The prevalence of anxiety symptoms and disorders among ophthalmic disease patients

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Abstract

Background: Progressive and irreversible vision loss has been shown to place a patient at risk of mental health problems such as anxiety. However, the reported prevalence of anxiety symptoms and disorders among eye disease patients vary across studies. Thus, this study aims to clarify the estimated prevalence of anxiety symptoms and disorders among ophthalmic disease patients.

Methods: Relevant studies on the prevalence of anxiety symptoms and disorders among eye disease patients were collected through international databases, PubMed, Scopus, and Web of Science. A random-effects model was used to determine the pooled prevalence of anxiety symptoms and disorders among ophthalmic disease patients.

Results: The 95 included studies yielded a pooled prevalence of 31.2% patients with anxiety symptoms and 19.0% with anxiety disorders among subjects with ophthalmic disease. Pediatric patients were more anxious (58.6%) than adults (29%). Anxiety symptoms were most prevalent in uveitis (53.5%), followed by dry eye disease (DED, 37.2%), retinitis pigmentosa (RP, 36.5%), diabetic retinopathy (DR, 31.3%), glaucoma (30.7%), myopia (24.7%), age-related macular degeneration (AMD, 21.6%), and cataract (21.2%) patients. Anxiety disorders were most prevalent in thyroid eye disease (TED, 28.9%), followed by glaucoma (22.2%) and DED (11.4%). When compared with healthy controls, there was a twofold increase on the prevalence of anxiety symptoms (OR = 1.912, 95% CI 1.463–2.5, \( p < 0.001 \)) and anxiety disorders (OR = 2.281, 95% CI 1.168–4.454, \( p = 0.016 \)).

Conclusion: Anxiety symptoms and disorders are common problems associated with ophthalmic disease patients. Thus, comprehensive and appropriate treatments are necessary for treating anxiety symptoms and disorders among ophthalmic disease patients.

Keywords: anxiety symptoms and disorders, ophthalmic disease, prevalence

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deterioration or limitations. As an example, vision loss is considered to be progressive and irreversible, placing the patient at increased risk of mental health problems which may negatively influence the individual’s quality of life. Several studies have shown the association between anxiety symptoms and ocular diseases. However, the reported prevalence of anxiety symptoms and disorders in patients with ocular diseases remains highly varied, ranging from 2.4% to 78% and 6.3% to 73%, respectively.

Meanwhile, early identification and management of anxiety is crucial in eye disease cases, as acute emotional stress can result in sudden intraocular pressure (IOP) elevation in the glaucomatous eye and has been associated with severe ocular hypertension. Due to the potential negative impact of poor mental health status on both the ophthalmic condition and general well-being of the patient, prompt identification and management of emotional and social factors correlated with anxiety should be taken into account in order to achieve optimal treatment. Indeed, patients with anxiety symptoms and disorders often experience significant impairment in functioning in global, social, occupational, and physical domains. Thus, identification of the impairment profile for those suffering from anxiety is essential to understand the hurdles that treatment may need to overcome. Altogether, in order to quickly identify and manage anxiety issues in ophthalmic disease subjects, decision-makers require a representative estimate on the prevalence of said condition. Hence, this study aims to systematically review the reported prevalence of both anxiety disorders and symptoms in ophthalmic disease patients, and to provide a pooled prevalence of anxiety among the eye disease patients.

Methods

Study criteria and search strategy

This study was performed according to the instructions of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Criteria of studies included in this meta-analysis were: (1) observational studies that reported either anxiety symptoms or disorders among patients with eye disease; (2) anxiety symptoms/states and disorders examined based on a validated methods/tools and clinical diagnosis, respectively; (3) ophthalmic diseases diagnosed based on the judgment of qualified ophthalmologists or medical records according to the International Classification of Disease and Codes (ICD-11); and (4) both adult and pediatric age were included. Relevant studies were searched from electronic databases such as PubMed, Scopus, and Web of Science, utilizing the following keywords: anxiety, prevalence/incidence, and eye/ocular disease/opthalmology until January 2022.

