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Original Article

Anxiety, depression, and sleep-related outcomes of glaucoma patients: systematic review and meta-analysis

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Objective: This study aims to synthesize data quantifying the prevalence and severity of common psychological conditions in patients with glaucoma.

Design: Systematic review and meta-analysis.

Methods: Databases including Ovid MEDLINE, CINAHL, EMBASE, PsycINFO, Cochrane Library, Web of Science, Open Grey, and ProQuest Theses and dissertations were searched. Two reviewers independently assessed and screened all studies, followed by quality assessment of included studies using the modified Downs and Black checklist. Data were pooled using fixed-effect and random-effects models.

Results: Of 2067 studies identified by the search strategy, 57 passed full-text screening, and 45 studies (4 995 538 subjects) were eligible for analysis. Overall, the prevalence of depression (effect size [ES] = 0.19, 95% CI 0.16−0.23; n = 31), anxiety (ES = 0.25, 95% CI 0.21−0.30; n = 18), and sleep disorders (ES = 0.47, 95% CI 0.26−0.68; n = 7) were high in patients with glaucoma. Similarly, symptomatic measurements of depression (standardized mean difference [SMD] = 0.46, 95% CI 0.19−0.73), anxiety (SMD = 0.44, 95% CI 0.08−0.81), and sleep quality (SMD = 0.72, 95% CI 0.22−1.21) were significant in glaucoma patients.

Conclusions: A higher prevalence and severity of depression, anxiety, and sleep disorders was experienced in patients with glaucoma compared with patients without glaucoma. Caregivers as well as health care providers may need to be aware of unique psychological and social stressors placed on glaucoma patients.

Objectif: Cette étude vise à résumer les données permettant de mesurer la prévalence et la gravité de troubles psychologiques courants chez des sujets qui présentent un glaucome.

Nature: Revue de synthèse systématique et méta-analyse.

Méthodes: Nous avons procédé à une recherche dans des bases de données, notamment Ovid MEDLINE, CINAHL, EMBASE, PsycINFO, Cochrane Library, Web of Science, Open Grey et ProQuest (thèses et mémoires). Deux examinateurs ont vérifié et filtré de manière indépendante toutes les études pour ensuite évaluer la qualité des études retenues à l'aide d'une version modifiée de la liste de vérification de Downs et Black. Les données ont été colligées à l'aide de modèles à effets fixes et à effets aléatoires.

Résultats: Sur les 2067 études recensées, 57 ont passé l'étape du filtre en texte intégral, et 45 (N = 4 995 538) étaient admissibles à l'analyse. Dans l'ensemble, la prévalence de la dépression (taille de l'effet [TE] = 0,19; intervalle de confiance [IC] à 95 % : 0,16−0,23; n = 31), de l'anxiété (TE = 0,25; IC à 95 % : 0,21−0,30; n = 18) et des troubles du sommeil (TE = 0,47; IC à 95 % : 0,26−0,68; n = 7) était élevée chez les patients qui présentent un glaucome. De même, la mesure symptomatique de la dépression (différence moyenne standardisée [DMS] = 0,46; IC à 95 % : 0,19−0,73), de l'anxiété (DMS = 0,44; IC à 95 % : 0,08−0,81) et de la qualité du sommeil (DMS = 0,72; IC à 95 % : 0,22−1,21) était significative en présence de glaucome.

Conclusions: En présence de glaucome, la prévalence et la gravité de la dépression, de l'anxiété et des troubles du sommeil sont plus élevées qu'en l'absence de glaucome. Aidants et professionnels de la santé doivent être conscients des facteurs de stress psychologique et social uniques qui pèsent sur les patients atteints de glaucome.

Glaucoma describes a heterogeneous group of diseases varying in etiology, epidemiology, and treatment. Glaucoma is characterized by atypical optic disc appearance and may lead to irreversible blindness.[1] Glaucoma is the second-leading cause of blindness globally and is increasing in prevalence year by year.[2,3] As the global population ages, glaucoma will become a much more frequent issue.[3]

Depression, anxiety, and sleep disorders remain highly important health issues in a global context. The prevalence of depression and anxiety was documented by the World Health Organization as being 5.5% and 3.6% in 2015, respectively.[4] The prevalence of sleep disorders globally is estimated to be higher, at 7.6%.[5] Losing one's sight is undoubtedly a troublesome experience that may cause distress in glaucoma patients. Previous literature supports a potential association between diseases of low vision, sleep disorders, and mental health status.[6−13] This is notably apparent in patients with glaucoma,[11,12] in whom poor mental health could substantially increase the risk of noncompliance with medical treatment.[14]

To our knowledge, no systematic review has assessed the overall psychosocial burden of patients with glaucoma, as measured by the severity and prevalence of depression, anxiety, and sleep disorders. To fill this gap, we conducted a

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systematic review and meta-analysis assessing the severity of psychological symptoms and the mental health status of glaucoma patients, as well as the impact of glaucoma on their vision-related quality of life (VRQoL).

