• **Meta-Analysis** •

Risk of anxiety and depression in patients with uveitis: a Meta-analysis

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Abstract

● **AIM:** To quantitatively evaluate the risk of anxiety and depression in patients with uveitis *via* performing a Meta-analysis.

● **METHODS:** Three electronic database (PubMed, Embase, and Cochrane Library databases) were searched for studies recording data about uveitis and anxiety as well as depression simultaneously up to January 2021. The incidence rate and standard mean difference (SMD) with a 95% confidence interval (95%CI) were calculated to analyse the association using random-effects models based on heterogeneity tests.

● **RESULTS:** In total, 12 observational studies containing 874 patients with uveitis were included. The results showed that there was a significant association between uveitis and anxiety (SMD=0.97, 95%CI: 0.39 to 1.54, *P*=0.0009) and depression (SMD=0.79, 95%CI: 0.51 to 1.07, *P*<0.00001). The overall morbidities of anxiety and depression in patients with uveitis were 39% and 17%, respectively. With subgroup analysis, the heterogeneity actually came from different kinds of uveitis. Specifically, the incidence rates of both anxiety and depression were relatively low in patients with anterior uveitis (33% and 15%), moderate in patients with infectious uveitis (46% and 22%), and high in patients with unspecified uveitis (59% and 35%).

● **CONCLUSION:** It is preliminarily indicated that patients with uveitis may have a high risk of anxiety and depression. Ophthalmologists and psychologists should pay more attention to the psychological state when dealing with patients with uveitis. Further high-quality studies with detailed direct data are needed to draw more precise conclusions.

● **KEYWORDS:** anxiety; depression; uveitis; Meta-analysis

INTRODUCTION

Uveitis is a common ocular disease that leads to approximately 5%-10% of visual impairment worldwide[1]. More importantly, it accounts for 5%-20% of legal blindness in developed countries and approximately 25% of blindness in the developing world[2], which brings a huge burden to both society and families. The classical categories of uveitis are divided by anatomical features, including anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis[3]. Other classifications of uveitis are characterized by the clinical course (acute, chronic, recurrent), histopathology (granulomatous, non-granulomatous), aetiology (infectious, non-infectious), and laterality (unilateral, bilateral)[4]. Uveitis can occur in people of any age. However, approximately 60%-80% of uveitis cases affect adults aged 20-50y[5], which happens to be the main workforce of society and the core members within families. There are many challenges facing the management of uveitis: the course of the disease varies; the manifestation can be very symptomatic or less symptomatic at the onset of the disease; the lifestyle of patients is strongly correlated with uveitis management; and the general conditions of patients are often involved in management. All these aspects can produce substantial impacts on the psychological health of patients, which can conversely influence the disease progression of uveitis patients.

Anxiety and depression are two commonly seen mental disorders that can increase disability and impair the quality of life of patients. The worldwide prevalence of anxiety and depression is approximately 7.3% and 6%, respectively[6-7]. Although anxiety disorders are the most prevalent psychiatric

disorders, the morbidity of depression is quickly growing. An estimation from the WHO showed that by 2030, major depression will become the leading cause of the global burden of disease[7]. In addition, anxiety and depression have become important comorbidities among patients with vision impairments, such as glaucoma and age-related macular degeneration[8-9]. On the other hand, mood disorders, including anxiety and depression, can lead to the discontinuation of treatment in patients with long-term auto-immune disease[10]. As uveitis is one of the leading blinding-causing ocular diseases and often requires close follow-up and long-term treatment, secondary anxiety or depression may trap patients with uveitis in a vicious cycle. Several observational studies have reported the incidence rates of anxiety and depression in patients with uveitis and discussed the possible relationship between these two kinds of diseases. However, the results presented high heterogeneity. The incidence rate of anxiety ranged from 13% to 65% and that of depression ranged from 2% to 37%. To estimate the overall risk of anxiety and depression in patients with uveitis and discover the source of heterogeneity across these studies, we performed this Meta-analysis to systematically assess the association between uveitis and the two major psychiatric disorders. Additionally, the relationship of these two aspects was further analysed in groups with different types of uveitis.

MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[11].

Search Strategy The following 3 databases were screened up to January 2021 to complete the study: PubMed, Embase, and the Cochrane Library. Searches were carried out using MeSH terms followed by free words. The MeSH term for uveitis was "uveitis", and free words included "uveitis", "ocular inflammation", "eye inflammation", "iridocyclitis", and "choroiditis". The MeSH terms for anxiety and depression were "anxiety" and "depression". Free words for anxiety and depression included "depression", "depressive disorder", "adjustment disorder", "mood disorder", "affective disorder", "depress*", anxiety, anxious, "anxiety disorder", and "distress". The search process was conducted by two independent authors. The literature selections are shown in the PRISMA flow diagram in Figure 1.