Data extraction and quality assessment

Data were extracted as follows: author, year of publication, study design, country, sample size, mean age of participants or otherwise indicated, type of disease, diagnostic method with its corresponding cutoff value, and the prevalence of anxiety disorders or symptoms. To assess the quality of the observational study, the Newcastle-Ottawa Scale (NOS) was applied. The maximum score for each study is 9. Studies scoring less than 5 were judged to be at a high risk of bias.

Statistical analysis

Prevalence estimates of anxiety symptoms and disorders were calculated from 95 studies. Heterogeneity was evaluated with the $I^2$ statistic, wherein $I^2$ values more than 50% indicated substantial heterogeneity. If heterogeneity existed, the random-effects model was then used; otherwise, the fixed-effects model was applied. Secondary analysis was used to evaluate the prevalence of anxiety symptoms and disorders among patients with ophthalmic disease relative to healthy subjects. A funnel plot and Begg’s test were used to investigate the publication bias if the pooled effect size consisted of 10 or more studies. Meta-analysis was performed utilizing Open Meta-Analyst software package. The value of 0.05 was indicative of statistical significance.

Results

Ninety-five studies were included in this meta-analysis, among which 81 evaluated anxiety symptoms while 14 evaluated anxiety disorders among patients with ophthalmic disease (Figure 1). The characteristics of the included studies are shown in Table 1. The prevalence of anxiety symptoms and disorders among ophthalmic disease patients ranged from 2.4% to 95.87% and 6.3% to 77.5%, respectively. The random-effect model was used because heterogeneity existed ($I^2 > 50$%). The overall pooled prevalences of
anxiety symptoms and disorders among patients with ophthalmic disease were 31.2% (6507/23,415 subjects, 95% CI 25.8%–36.7%, \( p < 0.001 \), Figure 2) and 19.0% (6502/60,174 subjects, 95% CI 16.1%–22%, \( p < 0.001 \), Figure 3), respectively. When the study was classified based on age, the pooled prevalence of anxiety symptoms in adult and pediatric patients were 29% (7726/33,981 subjects, 95% CI 25.8%–32.3%, \( p < 0.001 \)) and 58.6% (649/945 subjects, 95% CI 18.6%–98.5%, \( p = 0.004 \)), respectively (Figure 2).

Subgroup analysis was performed for studies evaluating anxiety symptoms and disorders among patients with the ophthalmic disease yielded similar findings. The highest prevalence of anxiety symptoms was observed in patients with uveitis [53.5%, 95% CI, 27.4%–79.6%, \( p < 0.001 \)]; patients with Behçet uveitis had a higher prevalence of anxiety symptoms (69.3%, 95% CI, 49%–89.6%, \( p < 0.001 \)) than those with any type of uveitis (43.3%, 95% CI, 9.9%–76.6%, \( p = 0.011 \), Figure 4(a)), followed by patients with dry eye disease (DED) (37.2%, 95% CI, 17.4%–40.5%, \( p < 0.001 \), Figure 4(b)), retinitis pigmentosa (RP) (36.5%, 95% CI, 19.8%–54.6%, \( p < 0.001 \), Figure 4(c)), diabetic retinopathy (DR) (31.3%, 95% CI, 13.5%–49.1%, \( p < 0.001 \), Figure 4(d)), glaucoma [30.7%, 95% CI, 22.3%–39%, \( p < 0.001 \); patients with primary-angle closure glaucoma (PACG) had a higher prevalence of anxiety symptoms (52.5%, 95% CI, 49.9%–80%, \( p < 0.001 \)) than those with primary-open angle glaucoma (POAG, 33.1%, 95% CI, 21%–45.2%, \( p < 0.001 \)) or any type of glaucoma (25.6%, 95% CI, 14.3%–36.9%, \( p < 0.001 \), Figure 5(a)), myopia (24.7%, 95% CI, 20%–29.4%, \( p < 0.001 \), Figure 5(b)), age-related macular degeneration [AMD, 21.6%, 95% CI, 12.5%–30.7%, \( p < 0.001 \), Figure 5(c);
Table 1. Characteristics of the included studies.