Two primary objectives were identified: (*i*) estimating the prevalence and severity of anxiety, depression, and sleep disorders in glaucoma patients and (*ii*) estimating the VRQoL of populations with glaucoma versus those without. We hypothesized that a greater prevalence and severity of depression and anxiety, as well as lower sleep quality and VRQoL scores, would be observed in patients with glaucoma.

Methods

Inclusion and exclusion criteria

Studies were included in the systematic review if they met the following criteria: the study followed an observational study design (cross-sectional, case−control, cohort, survey, or any combination of these); reported a clear case definition of glaucoma; reported measurements of depression, anxiety, sleep quality, or quality of life using a validated outcome assessment scale or using diagnostic criteria determining presence or absence of clinically important illness; reported data on outcome measures; reported data specific to patients with glaucoma if multiple eye diseases were included in the study; and had a sample size of more than 20 adult participants (18 years of age and older). Review articles, editorials, opinions, pilot studies, and case reports were excluded.

Although medication adherence is not a primary outcome of our meta-analysis, we included studies addressing medication adherence because of the association between patients' compliance and their mental health status.[14] Studies concerning sleep-related breathing disorders were excluded because a previous systematic review already addressed the association between obstructive sleep apnea syndrome and glaucoma.[15]

Outcome assessment scales

Scales commonly used for assessing depression in patients in addition to clinical diagnoses are the Beck Depression Inventory, Center for Epidemiologic Studies Depression Scale, Goldberg Anxiety and Depression Scale, Geriatric Depression Scale, Hamilton Depression Scale, Hospital Anxiety Depression Scale, Patient Health Questionnaire, and Zung Self-Rating Depression Scale.

Scales assessing anxiety in patients in addition to clinical diagnoses are the Generalized Anxiety Disorder questionnaire, Geriatric Anxiety Inventory, Goldberg Anxiety and Depression Scale, Hamilton Anxiety Scale, Hospital Anxiety and Depression Scale, State-Trait Anxiety Index, and Zung Self-Rating Anxiety Scale.

Scales assessing sleep disorders and sleep quality in patients are the Pittsburgh Sleep Quality Index and the Insomnia Severity Index.

Data sources and study selection

We identified indexed studies using Ovid MEDLINE, Ovid EMBASE, CINAHL, Cochrane Library, and ProQuest PsycINFO. All synonyms were considered with the help of an experienced information specialist. No limits were placed on publication date, age cohort, or language in the search strategy; however, studies were limited to English-language texts during full-text screening. Keyword search terms and Medical Subject Headings headings are shown in our MEDLINE search strategy, which was reformatted to conform to each database (Supplementary Table A, available online). Our initial database search was conducted in June 2018 and updated in December 2021 in an attempt to capture more recent studies.

We conducted a gray literature search using Web of Science, Open Grey, ProQuest Theses and Dissertations, and the University of Western Ontario's theses and dissertations online directory. Conference abstracts were retrieved from the European Society of Cataract and Refractive Surgeons, American Academy of Ophthalmology Annual Meeting, Association for Research in Vision and Ophthalmology Annual Meeting, Canadian Ophthalmology Society Annual Meeting, and the European Society of Ophthalmology Congress. We searched for manuscripts based on included conference abstracts exactly 6 months after the database search to include additional data not reported in conference abstracts. We included data from conference abstracts in the analysis when the corresponding manuscript was not published or unavailable. We did not encounter any situation warranting contact with authors during this review.

Covidence (Veritas Health Innovation, Melbourne, Australia) was used to extract author names, publication dates, and abstracts from search results.[16] Two independent reviewers (M.L.G. and B.C.) screened eligible articles based on their titles and abstracts, blinded to each another's choices. The independent decisions of both reviewers were recorded, and a consensus was reached between the 2 reviewers when a conflict occurred. Agreement was moderate ($P_O = 87.1\%$, $\kappa = 0.492$) in title and abstract screening. After initial screening, reviewers (M.L.G. and B.C.) collectively conducted a full-text review of included studies, reaching a consensus on each article. The full-text review addressed whether each article met a minimum sample size of 20 participants, addressed outcomes of interest in the full-text article, provided a case definition for glaucoma, was not a secondary study, had no intervention present, and was overall relevant to the psychosocial impacts of poor mental health and sleep disorders in glaucoma patients. Articles that were inaccessible through multiple avenues or were unavailable in English were excluded at this stage.

Data extraction

Information extracted from each article included first author, year of study publication, country of study, sample sizes, study design, target outcomes, case definition of glaucoma, gender ratios, supplementary information for assessing the risk of bias, psychological screening results, and VRQoL index data. Quantitative measures of anxiety, depression, and sleep disorders were extracted. If data were stratified, pooled estimates of population characteristics and outcome measures were calculated. One review author (M.L.G.) extracted data, which were reviewed by a senior author (M. M.) to determine eligibility for analysis. When the State-Trait Anxiety Index was used to assess anxiety and both state and trait domains were reported, only the STAI-T score was recorded because it alone has demonstrated discriminant validity for clinically important anxiety in elderly populations.[17]

Quantitative synthesis and analysis

Meta-analysis was used to combine findings from several independent studies that attempted to evaluate the mental health and sleep-related outcomes in patients with glaucoma. By statistically combining findings such as depression, anxiety, and sleep quality scores from these independent studies, the power of the analysis increased considerably, resulting in a single effect estimate called the *summary effect*.

