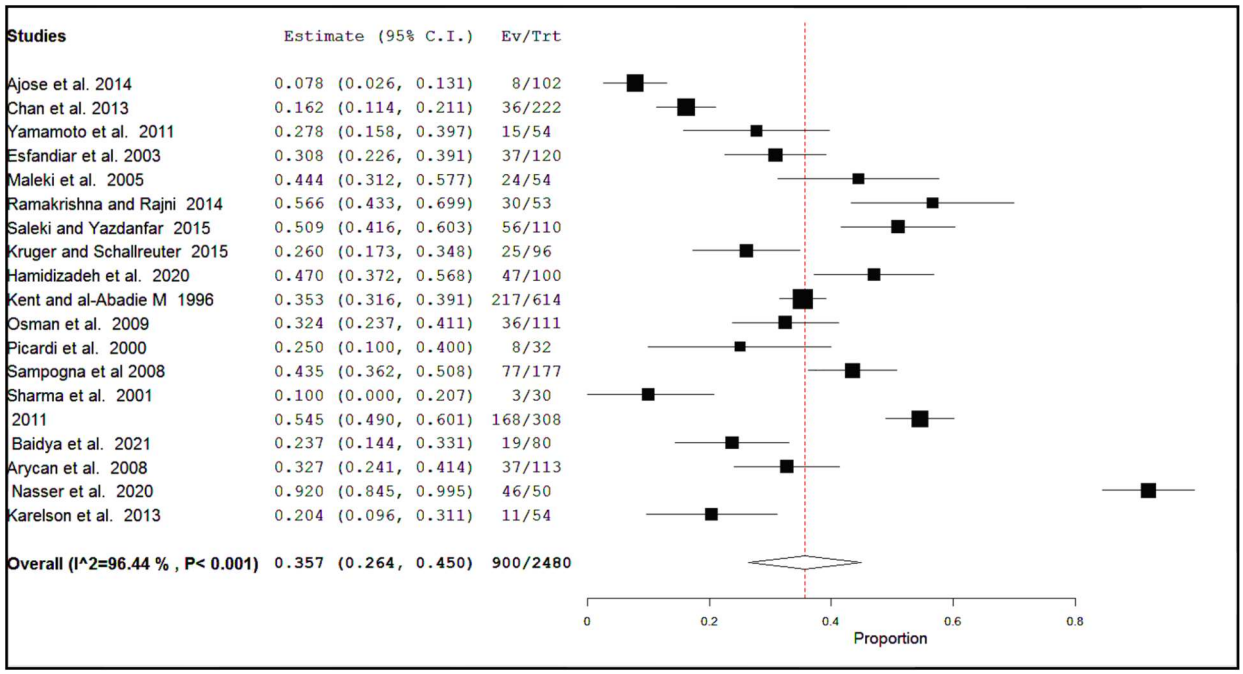

Figure 2: **Overall prevalence of depression in vitiligo cases.**

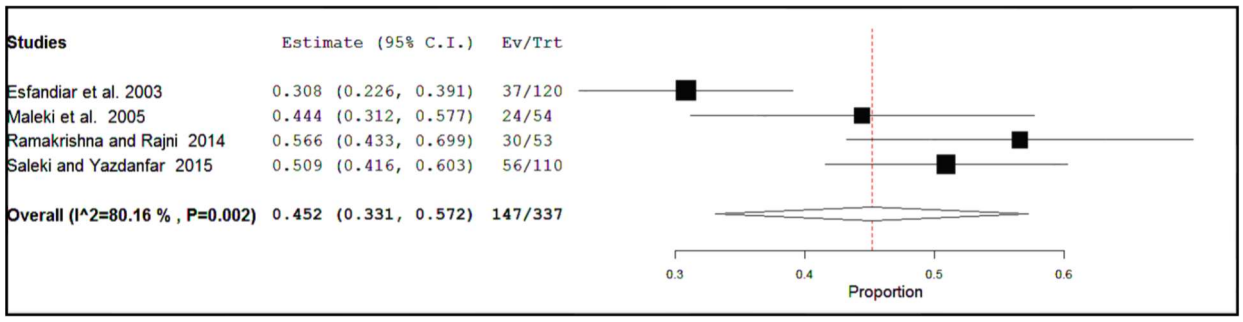

Figure 3: **Prevalence of depression in vitiligo cases according to Hamilton depression rating scale (HDRS)**