Inclusion and Exclusion Criteria Studies were considered eligible if they met the following criteria: 1) clinical studies focusing on anxiety and/or depression and uveitis; 2) the association between anxiety and/or depression and uveitis were discussed; and 3) the effect estimates of the psychological measurements could be extracted or calculated from available data. The exclusion criteria were as follows:
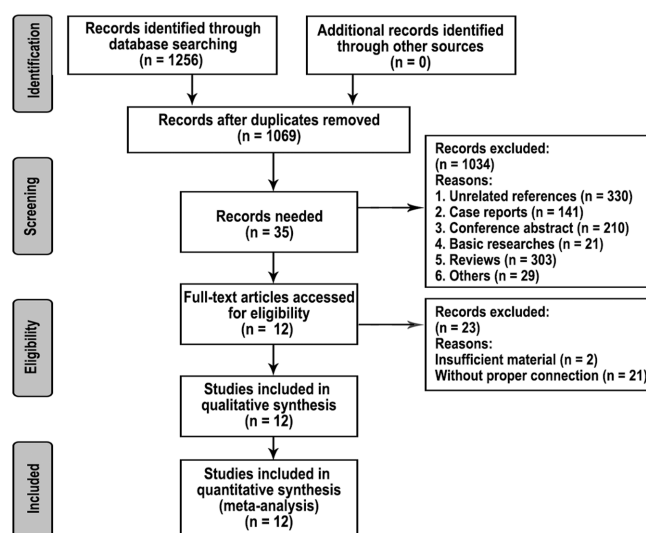
Figure 1 Flow chart of the literature search.

1) case reports, reviews, editorial comments, basic studies, unrelated references, and conference abstracts; 2) studies with insufficient information; and 3) other situations in which studies were not able to meet the inclusion criteria.

Outcomes Our primary outcome of interest was the number of anxiety and/or depression patients within the uveitis patient group. If the data within a study met our inclusion criteria, the article was included in our Meta-analysis. However, some studies only provided psychological test results. Our second outcome of interest was the specific psychological score of both the patient group and the control group. As there are different tests with various units and scales used to assess anxiety and depression, we mainly focused on the standard mean difference (SMD) in the subsequent Meta-analysis.

Data Extraction and Assessment of Study Quality We used a standard data extraction form to extract data, and the relevant data were independently extracted by two reviewers (Cui B and Jia HZ). The following aspects were considered for extraction: first author, publishing date, location of study, study design, source of the study population, study period, uveitis type, psychological disorder type, psychological measurement, and number of cases and controls. The Newcastle-Ottawa Scale (NOS), which contains 3 dimensions, selection, comparability, and exposure or outcome, with 8 items and a 9-star system, was used to assess the quality of both case-control studies. The Agency for Healthcare Research and Quality (AHRQ) scale, which contains 11 items with 1 star each, was used to assess the quality of cross-sectional studies. Two reviewers conducted the assessments independently.

Quantitative Synthesis of Non-comparative Binary Data Data from studies that only provided the patient number and did not include the control group were regarded as non-comparative binary data. Quantitative synthesis was carried out according to a previously published Meta-analysis[12]. In

brief, effect indicators with their standard errors (SEs) were calculated. When data were normally distributed, the following formulas were used for calculation:

$$P=X/n \qquad (1)$$

$$SE = \sqrt{P(1-P)/n} \qquad (2)$$

where P represents the incidence rate of anxiety or depression in uveitis patients, X represents the number of anxiety or depression patients among the total uveitis patients, and n represents the number of total uveitis patients. Otherwise, the following formulas were used for calculation:

$$P'=\text{In(odds)}=\text{In}(X/(n-X)) \qquad (3)$$

$$SE' = SE(\ln(odds)) = \sqrt{1/X + 1/(n-X)} \qquad (4)$$

where odds represent the ratio of the number of patients and nonpatients. The final incidence rate and related 95% confidence interval (CI) were further calculated using the following formulas:

$$P_f=OR/(1+OR) \qquad (5)$$

$$95\%CI \text{ (lower limit): } LL=LLOR/(1+LLOR) \qquad (6)$$

$$95\%CI \text{ (upper limit): } UL=ULOR/(1+ULOR) \qquad (7)$$

where odds ratio (OR), lower limit of the odds ratio (LLOR), and upper limit of the odds ratio (ULOR) were generated from the Meta-analysis.