STATA version 15.0 (STATA Corporation, College Station, Tex.) was used to conduct a meta-analysis. The standardized mean difference (SMD) of the mean scores of case versus control was chosen as the effect size. The SMD was stratified based on the use of scale and type of glaucoma. Studies were pooled using the fixed-effect model. To test heterogeneity, I^2 statistics was computed, and a χ^2 test was performed. In case of significant heterogeneity (i.e., a low *P* value, large χ^2 statistics, and I^2 statistics), analysis was

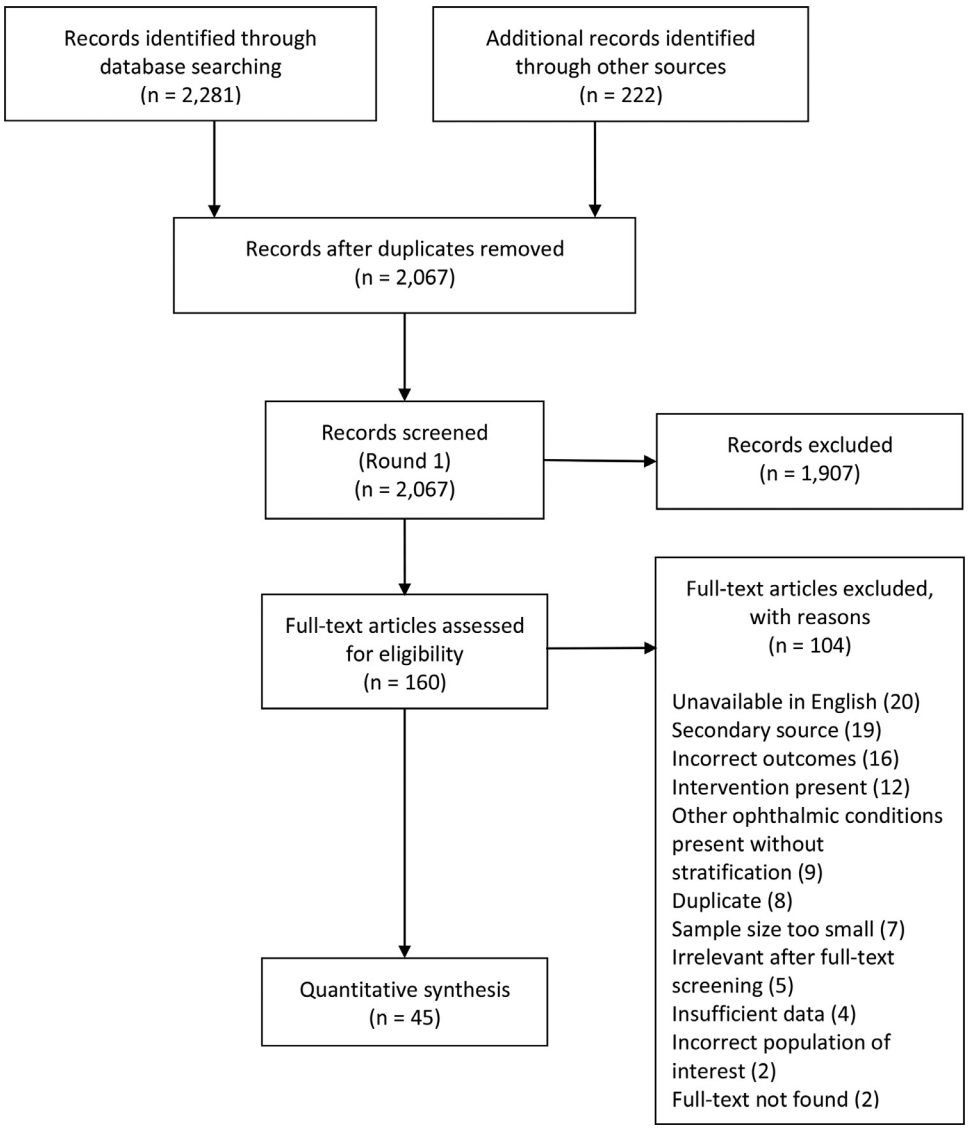


Fig. 1—PRISMA flow diagram.

redone to compute the random-effects model using the DerSimonian and Laird method. Forest plots also were generated. Funnel plots were used to assess the risk of publication bias.