| No | Study | Year  | Country | Disease | Age [Mean (SD)] | Study design | Assessment tools | Cutoff | Prevalence [case/participants] | NOS |
|----|-------|-------|---------|---------|----------------|--------------|-----------------|-------|------------------------------|-----|
| 1  | Agorastos et al. | 2013  | Germany | Glaucoma | 70.8 [8.4] | Cross-sectional study | STAI | >44 | 21% [18/86] | 6 |
| 2  | Ayaki et al. [a] | 2015  | Japan   | Glaucoma | 59.5 [19.9] | Cross-sectional study | HADS | ≥10 | 38.8% [42/109] | 6 |
| 3  | Cumurcu et al. | 2006  | Turkey  | Glaucoma [PXG + POAG] | 53.26 [13.22] 49.65 [11.11] | Case-control, Cross-sectional study | HARS | >17 | 9.6% [7/73] | 7 |
| 4  | Eramudugolla et al. [a] | 2013  | Australia | Glaucoma | 76.22 [2.89] | Population-based cross-sectional study | GADS | ≥4 | 8.7% [2/23] | 7 |
| 5  | Fasih et al. | 2010  | Pakistan | Glaucoma [POAG] | 56.21 [13.37] | Cross-sectional study | HADS-A | ≥11 | 33% [33/100] | 6 |
| 6  | Hwang and Kim | 2015  | Korea   | Glaucoma | 49.2 [10.6] | Cross-sectional study | HADS-A | ≥10 | 51.4% [37/72] | 6 |
| 7  | Kong et al. | 2015  | China   | Glaucoma [POAG + POAG] | 58.16 [14.42] 52.86 [12.64] | Cross-sectional study | SAS | ≥45 | 55% [55/100] | 7 |
| 8  | Lim et al. | 2016  | Singapore | Glaucoma [POAG + POAG] | 67.1 [12.0] | Cross-sectional study | HAM-A | >17 | 63% [61/97] | 6 |
| 9  | Mabuchi et al. | 2008  | Japan   | Glaucoma [POAG] | 66.9 [11.9] | Case-control study | HADS-A | ≥10 | 13% [30/230] | 7 |
| 10 | Otori et al. | 2017  | Japan   | Glaucoma | 62.4 [13.1] | Cross-sectional study | STAI | ≥45 | 78.0% [351/450] | 6 |
| 11 | Pei et al. | 2012  | China   | Glaucoma [POAG] | NA | Cross-sectional study | HADS-A | ≥10 | 26.7% [116/40] | 6 |
| 12 | Rezapour et al. [a] | 2018  | Germany | Glaucoma | 55 | Population-based cohort study | GAD-7 | ≥3 | 5.3% [18/333] | 7 |
| 13 | Siguan-Bell and Florcruz | 2019 | Philippine | Glaucoma | 61.6 [13.9] | Cross-sectional study | HADS-P | ≥11 | 15% [12/82] | 6 |
| 14 | Tastan et al. | 2010  | Turkey  | Glaucoma | 64.23 [13.15] | Case-control study | HADS | ≥8 | 40% [49/121] | 7 |
| 15 | Wu et al. [a] | 2019  | China   | Glaucoma | 57.59 [15.89] | Cross-sectional study | HADS-A | ≥10 | 12.2% [52/428] | 6 |
| 16 | Yochim et al. | 2012  | USA     | Glaucoma | 70 [9.2] | Cross-sectional study | GAI | ≥11 | 2.4% [1/41] | 6 |
| 17 | Zhang et al. [a] | 2018  | China   | Glaucoma | 57.20 [13.94] | Cross-sectional study | HADS-A | ≥8 | 29.6% [78/263] | 6 |
| 18 | Zhan and Zhilan | 2013  | China   | Glaucoma [POAG] | NA | Cross-sectional study | HAM-A | >17 | 59% [49/83] | 6 |
| 19 | Zhou et al. | 2013  | China   | Glaucoma | 55.40 [15.26] | Cross-sectional study | HADS-A | ≥10 | 22.92% [116/506] | 6 |