Statistical Analysis RevMan 5.3 was used to conduct the statistics and Meta-analysis. For non-comparative binary data, generic inverse variance was selected, and the risk difference (RD) and OR with a 95%CI were used to evaluate the association between uveitis and the risk of anxiety and depression. In addition to the main analysis, we also carried out the subgroup analysis based on the different types of uveitis. For continuous psychological scores, the SMD and a 95%CI were used to calculate the association. The Z-test was used to assess statistical significance. In addition to the total analysis, we also carried out subgroup analyses based on different uveitis types. The I-squared (I^2) statistic and Chi-square-based Q-test were used to investigate heterogeneity. Effect model selection was carried out according to the results of the heterogeneity test: $P>0.10$ for the Q-test and I^2 values less than 50% suggested no obvious heterogeneity across studies, and a fixed-effects (Mantel-Haenszel) model was applied; otherwise, a random-effects (DerSimonian-Laird) model was applied. P values <0.05 were considered statistically significant.

RESULTS

Characteristics of the Studies In total, 1256 studies were identified (PubMed=250; Embase=952; Cochrane Library=54) through January 2021. After removing 187 duplications, 330 unrelated articles and 21 basic studies, 210 conference abstracts, 141 case reports, and 303 reviews, 35 studies proceeded to the screening procedure. With full text reading, we further eliminated 2 studies with insufficient materials and 21 references whose results did not provide the proper

connection between uveitis and anxiety or depression. Most of these articles focused on the relationship between psychological symptoms and auto-immune diseases, such as Bechet's disease and juvenile idiopathic arthritis, rather than describing the association between psychological symptoms and uveitis secondary to these auto-immune diseases. For the two references with insufficient material, the study of Benros et al[13] only provided the incidence rate ratio of iridocyclitis and mood disorders in patients with or without infection. The number of patients with mood disorders could not be calculated. The detailed results of psychological tests were not presented either. The study of McKibbin and Dabbs et al[14] only provided the state-trait anxiety inventory (STAI) scores of uveitis patients in male and female groups with different age periods separately. The overall effect could not be estimated. In this way, we divided these articles into a group of insufficient materials. The remaining 12 studies were included[15-26]. After assessing the study quality, all 12 studies were selected to perform the quantitative synthesis. The flow diagram is shown in Figure 1.

All 12 included articles were published between 1987 and 2020. There were 3 case-control studies and 9 cross-sectional studies containing 874 uveitis cases. Eight studies focused on both anxiety and depression, and 4 studies provided only depression data. The Hospital Anxiety and Depression Scale (HADS) and Symptom Check List-90 (SCL-90) were used to assess both the anxiety and the depression states of patients. The STAI, Beck Anxiety Inventory (BAI), and Hamilton Anxiety Scale (HAM-A) were used to assess anxiety. The Beck Depression Inventory (BDI) was exclusively used to assess depression. Two studies focused on general uveitis, 2 on inflammatory uveitis, 5 on anterior uveitis, and 3 on uveitis following Bechet's disease. Nine studies provided non-comparative binary data, and 3 studies provided psychology test scores of both the patient and the control groups. Interestingly, the latter 3 studies all focused on uveitis following Bechet's disease. These characteristics and the methodological quality scores are shown in Tables 1 and 2.

Meta-analysis We first assessed the association of anxiety and uveitis. The overall results of the non-comparative binary data suggested that the incidence rate of anxiety within uveitis patients was 39% (95%CI: 0.20 to 0.59, $P<0.0001$; Figure 2). High heterogeneity was found (Chi^2=79.88, $P<0.00001$, I^2=95%). The SMD results showed that there was a significantly higher anxiety score in patients with uveitis (SMD=0.97, 95%CI: 0.39 to 1.54, $P=0.0009$; Figure 3). Moderate heterogeneity was found (Chi^2=7.60, $P=0.02$, I^2=74%).

We next assessed the association between depression and uveitis. The overall results of the non-comparative binary data suggested that the OR of depression within uveitis patients