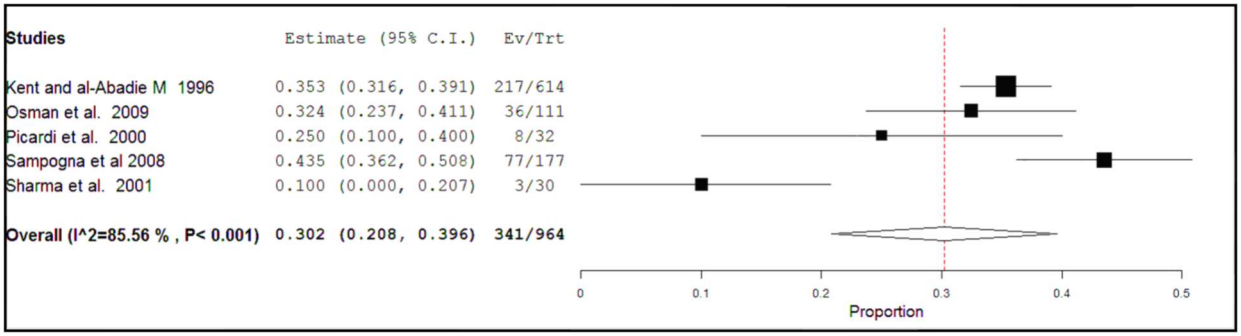

Figure 4: **Prevalence of depression in vitiligo cases according to the 12-item General Health Questionnaire (GHQ)**

OUTCOMES

Overall prevalence of depression in vitiligo cases

Nineteen studies were included in the analysis, with an overall 2480 vitiligo cases. Depression prevalence was estimated to be35% [95% CI= 0.26: 0.45]. However, there was heterogeneity across the studies regarding the exact prevalence of depression [I^2=96.44%, P<0.001] **Figure 2**. This may be due to different scores used to estimate depression prevalence. Therefore, we conducted a subgroup analysis using each score individually.

Four studies assessed depression prevalence in vitiligo cases according to the HDRS, with an overall of 337 vitiligo cases. Depression prevalence was estimated to be 45% [95% CI= 0.33: 0.57), I^2=80.1%, P=0.002] **Figure 3.** However, after performing sensitivity analysis by excluding **Esfandiar et al. (2003)**, we found there is no heterogeneity across the studies [I2=0%, P=0.447], with depression prevalence of 50% [95% CI= 0.44: 0.57].

Five studies assessed the prevalence of depression in vitiligo cases according to 12-item General Health Questionnaire (GHQ**)**. Depression prevalence was 30% [(95% CI= 0.20: 0.39), I^2=85.5%, P<0.001] **Figure4.**