(Continued)
| No | Study            | Year | Country          | Disease       | Age [Mean (SD)] | Study design    | Assessment tools | Cutoff | Prevalence (case/participants) | NOS |
|----|------------------|------|------------------|---------------|----------------|----------------|------------------|--------|--------------------------------|-----|
| 20 | Dayal et al.     | 2022 | India            | Glaucoma      | 59.2 [12.6]    | Cross-sectional study | HADS-A          | ≥8     | 6.5% [13/200]                 | 6   |
| 21 | Abe et al.       | 2021 | Brazil           | Glaucoma      | 70.14 [15.8]   | Cross-sectional study | HADS            | >12    | 4.65% [6/129]                 | 6   |
| 22 | Onwubiko et al.  | 2020 | Nigeria          | Glaucoma      | 18–72a         | Cross-sectional study | HADS            | ≥11    | 44% [80/182]                  | 6   |
| 23 | Shin et al.      | 2021 | China            | Glaucoma [POAG]| 54.14 [16.87]  | Cross-sectional study | BAI             | >10    | 16.7% [44/251]                | 6   |
| 24 | Zhang et al.     | 2021 | China            | Glaucoma [POAG]| 56.6 [15.7]    | Cross-sectional study | HADS            | ≥8     | 28.1% [18/64]                 | 6   |
| 25 | Au Eong et al.   | 2012 | Singapore        | AMD            | 68.1 [9.4]     | Cross-sectional study | EQ-5D [EQ_5]    | >1     | 20.7% [70/338]                | 6   |
| 26 | Augustin et al.  | 2007 | France/Germany/Italy | Wet AMD     | NA             | Cross-sectional study | HADS            | ≥8     | 50% [168/336]                 | 6   |
| 27 | Rezapour et al.  | 2020 | Germany          | AMD            | 54.4 [11.0]    | Cross-sectional study | GAD-7           | ≥3     | 4.2% [46/1089]                | 6   |
| 28 | Fernández-Vigo et al. | 2021 | Spain            | Wet AMD        | 80.9 [6.6]     | Cross-sectional study | HADS            | ≥10    | 25.5% [14/55]                 | 6   |
| 29 | Senra et al.     | 2017 | UK               | Wet AMD        | 80 [7.4]       | Cross-sectional study | HADS            | ≥8     | 17.3% [52/300]                | 6   |
| 30 | Eramudugolla et al. | 2013 | Australia        | AMD            | 75.63 [4.25]   | Population-based cross-sectional study | GADS           | ≥4     | 10.5% [2/19]                  | 7   |
| 31 | Evans et al.     | 2007 | UK               | AMD            | 85.7 [5.2]     | Population-based cross-sectional study | GHQ-28         | NA     | 9.6% [50/516]                 | 7   |
| 32 | Mathew et al.    | 2011 | Australia        | AMD            | 78.0 [7.7]     | Cross-sectional study | GADS           | ≥2     | 29.4% [43/145]                | 8   |
| 33 | Ryu et al.       | 2017 | Korea            | AMD            | 69.41 [7.74]   | Population-based cross-sectional study | EQ-5D [EQ_5]   | >1     | 17.6% [58/326]                | 7   |
| 34 | Hernández-Moreno et al. | 2021 | Portugal         | AMD + DR       | 68.8 [11.96]   | Cross-sectional study | HADS-A          | NA     | 18% [13/71]                   | 6   |
| 35 | Ayaki et al.     | 2019 | Japan            | DED            | 59.5 [19.9]    | Cross-sectional study | HADS            | ≥10    | 43.5% [107/247]               | 6   |
| 36 | Li et al. (a)    | 2011 | China            | DED            | 42             | Descriptive study   | SAS             | ≥45    | 30.3% [27/89]                 | 7   |
| 37 | Li et al. (b)    | 2018 | China            | DED            | 19.7 [2.7]     | Cross-sectional study | SAS             | ≥35    | 92.6% [87/94]                 | 7   |
| 38 | Liyue et al.     | 2015 | Singapore        | DED            | 54.49 [10.76]  | Cross-sectional study | HADS            | ≥8     | 26.1% [24/94]                 | 6   |
| No | Study | Year | Country | Disease | Age [Mean (SD)] | Study design | Assessment tools | Cutoff | Prevalence (case/participants) |