Table 1 Characteristics of the included studies with binary data

Author (y)	Country	Study design	Source of the study population	Study period	Uveitis type	Psychological measurement	Mood disorder type	Anxiety No.	Depression No.	Patient No.	Methodological quality
Canamary et al (2020)	Brazil	Cross-sectional study	Patients with diagnosis of ocular toxoplasmosis	2015-2016	Toxoplasmosis	HADS	Anxiety/depression	31	15	81	6
Sittivarakul and Wongkot (2019)	Thailand	Cross-sectional study	Patients with diagnosis of ocular inflammatory diseases	2015	Ocular inflammatory disease	HADS	Anxiety/depression	11	7	86	8
Silva et al (2019)	Brazil	Cross-sectional study	Patients with diagnosis of infectious or non-infectious uveitis	2013-2014	Uveitis	HADS	Anxiety/depression	52	26	80	7
Onal et al (2018)	Turkey	Cross-sectional study	Patients with diagnosis of active uveitis	2014	Uveitis	STAI/BDI	Anxiety/depression	52	37	99	6
Hoeksema and Los (2016)	The Netherlands	Cross-sectional study	Patients with diagnosis of HLA-B27 related anterior uveitis	2012	HLA-B27 related anterior uveitis	BDI	Depression	N/A	6	61	5
Hoeksema and Los (2014)	The Netherlands	Cross-sectional study	Patients with diagnosis of herpetic anterior uveitis	2012	Herpetic anterior uveitis	BDI	Depression	N/A	1	66	5
Maca et al (2013)	Austria	Case-control study	Patients with diagnosis of acute anterior uveitis	2010-2012	Acute anterior uveitis	BDI	Depression	N/A	6	35	6
Maca et al (2011)	Austria	Cross-sectional study	Patients with diagnosis of HLA-B27 related anterior uveitis	2006-2008	HLA-B27 related anterior uveitis	BDI	Depression	N/A	21	171	6
Secchi et al (1987)	Italy	Cross-sectional study	Patients with diagnosis of recurrence anterior uveitis	N/A	Recurrent anterior uveitis	SCL-90	Anxiety/depression	17	16	60	6

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; N/A: Not applicable; SCL-90: Symptom Check List-90; STAI: State-trait anxiety inventory.

Table 2 Characteristics of the included studies with continuous data

Author (y)	Country	Study design	Source of the study population	Study period	Uveitis type	Psychological measurement	Mood disorder type	Patient No.	Control No.	Methodological quality
Altunkaynak et al (2018)	Turkey	Case-control study	Patients with diagnosis of Bechet's disease	N/A	Bechet's disease with ocular involvement	HAM-A/BDI	Anxiety/depression	30	20	6
Ucar et al (2017)	Turkey	Case-control study	Patients with diagnosis of Bechet's disease	N/A	Bechet's disease with ocular involvement	STAI/BDI	Anxiety/depression	60	26	6
Tanriverdi et al (2003)	Turkey	Cross-sectional study	Patients with diagnosis of Bechet's disease	2000-2001	Bechet's disease with ocular involvement	BAI/BDI	Anxiety/depression	45	45	5

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale; N/A: Not applicable; STAI: State-trait anxiety inventory.
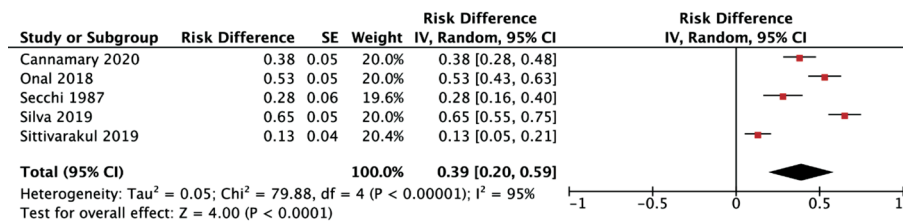
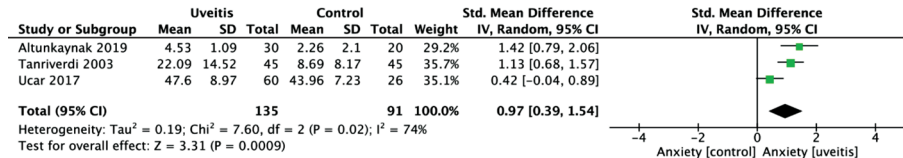**Figure 2 A forest plot diagram presenting the incidence rate of the anxiety in patients with uveitis.**

Figure 3 A forest plot diagram presenting the association between the uveitis and the anxiety based on the results of anxiety tests.
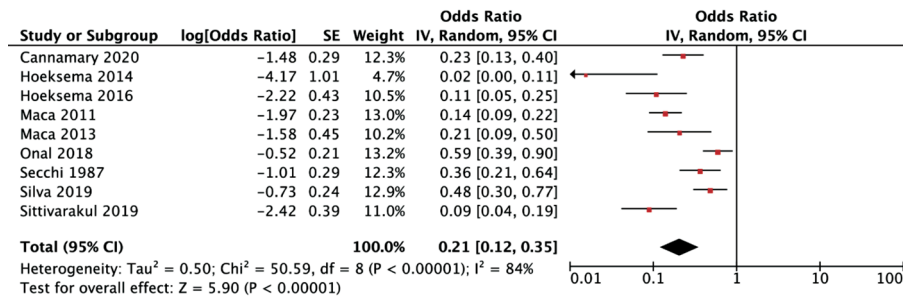