Quality assessment

Two reviewers assessed each study for quality and risk of bias using the Downs and Black checklist, a 27-item measure assessing completeness of reporting, external and internal validity, selection bias, and other measures of potential bias in both randomized and nonrandomized studies.[18,19] While specific scales exist to evaluate various observational study designs, the Downs and Black checklist was used to maintain uniformity of assessment across all studies. Reviewers were blinded to each other's choices during the quality-assessment process. Overall, the quality of studies was moderate, with an average score of approximately 15 of 27.

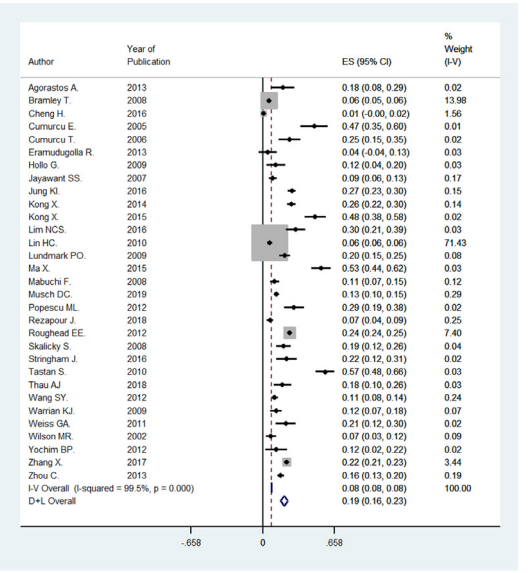
Results

Search results

Database searches yielded 2281 records across 5 databases. Gray literature searches identified 222 additional records. After duplicates were removed electronically using Covidence, 2067 unique records were subject to title and abstract screening. A total of 160 studies were relevant to the subject matter of interest, and 45 of 2067 studies indexed by our searches passed the second stage of screening and had sufficient data for quantitative synthesis. Reasons for exclusion during full-text screening are outlined in Fig. 1. Study results evaluating depression, anxiety, and sleep disorders in patients with glaucoma are represented in Fig. 2A–C, respectively. Studies evaluating depression, anxiety, and sleep disorders in patients with different types of glaucoma compared with control individuals are represented in Fig. 3A–C, respectively.

Study characteristics

Table 1 summarizes the study characteristics of 45 studies.[9,11,12,20–61] included for quantitative synthesis. Studies were conducted in the following countries: 13 in the United States, 6 in Japan, 5 in China, 3 in Australia, 3 in Germany, 3 in Turkey, 2 in Canada, 2 in Taiwan, and 1 each in Brazil, France, Greece, Israel, Italy, Nigeria, Norway, and Singapore. A total of 38 of 45 studies (84%) evaluated depression,[9,11,12,21,23–28,30–39,41,43–52,55–61] 21 of 45 (47%) evaluated anxiety,[12,21,22,25–27,32–34,37–39,42,44–46,50,51,59–61] 9 of 45 (20%) evaluated sleep disorders,[12,20,21,24,26,29,37,44,54] and 9 of 45 (20%) evaluated quality of life.[11,33,34,40,42,48,51–53] Despite the adequate number of studies evaluating quality of life, too few had an adequate control group to provide meaningful estimation.



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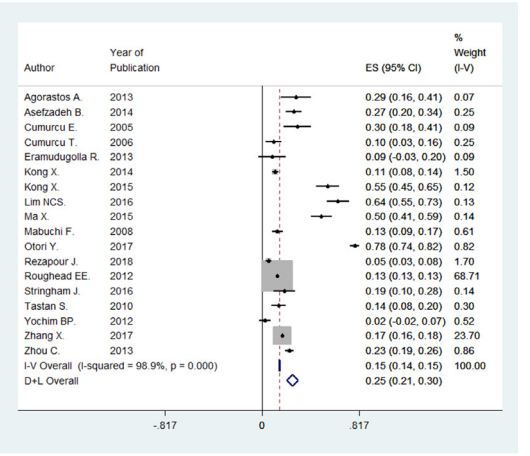

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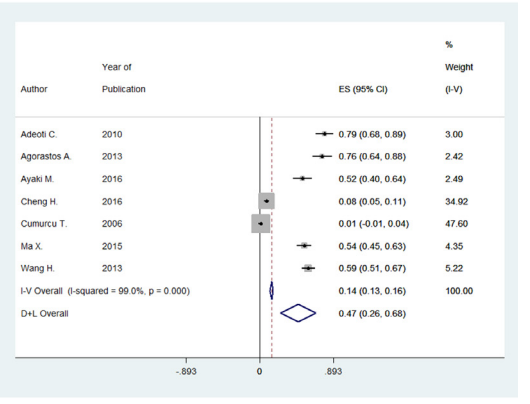