|----|-------|------|---------|---------|-----------------|-------------|----------------|--------|------------------------------|
| 39 | Na et al. | 2015 | Korea | DED | 44.9 (0.8) | Population-based cross-sectional study | EQ-5D (EQ_5) | > 0.5 | 17.5% (142/816) |
| 40 | Wen et al. | 2012 | China | DED | 41 (15) | Cross-sectional study | SAS | > 1 | 61.8% (177/283) |
| 41 | Yilmaz et al. | 2015 | Turkey | DED | 41* | Case-control study | DASS | > 7 | 63.3% (77/121) |
| 42 | Wi et al. | 2019 | China | Anxiety states | 45.52 (12.8) | Case-control study | GAD-7 | > 7 | 39% (41/106) |
| 43 | Kizawa et al. | 2018 | Japan | Cataract | 61.3 (18.1) | Population-based cross-sectional study | HAM-A | > 14 | 17% (10/60) |
| 44 | Bilal et al. | 2019 | USA | DED | 65.5 (13.3) | Prospective study | SAS | > 10 | 0.2% (2/194) |
| 45 | Zhang et al. | 2016 | China | DED | 46.8 (11.1) | Case-control study | GAD-7 | > 0.5 | 22.2% (22/100) |
| 46 | Yilmaz et al. | 2018 | Turkey | Cataract | 84.7 (15.3) | Population-based cross-sectional study | STAI-I | > 40 | 58.6% (34/58) |
| 47 | Eramudugolla et al. | 2013 | Australia | Cataract | 70.23 (9.7) | Population-based cross-sectional study | STAI-II | > 40 | 28.4% (28/100) |
| 48 | Evans et al. | 2007 | UK | Cataract | 67.3 (15.3) | Descriptive study | GAD-28 | > 0.5 | 63.3% (67/100) |
| 49 | Zhang et al. | 2018 | China | Cataract | 70.23 (9.7) | Cross-sectional study | HADS-A | > 8 | 17.8% (17/100) |
| 50 | Onal et al. | 2017 | Turkey | Cataract | 67.3 (15.3) | Cross-sectional study | STAI-I | > 8 | 17.8% (17/100) |
| 51 | Sittivarakul and Wongkot | 2018 | Thailand | Uveitis | 43.9 | Cross-sectional study | STAI-II | > 8 | 17.8% (17/100) |
| 52 | Eser-Öztürk et al. | 2021 | Turkey | Behçet Uveitis | 34.76 (11.1) | Cross-sectional study | STAI-I | > 8 | 17.8% (17/100) |
| 53 | Silva et al. | 2017 | Brazil | Uveitis | 42.8 (14.8) | Cross-sectional study | HADS | > 5 | 65.1% (52/80) |
| 54 | Heindl et al. | 2021 | Germany | Unilateral anophthalmic | 62.54 (16.7) | Cross-sectional study | GAD-7 | > 5 | 44.7% (21/29) |
| 55 | Ayaki et al. | 2018 | Japan | Retinal disease | 59.5 (19.9) | Cross-sectional study | HADS | > 10 | 42.3% (12/29) |
| 56 | Ayaki et al. | 2016 | Japan | IOL | 59.5 (19.9) | Cross-sectional study | HADS | > 10 | 28.4% (8/29) |
| No | Study                                      | Year | Country   | Disease                  | Age [Mean (SD)] | Study design               | Assessment tools | Cutoff | Prevalence [case/participants] | NOS |
|----|--------------------------------------------|------|-----------|--------------------------|-----------------|-----------------------------|------------------|-------|-------------------------------|-----|
| 58 | Ayaki et al. [f]                           | 2019 | Japan     | Lid/Conjungtiva          | 59.5 [19.9]     | Cross-sectional study       | HADS             | ⩾10  | 41.8% [121/289]               | 6   |
| 59 | Chaumet-Riffaud et al.                     | 2017 | France    | RP                       | 38.2 [7.1]      | Cross-sectional study       | HADS             | ⩾8   | 36.5% [54/148]                | 6   |
| 60 | Eramudugolla et al. [d]                    | 2014 | Australia | Co-morbid eye diseases   | 79.94 [4.91]    | Population-based cross-sectional study | GADS             | ⩾4   | 11.8% [6/51]                  | 7   |
| 61 | Evans et al.                               | 2007 | UK        | Eye disease [a]          | 83.4 [5.1]      | Population-based cross-sectional study | GHQ-28           | NA    | 9.7% [25/259]                 | 7   |
| 62 | Evans et al.                               | 2007 | UK        | Refractive Error         | 83.1 [5.0]      | Population-based cross-sectional study | GHQ-28           | NA    | 9.8% [44/450]                 | 7   |