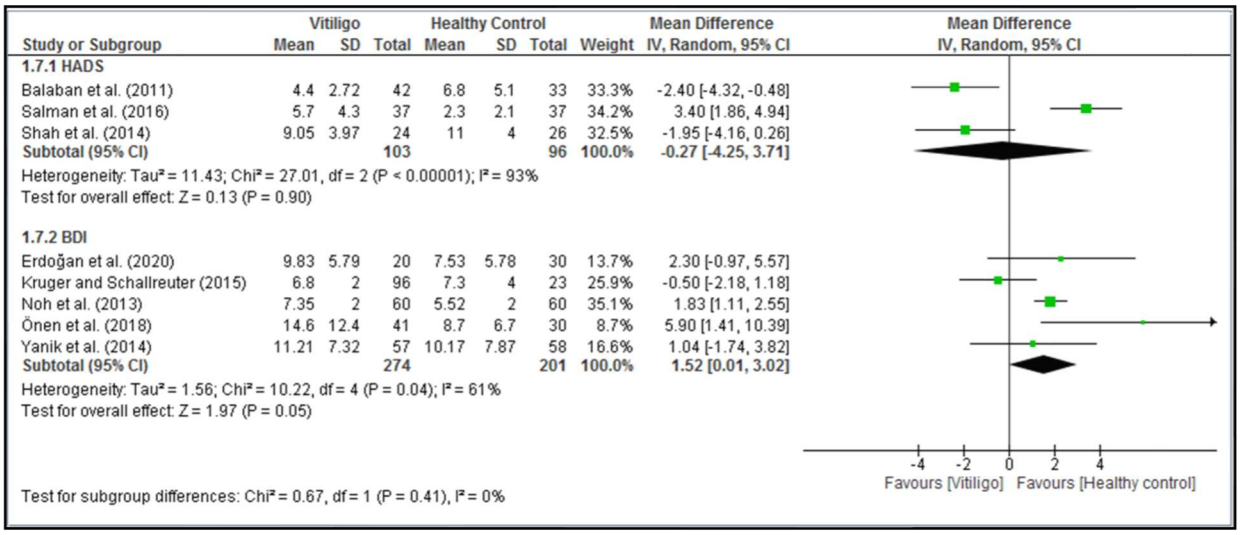

Figure 5: Comparison between vitiligo cases and other groups A) Hospital Anxiety and Depression Scale (HADS) B) Beck Depression Inventory (BDI)

Figure 6 A)

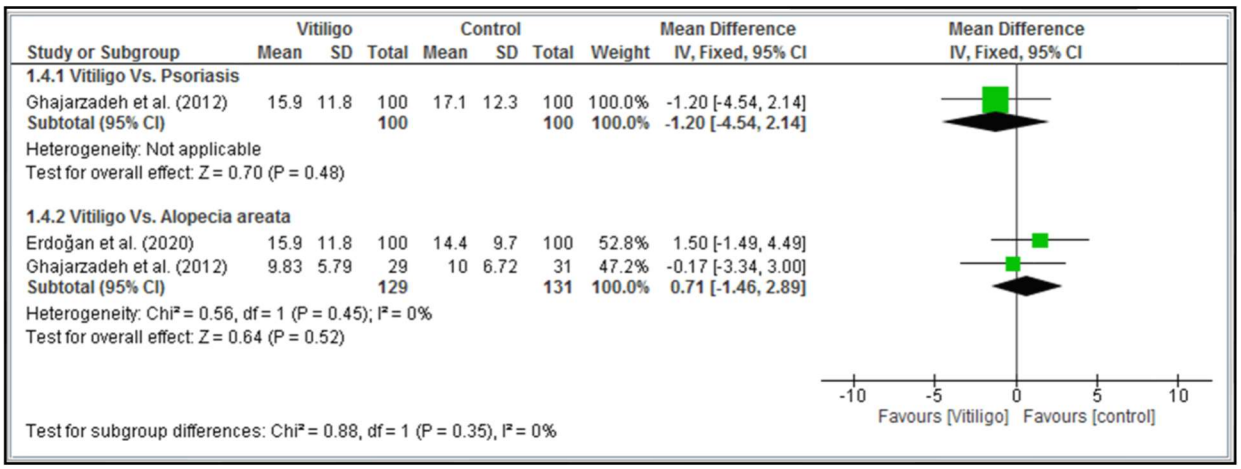

Figure 6 B)

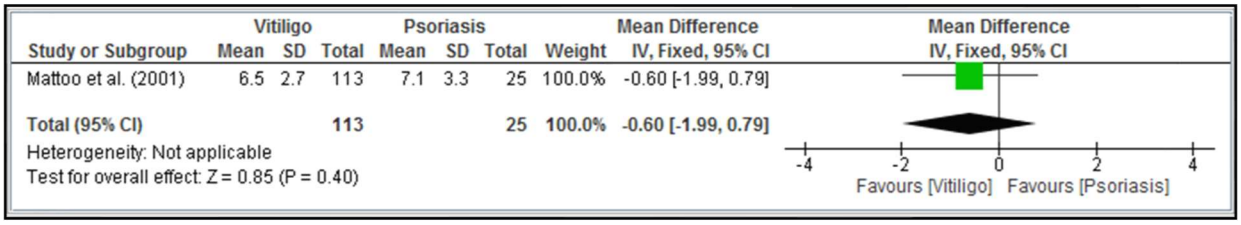

Figure 6: Comparison between vitiligo cases and other skin conditions according to A) BDI, B) GHQ