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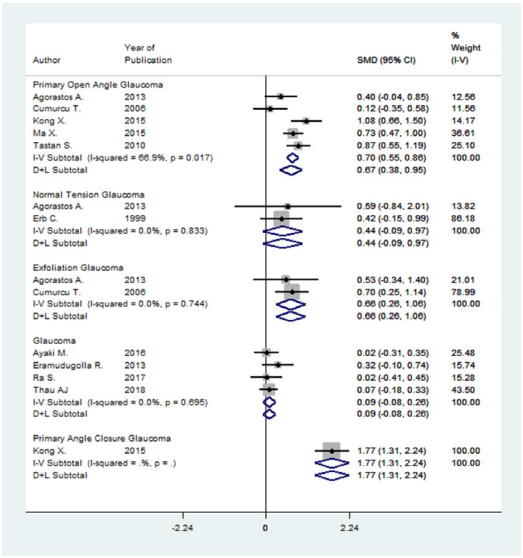
Fig. 2—(A) Forest plot for prevalence of depression in patients with glaucoma. (B) Forest plot for prevalence of anxiety in patients with glaucoma. (C) Forest plot for prevalence of sleep disorders in patients with glaucoma.



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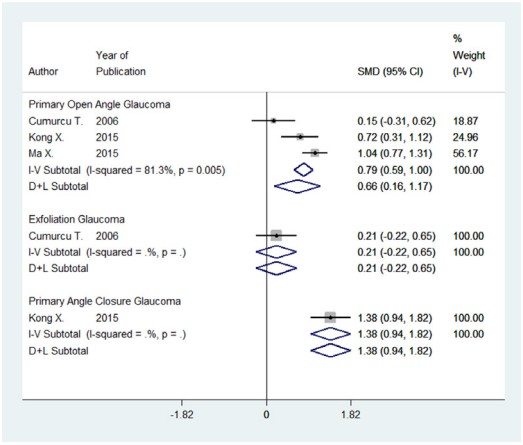

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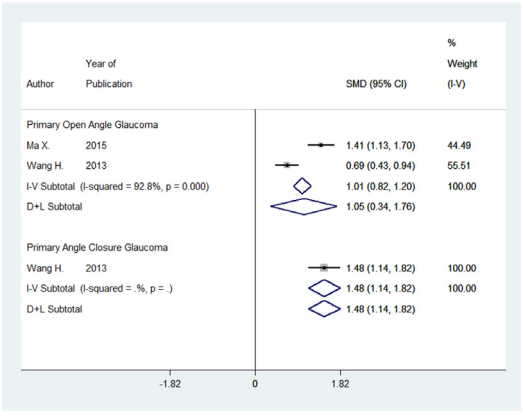

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Fig. 3—(A) Forest plot for relative severity of depression in patients with glaucoma compared with control individuals. (B) Forest plot for relative severity of anxiety in patients with glaucoma compared with control individuals. (C) Forest plot for relative sleep quality in patients with glaucoma compared with control individuals.

For studies evaluating depression, 8 of 38 (21%) used the Hospital Anxiety and Depression Scale,[12,25,33,38,39,44,51,61] 7 of 38 (18%) used a previous clinical diagnosis,[11,23,24,35,46,50,60] 6 of 38 (16%) used the Center for Epidemiologic Studies Depression Scale,[31,36,41,43,57,58] and 5 of 38 (13%) used the 15-item Geriatric Depression Scale.[9,48,52,56,59] Other depression scales of note that were used were the Patient Health Questionnaire, the Beck Depression Inventory, the Gotland Male Depression Scale, the Goldberg Anxiety and Depression Scale, and the Zung Self-Rating Depression Scale.

In studies evaluating anxiety, 8 of 21 (38%) were measured with the Hospital Anxiety and Depression Scale,[12,25,33,38,39,44,51,61] and 4 of 21 (19%) used previous clinical diagnosis[22,46,50,60] as the criterion for anxiety status. In studies evaluating sleep quality and sleep disorders, 6 of 9 (67%) used the Pittsburgh Sleep Quality Index,[12,20,21,37,44,54] 2 of 9 (22%) used a clinical diagnosis,[24,26] and 1 of 9 (11%) used the Insomnia Severity Index.[29]

Primary outcomes

Depression prevalence and severity in patients with glaucoma. Overall, the prevalence of depression in patients with glaucoma was 19% (95% CI 0.16—0.23; Fig. 2A). Patients with glaucoma were more likely to have depression and had greater severity of depressive symptoms (SMD = 0.46, 95% CI 0.19—0.73) than the reference population of patients without glaucoma. Depression was observed to be more severe in patients with primary angle-closure glaucoma (SMD = 1.77, 95% CI 1.31—2.24) than in patients with other types of glaucoma (Fig. 3A), similar to findings observed by Kong et al.[31] Thus, our results indicate significant depression ands depressive symptoms in patients with glaucoma compared with control individuals, which caregivers and care providers need to be aware of.

Anxiety prevalence and severity in patients with glaucoma. The prevalence of anxiety in patients with glaucoma was 25% (95% CI 0.21—0.30; Fig. 2B). In addition, patients with glaucoma were more likely to have anxiety, and the severity of anxiety-related symptoms was also greater (SMD = 0.44, 95% CI 0.08—0.81) compared with control individuals. Furthermore, significant anxiety levels were observed in patients with primary angle-closure glaucoma (SMD = 1.38, 95% CI 0.94—1.82) and primary open-angle glaucoma (SMD = 0.66, 95% CI 0.16—1.17; Fig. 3B). A nonsignificant anxiety level was observed in exfoliation patients with glaucoma (SMD = 0.21, 95% CI −0.22 to 0.65) compared with control individuals (Fig. 3B).