Figure 4 A forest plot diagram presenting the odds ratio of the depression in patients with uveitis. Incidence rate can be calculated with formula 5.
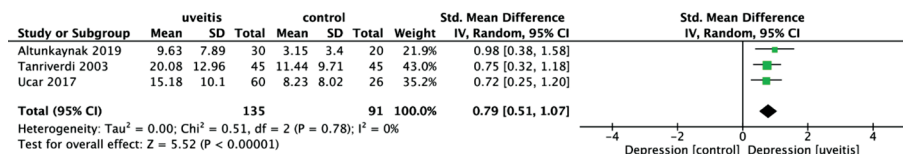

Figure 5 A forest plot diagram presenting the association between the uveitis and the depression based on the results of depression tests.

was 0.21 (95%CI: 0.12 to 0.35, $P<0.00001$; Figure 4). High heterogeneity was found (Chi^2=50.59, $P<0.00001$, I^2=84%). Using formulas 5, 6, and 7, the incidence rate of depression within uveitis patients and the corresponding 95%CI could be calculated: P=17%, 95%CI: 0.11 to 0.26. The SMD results also showed that there was a significantly higher depression score in patients with uveitis (SMD=0.79, 95%CI: 0.51 to 1.07, $P<0.00001$; Figure 5). Low heterogeneity was found (Chi^2=0.51, P=0.78, I^2=0%).

Subgroup Analysis Subgroup analyses were conducted according to different types of uveitis. There were four kinds of uveitis in the included studies: anterior uveitis, infectious uveitis, unspecified uveitis, and uveitis in Bechet's disease. In patients with anterior uveitis, the results showed that the incidence rate of anxiety was 33% (95%CI: 0.22 to 0.45, $P<0.00001$; Figure 6A). Low heterogeneity was found (Chi^2=1.69, P=0.19, I^2=41%). The OR of depression was 0.18 (95%CI: 0.10 to 0.33, $P<0.00001$; Figure 6B). Moderate heterogeneity was found (Chi^2=19.79, P=0.001, I^2=75%). Using formulas 5, 6, and 7, the incidence rate of depression within patients with anterior uveitis and the corresponding

95%CI could be calculated: P=15%, 95%CI: 0.09 to 0.25. For infectious uveitis, the results showed that the incidence rate of anxiety was 46% (95%CI: 0.27 to 0.65, $P<0.00001$; Figure 7A). Moderate heterogeneity was found (Chi^2=3.20, P=0.07, I^2=69%). The incidence rate of depression was 22% (95%CI: 0.14 to 0.31, $P<0.00001$; Figure 7B). Low heterogeneity was found (Chi^2=1.56, P=0.21, I^2=36%). For unspecified uveitis, the results showed that the incidence rate of anxiety was 59% (95%CI: 0.47 to 0.71, $P<0.00001$; Figure 8A). Moderate heterogeneity was found (Chi^2=2.88, P=0.09, I^2=65%). The incidence rate of depression was 35% (95%CI: 0.28 to 0.42, $P<0.00001$; Figure 8B). Low heterogeneity was found (Chi^2=0.32, P=0.57, I^2=0%). Interestingly, the Meta-analysis in the subgroup of uveitis in Bechet's disease exactly aligned with the SMD results mentioned above, which can be found in the previous paragraph (Figures 3 and 5).