Comparison between vitiligo cases and other groups

Two scores were used to compare vitiligo cases and healthy control; HADS and BDI. We analyzed results from eight studies; 377 patients in vitiligo groups were compared to 297 healthy controls. We found that both groups performed equally in both scores with no statistically significant difference regarding HADS score [MD = -0.27, (95%= -4.25: 3.71), I^2=93%, P<0.001] **and but there was significant difference regarding** DI score [MD = 1.52, (95% CI= 0.01: 3.02), I^2=61%, P=0.041]**.** However, it is worth noticing that studies were not consistent regarding score estimation for each group. **Figure 5**

Vitiligo cases other skin conditions

We identified four studies that compared vitiligo to psoriasis and alopecia areata. According BDI, mean depression score was similar in vitiligo cases compared to psoriasis and alopecia areata. [MD = -1.20, (95% CI= -4.50: 2.15), and [MD = 0.71, (95% CI= -1.46: 2.89), I^2=0%, P=0.45] respectively **Figure 6a**. Also using GHQ scale, vitiligo cases and psoriasis case had similar score [MD = -0.60, (95% CI= -1.99: 0.79) **Figure 6b.**

Relation between gender and depression in vitiligo cases

We summarized the mean depression scores in the males and females' groups in **Table 2**. A total of 256 females were included versus 195 males. Mean scores were higher in female groups across different scales. This finding was consistent across the studies. We graphically represented these data in a forest plot, as shown in **Figure 8**. We were able to pool data from two studies, **Saleki and Yazdanfar (2015) and Sangma et al. (2015);** both studies were consistent in their findings [MD = 3.58, (95% CI= 2.61: 4.55), I^2=0%, P=0.46] **Figure 8**.

Table 2: Mean scores of depressions in females versus males

Study ID	score	Females			Males		
		Mean	SD	N	Mean	SD	N
Balaban et al. (2011)	HADS	8.7	5.42	23	4.6	3.7	19
Saleki and Yazdanfar (2015)	HDRS	8.82	3.7	62	5.52	2.84	48
Sangma et al. (2015)	HAMD	10.7	3.7	59	6.63	4.28	41
Sawant et al. (2019)	BDI	28.04	20.5	44	17.37	17.16	56
Hamidizadeh et al. (2020)	GHQ	27.74	15.55	68	23.68	14.18	31