Anxiety states

| No | Study                                      | Year | Country   | Disease                  | Age [Mean (SD)] | Study design               | Assessment tools | Cutoff | Prevalence [case/participants] | NOS |
|----|--------------------------------------------|------|-----------|--------------------------|-----------------|-----------------------------|------------------|-------|-------------------------------|-----|
| 63 | Evans et al.                               | 2007 | UK        | Eye disease [b]          | 85.5 [5.9]      | Population-based cross-sectional study | GHQ-28           | NA    | 9.4% [30/316]                 | 7   |
| 64 | Kempen and Zijlstra                        | 2014 | The Netherlands | Low vision            | 77.4 [8.8]      | Cross-sectional study       | HADS             | ⩾8   | 14.9% [22/148]                | 7   |
| 65 | Kleinenschmidt et al.                      | 1995 | USA       | Visual impairment        | 76.85           | Cross-sectional study       | STAI             | ⩾45  | 25% [20/80]                   | 6   |
| 66 | Łazarczyk et al.                           | 2016 | Poland    | Myopia                  | 13-17           | Cross-sectional study       | STAIC            | ⩾7   | 22.8% [26/114]                | 7   |
| 67 | Rees et al.                                | 2016 | Australia | DR, DME                 | 64.9 [11.6]     | Cross-sectional study       | HADS             | ⩾8   | 22.7% [118/519]               | 6   |
| 68 | Zhang et al.                               | 2021 | China     | DR                       | 56.7 [11.6]     | Cross-sectional study       | HADS-A           | ⩾9   | 41.1% [43/105]                | 7   |
| 69 | Richards et al.                            | 2014 | UK        | Ptosis                   | 61.6 [15.3]     | Cross-sectional study       | HADS             | ⩾11  | 27.9% [17/61]                 | 7   |
| 70 | Sianohara et al.                           | 2017 | Japan     | RP                       | 60.7 [15.4]     | Cross-sectional study       | HADS-A           | ⩾8   | 37% [41/112]                  | 6   |
| 71 | van der Aa et al. [a]                      | 2015 | The Netherlands | Eye disease       | 73.7 [12.3]     | Cross-sectional study       | HADS-A           | ⩾8   | 18% [45/246]                  | 6   |
| 72 | van der Aa et al. [b]                      | 2015 | The Netherlands | Eye disease       | 77.6 [9.27]     | Cross-sectional study       | HADS-A           | ⩾8   | 7.48% [46/615]                | 7   |
| 73 | Wong and Yu                                | 2013 | China     | GO                      | 54               | Cross-sectional study       | HADS             | ⩾8   | 19% [23/122]                  | 7   |
| 74 | Ye et al.                                  | 2015 | China     | Eye enucleation          | 36.3 [12.6]     | Cross-sectional study       | HADS             | ⩾8   | 40% [78/195]                  | 6   |
| 75 | Yokoi et al.                               | 2013 | Japan     | Myopia                  | 60              | Cross-sectional study       | HADS-A           | ⩾8   | 25.9% [53/205]                | 7   |
| 76 | Mao et al.                                 | 2021 | China     | Intermittent Exotropia   | 8.17 [2.81]     | Cross-sectional study       | HADS-A           | ⩾8   | 95.87% [373/389]             | 7   |