DISCUSSION

As mood disorders secondary to uveitis can bring about a poor prognosis for patients, it is necessary to determine the risk level of these psychiatric disorders in patients with uveitis. This Meta-analysis quantitatively evaluated the
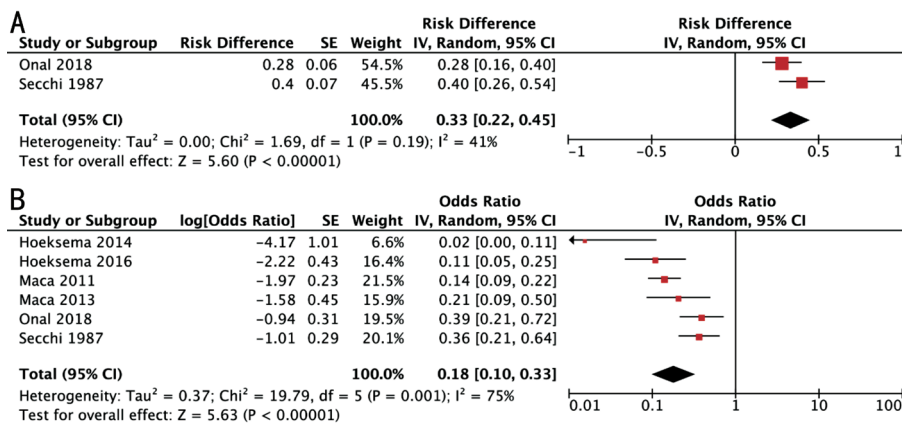
Figure 6 A subgroup analysis of forest plot diagram presenting the incidence rate of anxiety and odds ratio of depression in patients with anterior uveitis. Incidence rate of depression can be calculated with formula 5 A: Anxiety; B: Depression.
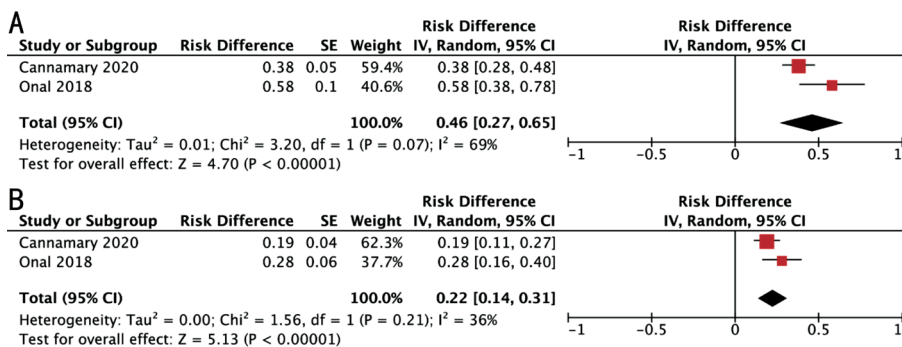

Figure 7 A subgroup analysis of forest plot diagram presenting the incidence rate of the anxiety and the depression in patients with infectious uveitis A: Anxiety; B: Depression.
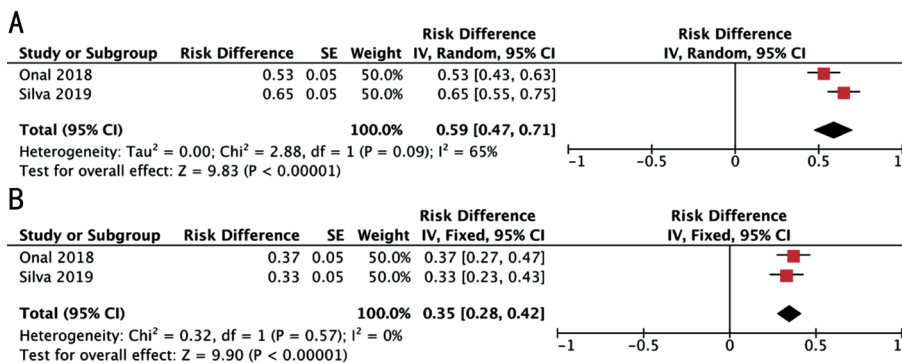

Figure 8 A subgroup analysis of forest plot diagram presenting the incidence rate of the anxiety and the depression in patients with unspecified uveitis A: Anxiety; B: Depression.

association between uveitis and anxiety and depression as well as the association between these two aspects in groups with different types of uveitis. In this study, 874 patients within 12 observational studies were included to explore this association and simultaneously examine the incidence rate of anxiety and depression in patients with uveitis. The results showed that the overall morbidities of anxiety and depression in patients with uveitis were 39% and 17%, respectively. By analysing the psychological scores with control groups from 3 studies, we confirmed that there is a significant association between uveitis and both anxiety and depression. Moreover, with subgroup analysis, we further found the incidence rate of these two

psychiatric disorders within different uveitis subtypes. Current findings have improved the understanding of the relationship between uveitis and anxiety and depression, drawing ophthalmologists' attention and awareness of the potentially unhealthy psychological conditions of patients with uveitis.

In this Meta-analysis, the incidence rate of both anxiety and depression in patients with uveitis was higher than that in the general population, indicating that uveitis is closely linked to mental activities in patients. There are a certain number of subtypes of uveitis that have a relatively poor prognosis. Patients suffer a heavy psychological burden in worrying about the risk of blindness. Additionally, several types of uveitis

require long-term treatment and follow-up, which is both time- and labour-consuming. Even when the progression of uveitis is under control, patients may still worry about the recurrence of the disease. Considering that uveitis can be influenced by the general condition of patients, doctors often ask patients to maintain a strict diet. More importantly, uveitis is usually accompanied by vision loss. This symptom can influence the lives of patients in various ways: disability in driving a vehicle, decrease in work and study efficiency, difficulties in watching screens, and requirements in basic life support. All these aspects can substantially influence the mental health of patients with uveitis.