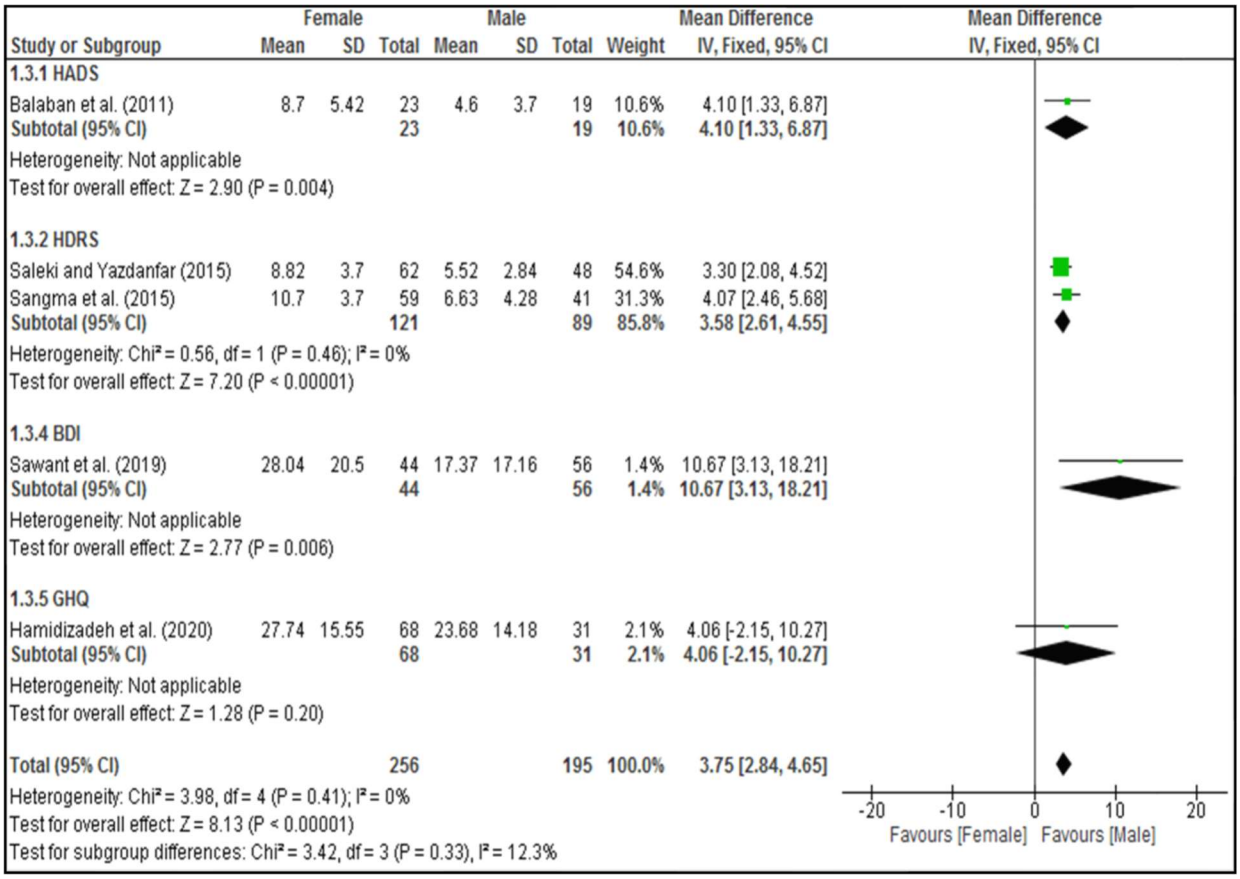

Figure 7: **Comparison between Females and male vitiligo cases**

DISCUSSION

Chronic disorders including heart failure, Parkinson's disease, diabetes, and others have all been linked to higher rates of depression in patients. Vitiligo is the most frequent depigmenting condition; however, there are no efficient or adequate therapies for the disease at this time.[16] Mental health is undoubtedly affected by Vitiligo's characteristics. In vitiligo, the loss of pigmentation has been linked to neuroendocrine dysregulation, which is thought to be a cause of depression. It has been speculated that elevated levels of acetylcholine (Ach)and norepinephrine (NE) have a significant impact.[17] It was shown that up to 62.5% of instances of skin pigmentation loss were caused by psychosocial factors.[18] Mental stress triggers an increase in catecholamines, which bind to and activate alpha-receptors in skin arterioles and cause vasoconstriction, oxygen radical overproduction, and eventually melanocyte death.[19,20] Acetylcholinesterase (AchE) activity is likewise lowered in vitiliginous skin during depigmentation, resulting in higher suppression of dopa oxidase activity in melanocytes by Ach.[21] Patients with both vitiligo and depression may benefit from amitriptyline, an antidepressant with significant anticholinergic action, and a mild NE reuptake inhibition, according to Namazi.[17] Psychological stress may be detected in individuals with vitiligo by using the Vitiligo Impact Scale-22 (VIS-22), a quality-of-life assessment specifically designed for people with vitiligo.[22] Cognitive-behavioral therapy (CBT) for stress reduction may be beneficial to these patients, which may improve repigmentation.[23]

In this systematic review and meta-analysis, our findings showed that the overall prevalence of depression among patients with vitiligo was 35% (26% - 45%). Moreover, we observed a variation in the prevalence based on the used tool, for example, the GHQ revealed 30% (20% - 39%) and the HDRS revealed 50% (44% - 57%). Our analysis demonstrated no significant difference between vitiligo and healthy cases in terms of **HDRS and DBI**. Moreover, there was no significant difference between vitiligo and psoriasis in terms of GHQ and BDI scores. In addition, patients with vitiligo and alopecia areata were comparable in terms of BDI scores. When comparing both genders, mean scores were higher in female groups across different scales.