(Continued)
| No | Study                        | Year | Country      | Disease                                | Age [Mean (SD)] | Study design          | Assessment tools | Cutoff | Prevalence (case/participants) | NOS |
|----|------------------------------|------|--------------|----------------------------------------|-----------------|-----------------------|------------------|--------|--------------------------------|-----|
| 77 | Magdalene et al.             | 2021 | India        | Severe visual impairment and blindness | <18+            | Cross-sectional study | DASS            | >7     | 56.56% [250/442]               | 7   |
| 78 | Canamary et al.              | 2019 | Brazil       | Ocular toxoplasmosis                    | 41.5 [14.5]     | Cross-sectional study | HADS-A          | ≥8     | 38.3% [31/81]                  | 6   |
| 79 | Gollrad et al.               | 2021 | Germany      | Uveal melanoma                         | 59.12 [13.6]    | Prospective study     | GAD-7           | ≥5     | 57.2% [75/131]                 | 6   |
| 80 | Kagedi et al.                | 2020 | Congo        | PCV                                    | 66.1 [6.9]      | Prospective case-control study | HADS-A          | ≥8     | 73.3% [11/15]                  | 6   |
| 81 | Frank et al.                 | 2019 | USA          | Visual impairment                       | ≥65+            | Cohort                | PHQ-4-A         | >3     | 27.2% [2063/7584]              | 7   |

Anxiety disorders

| No | Study                        | Year | Country      | Disease        | Age [Mean (SD)] | Study design          | Assessment tools | Cutoff | Prevalence (case/participants) | NOS |
|----|------------------------------|------|--------------|----------------|-----------------|-----------------------|------------------|--------|--------------------------------|-----|
| 1  | Bernabei et al.              | 2011 | Italy        | Visual impairment | 71.9 [7.7]     | Cross-sectional study | Clinical diagnosis | NA     | 10.6% [11/104]                | 7   |
| 2  | Bunevicius et al.            | 2005 | Lithuania    | GO             | 45 [14]         | Cross-sectional study | MINI             | NA     | 73% [22/30]                   | 7   |
| 3  | Chiang et al.                | 2013 | Taiwan       | Blepharitis    | 54.8 [18]       | Cross-sectional study | Clinical diagnosis | NA     | 9.5% [932/9764]               | 7   |
| 4  | Hassan et al.                | 2015 | USA          | Strabismus     | NA              | Cross-sectional study | Clinical diagnosis | NA     | 21.9% [65/297]                | 6   |
| 5  | Jacob et al.                 | 2017 | Germany      | AMD            | 75.7 [10.1]     | Retrospective cohort study | Clinical diagnosis | NA     | 11.7% [887/7580]             | 6   |
| 6  | Li et al. [c]                | 2011 | USA          | Eye disease    | 75.8 [0.1]      | Cross-sectional study | Clinical diagnosis | NA     | 6.5% [1461/22482]             | 7   |
| 7  | van der Vaart et al.         | 2015 | The Netherlands | DED           | NA              | Cross-sectional study | Clinical diagnosis | NA     | 11.4% [823/7207]             | 7   |
| 8  | Zhang et al. [f]             | 2017 | USA          | Glaucoma       | NA              | Retrospective case-control study | Clinical diagnosis | NA     | 17% [1916/11234]             | 8   |
| 9  | Berchuck et al.              | 2020 | USA          | Glaucoma       | 60.0 [14.2]     | Cohort                | Clinical diagnosis | NA     | 28% [113/408]                | 8   |
| 10 | Steven et al.                | 2016 | Germany      | DED            | NA              | Retrospective cohort study | Clinical diagnosis | NA     | 7.7% [4/52]                  | 6   |
| 11 | Abdel-aty and Kombo          | 2021 | USA          | Non-Infectious Scleritis                | NA              | Cross-sectional study | Clinical diagnosis | NA     | 9.3% [15/162]                | 6   |
| 12 | Cockerham et al.             | 2021 | USA          | TED            | 45.2 [7.6]      | Cross-sectional study | Clinical diagnosis | NA     | 34% [34/100]                 | 7   |

(Continued)
Table 1. (Continued)

| No | Study design | Assessment tools | Cutoff | Prevalence (case/participants) |
|----|--------------|-----------------|-------|------------------------------|
| 13 | Retrospective cohort study | Clinical diagnosis | NA | 26% (188/714) |
| 14 | Prospective study | Clinical diagnosis | NA | 77.5% (31/40) |