Our results also showed that the incidence rate of anxiety in patients with uveitis was higher than that of depression. This result followed the trend that the overall prevalence of anxiety among people is higher than that of depression[27]. However, the incidence rate of anxiety is nearly twice as high as that of depression. Anxiety is often linked with fear. The physiological origin of anxiety may be based in the amygdala of anxious subjects, which can predispose them to attend to fear related to environmental threats[28-29]. On the other hand, depression tends to be associated with sadness or hopelessness. An interconnection among the hippocampus, amygdala, and frontostriata is the physiological basis of depression[30]. The common feeling in patients with uveitis is the fear of vision loss at the onset of the disease. With the progression of uveitis, this fear may continually accumulate and eventually develop into anxiety. However, when a poor prognosis is given to patients or severe permanent vision damage occurs, patients can feel both hopelessness and sadness, which may ultimately turn into depression. As fearful feelings always exist during the disease but sadness or hopelessness only present at certain timepoints or endpoints, the corresponding incidence rate of anxiety can be higher than that of depression.

In the current study, subgroup analysis based on different types of uveitis was carried out. In total, 4 kinds of uveitis were analysed, including anterior uveitis, inflammatory uveitis, unspecified uveitis, and uveitis in Bechet's disease. The incidence rates of both anxiety and depression were highest in unspecified uveitis: 59% and 35%, respectively. In this subgroup, 72.5% and 42.4% of patients diagnosed with posterior uveitis or panuveitis were included in Silva *et al*'s[23] and Onal *et al*'s[21] studies, respectively. As the course of posterior uveitis and panuveitis lasts a relatively long time and both can bring severe consequences to patients[31], it is reasonable that the incidence rates of anxiety and depression in these groups reach a relatively high level. In contrast, the incidence rates of anxiety and depression in patients with anterior uveitis were 33% and 15%, respectively, which were slightly lower than the overall incidence rates. Considering autoimmune

factors, anterior uveitis can be more controllable than posterior uveitis, as some topical or local treatments can be effective in the former situation[32]. However, posterior uveitis often requires local or systemic therapy to control the progression of the disease[32], which can result in the higher incidence rate of anxiety and depression in this group. On the other hand, patients with infectious uveitis showed above-average incidence rates of anxiety and depression of 46% and 22%, respectively. Although many pathogens causing infectious uveitis are treatable[33], these diseases can still bring significant vision damage to patients, especially those with late-discovered stages. To better improve the mental condition of patients with infectious uveitis, efforts need to be made not only in psychological interventions but also in early diagnosis and in-time treatment[34]. For uveitis in Bechet's disease, unfortunately, all three articles only provided the score of psychiatric tests, rather than the specific number of patients with psychological disorders. It is certain that patients within this group suffered a higher incidence rate of anxiety and depression (Figures 3 and 5). Considering the significant association between Bechet's disease and anxiety and depression[35], we believe that patients with uveitis secondary to Bechet's disease also have a relatively high incidence rate of these psychological disorders.

As uveitis is often secondary to some systemic diseases, the relationship between the psychological conditions and these diseases should be discussed. In all included studies, Hoeksema and Los[18] found that among the 61 uveitis patients, 6 of them had mild depression and 5 out of these 6 patients had ankylosing spondylitis, indicating that systemic disease may be a potential reason for the development of mental disorders. However, Maca *et al*[19] found that the coexistence of an additional spondylarthropathy in uveitis patients didn't affect the depression score. Onal *et al*[21] found that no juvenile idiopathic arthritis-uveitis (JIA-U) patient showed depression, but 2% JIA-U patients showed anxiety. The variation of data is obvious. Different kinds of systemic diseases as well as inadequate included studies might be the reason. A recent study from McDonald *et al*[36] showed that there were no significant depressive or anxious symptoms presented in patients with JIA-U. As JIA typically restricts in juvenile and the female-to-male ratio of JIA-U was 2.5:1[37], other factors like age, gender, and duration of uveitis should also be taken into consideration. Onal *et al*[21] showed that patients screened positive for anxiety were significantly younger and had significantly earlier onset of uveitis, indicating that age may be an important potential factor for causing mental disorders of patients with uveitis. For gender factor, Maca *et al*[19] found that there were 36% of women and 28.9% of men exhibited depressive mood respectively, but the difference between genders was insignificant. Similar results were also