Subclinical depression or severe depressive symptoms may be present in a considerable proportion of vitiligo patients, affecting their quality of life. More than a third of vitiligo patients reported symptoms measured by standardized questionnaires, which may capture milder somatic symptoms that may not yet meet the complete criteria for clinical depression. Patients with psoriasis were reported to have both physical and psychosocial impairment.[24] Psoriasis patients had a significantly higher rate of mental morbidity than vitiligo patients in the Sharma et al. study (p=0.0028), which was determined by applying the GHQ-H. The prevalence of depression was 23.3% and 10% in psoriasis and vitiligo respectively and anxiety was observed in 3.3% of each group. Sleep problems were reported by 56.6% of people with psoriasis and 20% of those with vitiligo as the most prevalent complaint.[25]

Using data from 25 studies including 2708 patients, Lai et al. analyzed the prevalence of depression and general health in adults with vitiligo throughout the world.[26] Depression affected 25.3% of vitiligo patients, according to ICD codes. A prevalence of 12.2% was found when adopting DSM-IV criteria; however, a prevalence of 33.6% was found when using self-reported surveys. Using questionnaires to assess prevalence was shown to be more accurate than relying on clinical diagnosis. As a result, questionnaires such as the HAD and CES-D are often used to quantify the presence of depressive symptoms rather than the entire criteria for a diagnosis of clinical depression. When they combined depression-specific self-reported questionnaires, the overall prevalence of depression was comparable to our (34%). Patients with vitiligo have been shown to be more susceptible to depression than healthy controls (without adjustment for confounders). Patients with vitiligo were not compared to those with other skin disorders for depression prevalence.[26] Osinubi et al., also conducted a meta-analysis to assess the prevalence of psychological co-morbidity in patients with vitiligo. They included 29 studies with 2530 patients. Both depression and anxiety were evaluated with an estimated prevalence of 29% and 33%, respectively. When they pooled the findings of clinical diagnosis tools, the estimated prevalence was 21% for depression and 15% for anxiety.[27] Another meta-analysis by Wang et al. showed that the overall prevalence of depression in patients with vitiligo was 29%, 8% by DSMIV and ICD-10 clinical diagnosis, and 33% by the validated screening rating scales. Patients with vitiligo were almost five times as likely to be depressed than those without the condition. Depression was found to be more common in Asian and female vitiligo patients than in Caucasian and male patients, according to subgroup analysis. When compared to previous questionnaires, the HDRS questionnaire had a greater pooled prevalence of depressive symptoms (56%) and a lower heterogeneity.[28]

The inclusion of patients from different countries, a large sample size, and studies using different screening methods for depression are the main strength points. Another strength point is the comparison between vitiligo, healthy controls, and other depigmentation disorders. Multiple studies together enhance statistical power and allow for a more accurate estimation of depression prevalence and risk in vitiligo patients. It also makes evaluating the impact of screening methods on the prevalence of depression easier.

On the other hand, we acknowledge that our study has some limitations, including the moderate to high heterogeneity between the included studies, which might be explained by the broad inclusion criteria

used in conducting this meta-analysis. However, we employed a random-effects model and conducted a sensitivity analysis and subgroup analysis to reduce the heterogeneity. It is essential to mention that the majority of studies included did not have the main purpose of determining the prevalence or risk of depression. There is a risk of bias since vitiligo patients are often referred to tertiary referral institutions in many studies, which may lead to selection and referral biases. The type and severity of vitiligo, which might be potential causes of heterogeneity, were also not easily accessible in most investigations. Depressive symptoms were shown to be more strongly linked to the location and amount of vitiligo than to the kind of vitiligo itself, according to several studies. Overexposed areas, such as genitalia, and depigmentation patches tend to have a greater effect.[29-32] More than half of the studies included in this review lacked proper controls, exposing the findings to the influence of a variety of potentially confounding variables. According to the NOS categorization, just a few of the studies included in this meta-analysis were considered to be of high quality. There were no significant differences in the pooled findings based on the quality of studies. Another limitation is that the depression rating scale or inventory employed in the study has not been validated in individuals with vitiligo. These screening tools for depression in dermatological conditions should be tested in future validation studies.

In conclusion, the current evidence suggests that patients with vitiligo have a high risk and prevalence of depression. Different questionnaires have yielded variable prevalence due to the different assessment domains and validation methods. There was no significant difference between vitiligo and psoriasis in terms of GHQ and BDI scores. In addition, patients with vitiligo and alopecia areata were comparable in terms of BDI scores. When comparing both genders, mean scores were higher in female groups across different scales.

CONFLICT OF INTEREST

All authors confirm no financial or personal relationship with a third party whose interests could be positively or negatively influenced by the article's content.

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