Sleep disorder prevalence and severity in patients with glaucoma. Sleep disorders were observed frequently in patients with glaucoma, with a prevalence of 47% (95% CI 0.26—0.68; Fig. 2C). Additionally, significantly worse sleep quality was observed in patients with primary angle-closure glaucoma (SMD = 1.48, 95% CI 1.14—1.82) and primary open-angle glaucoma (SMD = 1.05, 95% CI 0.34—1.76;

Table 1—Study characteristics for studies eligible for meta-analysis investigating depression, anxiety, sleep disorders, or vision-related quality of life in glaucoma patients

Author (year)	Study design	Study location	Outcomes assessed	Scales used	Case (n)	Control (n)
Adeoti (2010)[20]	C/S	Nigeria	Sleep	PSQI	56	NA
Agorastos (2013)[21]	C/C	Germany	Depression, anxiety, sleep	BDI-II, STAI-T, PSQI	49	37
Asefzadeh (2014)[22]	C/S	United States	Anxiety	Anxiety dx	161	NA
Ayaki (2016)[12]	C/S	Japan	Depression, anxiety, sleep	HADS-D, HADS-A, PSQI	69	71
Bramley (2008)[23]	Cohort	United States	Depression	Depression dx	14 301	167 621
Cheng (2016)[24]	C/S	Taiwan	Depression, sleep	Depression dx, sleep disorder dx	292	95
Cumurcu E. (2005)[25]	C/S	Turkey	Depression, anxiety	HADS-D, HADS-A	61	NA
Cumurcu T. (2006)[26]	C/C	Turkey	Depression, anxiety, sleep	HAM-D, HAM-A, sleep disorder dx	73	40
Eramudugolla (2013)[27]	C/S	Australia	Depression, anxiety	GADS-D, GADS-A	23	375
Erb (1999)[28]	C/C	Germany	Depression	BDI	24	24
Giraud (2016)[29]	Abstract	France	Sleep	ISI	26	46
Hollo (2009)[30]	Cohort	Norway	Depression	BDI	58	NA
Jayawant (2007)[31]	C/S	United States	Depression	CES-D	268	NA
Jung (2016)[11]	C/S	United States	Depression; QoL	Depression dx, EQ-5D	570	11 509
Kong (2014)[32]	C/S	China	Depression, anxiety	SDS, SAS	100	50
Kong (2015)[33]	C/C	China	Depression, anxiety, QoL	HADS-D, HADS-A, VFQ-25	500	NA
Lim (2016)[34]	C/S	Singapore	Depression, anxiety, QoL	HAM-D, HAM-A, VFQ-25	100	NA
Lin (2016))[35]	C/C	Taiwan	Depression	Depression dx	76 673	230 019
Lundmark (2009)[36]	C/S	Canada	Depression	CES-D	258	NA
Ma (2015)[37]	C/C	China	Depression, anxiety, sleep	SDS, SAS, PSQI	120	120
Mabuchi (2008)[38]	C/C	Japan	Depression, anxiety	HADS-D, HADS-A	230	230
Mabuchi (2012)[39]	C/S	Japan	Depression, anxiety	HADS-D, HADS-A	408	NA
Machado (2016)[40]	Abstract	Brazil	QoL	VFQ-25	22	NA
Musch (2019)[41]	Cohort	United States	Depression	CES-D (short)	607	NA
Otori (2017)[42]	C/S	Japan	Anxiety, QoL	STAI-S, VAQ	472	NA
Pappa (2006)[43]	C/S	Greece	Depression	CES-D	100	NA
Popescu (2012)[9]	C/C	Canada	Depression	GDS-15	91	88
Ra (2017)[44]	C/S	Japan	Depression, anxiety, sleep	HADS-D, HADS-A, PSQI	32	61
Rezapour (2018)[45]	Cohort	Germany	Depression, anxiety	PHQ-9, GAD-2	293	14 364
Roughead (2012)[46]	Cohort	Australia	Depression, anxiety	Depression dx, anxiety dx	25 984	NA
Scuderi (2011)[47]	C/S	Italy	Depression	GMDS	91	NA
Skalicky (2008)[48]	C/S	Australia	Depression, QoL	GDS-15	131	34
Sleath (2014)[49]	C/S	United States	Depression	PHQ-9	228	NA
Stringham (2016)[50]	C/S	United States	Depression, anxiety	Depression dx; anxiety dx	74	NA
Tastan (2010)[51]	C/C	Turkey	Depression, anxiety, QoL	HADS-D, HADS-A, VFQ-39	121	64
Thau (2018)[52]	C/S	United States	Depression, QoL	GDS-15, VFQ-25	90	178
Uenishi (2003)[53]	C/S	Japan	QoL	VFQ (Japan-modified)	88	22
Wang H. (2013)[54]	C/C	China	Sleep	PSQI	140	199
Wang S. (2012)[55]	C/S	United States	Depression	PHQ-9	453	6,307
Warrian (2009)[56]	C/S	United States	Depression, QoL	GDS-15, VFQ-25	148	NA
Weiss (2011)[57]	C/S	Israel	Depression	CES-D	76	NA
Wilson (2002)[58]	C/C	United States	Depression	CES-D	121	135
Yochim (2012)[59]	C/S	United States	Depression, anxiety	GDS-15, GAI	41	NA
Zhang (2017)[60]	C/C	United States	Depression, anxiety	Depression dx; anxiety dx	11 234	4 428 284
Zhou (2013)[61]	C/S	United States	Depression, anxiety, QoL	HADS-D, HADS-A, CHI-GQL-15	508	NA