presented in their following study[20]. However, Sittivarakul and Wongkot[24] found that the anxiety score was higher in female and the depression score was slightly higher in male. Neither of these differences were significant. Homogeneously, the anxiety score of female patients with Behcet's uveitis was insignificantly higher than that of male patients[25]. Overall, though differences are insignificant, it seems that female uveitis patients are more likely to suffer mental disorders than their male counterpart. As for the duration factor, two studies recorded the data of mental health at the initial visit and the follow-up visit. Results showed that the number of depressive patients dropped at the follow-up visit compared to that at the initial visit in the first study[20]. The results of the second study showed that the depression rate remained unchanged, while the anxiety rate decreased[22]. These results implied that patients suffered greater psychological pressure at the onset of the uveitis. Along with the application of medication, the pressure might get slightly relieved. In summary, though trends among these factors have been detected, the number of related studies is still limited. In addition, data in all these aspects are either sparse or fragmental. More direct studies should be carried out in the future to perform quantitative analysis and draw more precise conclusion.

In the main Meta-analysis, obvious heterogeneity was observed. To further discover the source of the heterogeneity, we chose subgroup analysis. By quantitative synthesis of the four categories mentioned above, we found that the heterogeneity in each subgroup apparently decreased. Only low to moderate heterogeneity was found, which indicated that the heterogeneity within our study came from the differences among different types of uveitis. However, as the included studies were limited, few articles were chosen to perform the subgroup analysis. This could also result in the generation of heterogeneity both in the main Meta-analysis and in the subgroup analysis. In addition, studies being carried out in different regions, subjective answers to psychological tests, different designs of studies, and diverse patient groups can all become sources of heterogeneity.

In addition, the systemic corticosteroid treatment is often necessary for patients with uveitis, especially for those with systemic autoimmune diseases. However, psychiatric side-effects sometimes follow the administration of corticosteroid treatment. Cumulative data confirmed that clinically significant anxiety was the complication of corticosteroid treatment[38]. Besides, this treatment is also linked to depression. Study showed that 8-day administration of corticosteroid would result in 10%-12% patients developing depressive disorders[39]. Animal study also confirmed the depression-inducing effect of corticosteroid exposure[40]. As the end product of hypothalamus-pituitary-adrenal (HPA) axis, cortisol is closely linked to stress response. Prolonged and excessive activation of HPA axis can result in the development of psychiatric disorders[41]. Long-term corticosteroid treatment may mimic the prolonged activation of HPA axis and further interfere with normal response to stress, which can contribute to the development of both anxiety and depression disorders. In recent years, the introduction of biologics treatments including adalimumab and tocilizumab significantly improved the visual prognosis of patients with non-infectious uveitis and Behcet's disease related uveitis[42-44]. Compared with traditional corticosteroid and immunosuppression treatments, biologics treatments present better prognosis and less side effects. As psychological conditions lean on patients' physiological state, biologics treatments might play a positive role in reducing the anxiety and depression level of patients with uveitis.

It is worth noting that these mental disorders can be negative for uveitis or even trap patient in a vicious cycle. Physical and mental health are correlated. Patients with mental health conditions have a higher risk of developing physical illness. Conversely, patients with physical illness have a greater chance of developing mental health problems[45]. More specific to uveitis, the general conditions, especially the state of the immune system, of patients are closely linked with the disease. Studies have found that immunosuppression can be caused by interactions among behaviour, neurobiology, and the endocrine system[46]. Homeostatic fluctuations of the immune system can become both the cause and the effect of uveitis. Hence, when dealing with patients with uveitis, ophthalmologists should pay extra attention to patents' mental health and apply interventions if necessary.

There were several limitations in this study. First, the number of included studies was limited. In addition to the indirect data being used, the Meta-analysis was insufficiently performed, which could reduce the quality of evidence. Second, confounding factors could not be excluded. A history of ocular surgery, the use of systemic corticosteroids, an inconsistent stage of uveitis, and many other factors can all significantly influence the mental assessments of patients, which results in potential bias in the study. Third, scales used to measure both anxiety and depression in the included studies are different, which may generate heterogeneity to the final quantitative result. Forth, the biological mechanism underlying the association between uveitis and the risk of anxiety and depression cannot be clearly pointed out in the current study. Therefore, more studies directly discovering the association between uveitis and psychological disorders with clear subgroup data should be carried out and included in future reviews.

In summary, there is a significant association between uveitis and the risk of anxiety and depression. The overall morbidities

of anxiety and depression in patients with uveitis are 39% and 17%, respectively. Specifically, the incidence rates of both anxiety and depression are relatively low in patients with anterior uveitis (33% and 15%), moderate in patients with infectious uveitis (46% and 22%), and high in patients with unspecified uveitis (59% and 35%). Due to the limited number of studies, there should be more studies examining the association between uveitis and psychological disorders with clear subgroup data to draw more precise conclusions in future reviews.

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