Note: Total sample size: 135 565 cases, 4 859 973 controls.
C/S = cross-sectional analysis/design; C/C = case–control analysis or design; Dx = diagnosis; QoL = quality of life; N/A = not applicable; scales used: BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; CHI-GQL = Chinese Glaucoma Quality of Life Scale; EQ-5D = EuroQoL-5D; GAD = Generalized Anxiety Disorder Scale; GAI = General Anxiety Inventory; GDS = Geriatric Depression Scale; GADS = Goldberg Anxiety and Depression Scale; GMDS = Gotland Male Depression Scale; HAM = Hamilton Anxiety and Depression Scale; HADS = Hospital Anxiety and Depression Scale; ISI = Insomnia Severity Index; PHQ = Patient Health Questionnaire; PSQI = Pittsburgh Sleep Quality Index; STAI = State-Trait Anxiety Inventory; VAQ = Visual Activities Questionnaire; VFQ = Visual Function Questionnaire; SAS = Zung Self-Rating Anxiety Scale; SDS = Zung Self-Rating Depression Scale.

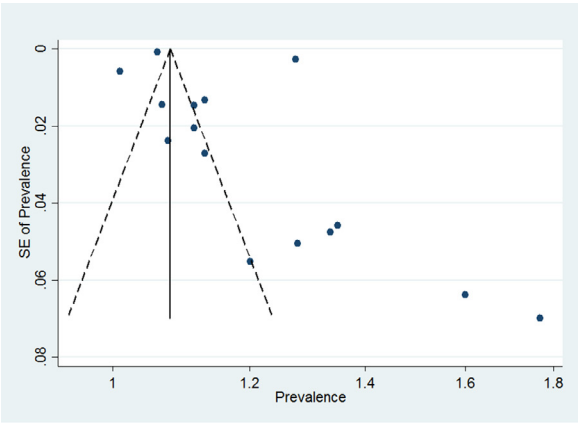
Fig. 3C). Overall, patients with glaucoma had poorer sleep quality (SMD = 0.72, 95% CI 0.22−1.21) compared with control individuals (Fig. 3C). While some studies reported quality-of-life measures, there were too few studies to provide any meaningful inference.

Publication bias

Figure 4 provides funnel plots for studies evaluating depression, anxiety, and sleep disorder prevalence in patients with glaucoma. The included studies were scattered from the top to bottom right and top left corners of the plot. Therefore, publication bias could not be concluded. In part, the reason was difficulty in interpretation of funnel plots for a small group of studies, high heterogeneity (see below), and small effect sizes. Additionally, publication bias is only one of the numerous possible explanations for funnel plot asymmetry.

Discussion

Glaucoma is one of the most common causes of irreversible blindness in the world. In this study, we were able to examine the impact of glaucoma on the mental health of patients. Our meta-analysis results indicated significant depression, anxiety, and sleep disorders in patients with glaucoma compared with people without glaucoma. In addition, patients with glaucoma had severe depressive and



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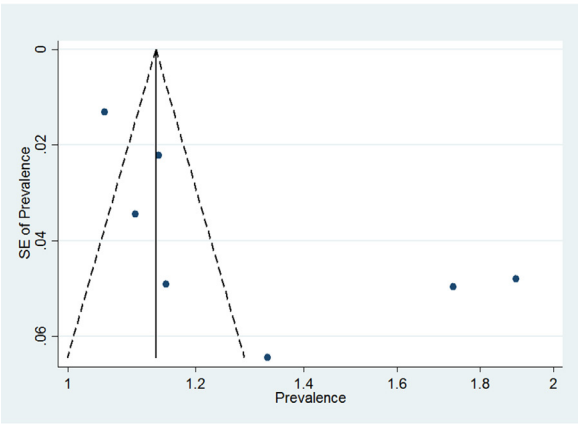

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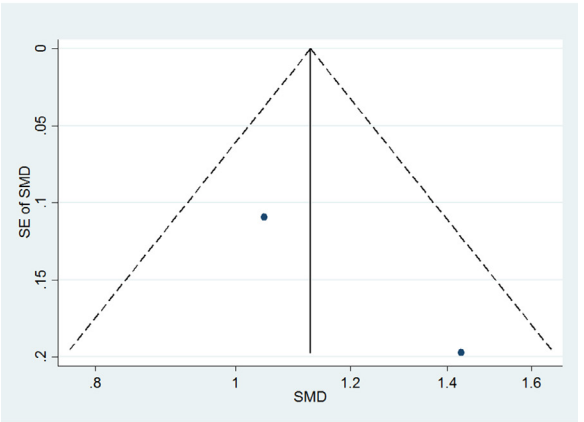

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Fig. 4—(A) Funnel plot for studies evaluating depression in patients with glaucoma. (B) Funnel plot for studies evaluating anxiety in patients with glaucoma. (C) Funnel plot for studies evaluating sleep disorders in patients with glaucoma.

anxiety symptoms along with poorer sleep quality. Our results expand on depression prevalence estimates provided by Zheng et al.,[13] noted in our meta-analysis. Substantial heterogeneity was observed; therefore, a random-effects model was employed when needed. Study quality, as measured with the Downs and Black checklist, was moderate for all studies examined.

The significant prevalence of depression, anxiety, and sleep disorder can be explained by glaucoma severity. Additionally, when patients are diagnosed with glaucoma, they become anxious about the potential of losing their eyesight. This distress may be reflected in patients' questionnaire results. Although there are few quality-of-life data among our collected studies, it is likely that anxiety, depression, and sleep disorders in patients with glaucoma hinder their quality of life, affect their psychological well-being, and potentially affect medication adherence.[14] Reduced adherence to glaucoma medications can worsen glaucoma progression, leading to further distress and worse quality of life in patients. Reiterating a point addressed by Zhang et al.,[60] the association between each of depression, sleep disorders, anxiety, and glaucoma should be a matter of concern for ophthalmologists, optometrists, and primary care providers.

There was heterogeneity among the studies in some cases. As a result, a random-effects model was generated, when necessary. There are many possible reasons for the presence of heterogeneity, including differences between the study populations, variability in the locations where the studies were performed, different follow-up periods, and differences in study design. Regarding the funnel plots, we were not able to conclude the presence of publication bias. Factors contributing to this difficulty include high heterogeneity and a small number of studies.

The trend in the values for the kappa statistics is also important to discuss. Cohen's κ value was 0.49 for the title and abstract screening stage and 0.78 for the full-text screening stage. This can be explained by the fact that many articles in the abstract screening did not display an abstract, making it much more difficult to assess their relevance consistently. When we assessed full-text manuscripts, it was much easier to assess whether an article met inclusion and exclusion criteria because of the increased level of detail available, as well as the more specific exclusion criteria at this stage.

Limitations are inherent in any systematic review and meta-analysis due to variability in the included articles. First, an association between depression, anxiety, sleep disorders, and glaucoma could not be determined because of the limited availability of evidence. Second, there were limited data on the severity of depression, anxiety, sleep disorders, and overall quality-of-life studies. Therefore, higher-quality etiologic studies with long-term follow-up data are needed. Third, meta-analyses of observational studies are subject to the biases of included studies and their designs.[62]

Examples of potential factors influencing estimates of psychosocial well-being in the included studies other than glaucoma severity and psychological disorders include income status, socioeconomic status, age, degree of social connectivity, the presence of other undiagnosed ocular conditions and systemic comorbidities, medication compliance, variable time from diagnosis to a psychological evaluation, social

desirability bias observed on patient-reported outcome scales, and unintentional effects of glaucoma medications. These additional factors, in addition to variations in study design and sampling, may contribute to the high heterogeneity in the study results observed in this review.

Fourth, an important limitation is that although most studies had control groups from populations and settings similar to that of the glaucoma case group, it is possible that in some larger samples, patients with other eye conditions made up some fraction of this group. Because patients with eye conditions are likely to have issues such as depression,[13] our results are consistent with most study findings.

Fifth, only properly indexed studies can be reliably retrieved using our literature search strategy. Although filters designed to retrieve nonrandomized studies have consistently lacked the sensitivity required for a systematic review,[63] we made an attempt to mitigate this using broad text word searches in addition to subject header searches for all databases. Sixth, studies were excluded because of insufficient information for analysis. These studies, if included, may have no to minimal influence on study results due to insufficient data for analysis. In addition, a random-effects model was used for the meta-analysis to account for between-study heterogeneity.

Conclusions

Glaucoma is likely associated with higher rates of depression, anxiety, and sleep disorders as well as a greater severity of symptoms in glaucoma patients. Further research should attempt to infer causality about this association and describe the characteristics most related to depression, anxiety, and sleep disorders in these patients. An open dialogue with patients that facilitates discussions about mental well-being and directs them to appropriate support services may help patients with glaucoma.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2022.02.010.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

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