For the secondary analysis, 22 and 8 studies evaluating anxiety symptoms and disorders among patients with the ophthalmic disease were analyzed. The overall results indicated that relative to healthy controls, patients with ocular disease exhibit nearly a twofold increase of experiencing anxiety symptoms (OR = 1.912, 95% CI 1.463–2.5, p < 0.001, Figure 7(a)), of which patients with DED had slightly higher anxiety symptoms (OR = 2.19, 95% CI 1.411–3.399, p < 0.001, Figure 7(b)) than those with glaucoma (OR = 1.822, 95% CI 1.058–3.135, p = 0.03, Figure 7(c)), but these findings were not observed in patients with myopia nor AMD (Supplemental Figure 1A and B). In line, the risk of developing anxiety disorders among ophthalmic disease patients was two times higher than in control subjects (OR = 2.281, 95% CI 1.168–4.454, p = 0.016, Figure 8). The funnel plot generated from 22 studies was symmetrical (Supplemental Figure 1 C) with the Begg’s test (p = 0.108), indicating no evidence of publication bias.

Discussion
This study showed that the prevalence of anxiety symptoms and disorders among patients with ophthalmic disease were relatively higher than that reported in the general population. We also found that anxiety symptoms and disorders were two times more prevalent among patients with ophthalmic disease than control subjects. Based on the type of eye disease, the highest prevalence of anxiety symptoms was found in patients with uveitis, followed by DED, RP, glaucoma, myopia, AMD, and cataract. Similarly, anxiety disorders were also commonly occurred in patients with glaucoma and DED in addition to TED. It is interesting to note that pediatric patients with ocular disease tended to have a higher prevalence of anxiety symptoms than adults. This is because children may have low coping strategies against potentially

patients with wet AMD had a higher prevalence of anxiety symptoms (34.3%, 95% CI, 16.6%–52%, p < 0.001) than those with any type of AMD (15.3%, 95% CI, 8.3%–22.3%, p < 0.001, Figure 5(c)), and cataract (21.2%, 95% CI, 7.8–34.6%, p = 0.002, Figure 5(d)). For anxiety disorders, the highest prevalence was detected in patients with thyroid eye disease (TED) (28.9%, 95% CI, 21.8%–36%, p < 0.001, Figure 6(a)), followed by patients with glaucoma (22.2%, 95% CI, 11.7%–32.6%, p < 0.001, Figure 6(b)) and DED (11.4%, 95% CI, 10.5%–12.2%, p < 0.001, Figure 6(b)).

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Figure 2. Forest plot of the 81 studies estimating the pooled prevalence of anxiety symptoms among patients with ophthalmic disease, of which 3 studies were conducted in pediatric patients.
stressful situations or alternatively, both primary and secondary control coping may not fully develop in early childhood due to a lack of concrete operational cognitive capacities. Although most of the studies showed low-risk of bias, heterogeneity was observed across the studies. This is possibly due to a variety of detection methods/assessment tools and its cutoff value.

Our study suggests that a higher prevalence of anxiety symptoms was frequently occurred in patients with chronic eye disease (in our study, we reported such as Behçet uveitis, TED, glaucoma, RP, DR, macular degeneration, uncorrected refractive error, and cataract). More than 50% of patients with Behçet uveitis had experience anxiety symptoms. Indeed, depression and anxiety are consistently observed disorders in Behçet’s disease (BD) individuals across studies. It is notable that in 2017, a meta-analysis performed by Wan et al. indicates that DED is associated with nearly a three times increase in the prevalence of anxiety. Recently, Basilious et al. indicated possible interrelationships between DED severity with anxiety symptoms. In agreement with this finding, Zhang et al. demonstrated that glaucoma patients exhibit a 10-fold increase in the risk of developing anxiety disorders. In addition, for the first time, we have shown a higher prevalence of anxiety symptoms in PACG than POAG subjects. This is possibly because relative to POAG, PACG carries a three-fold increased risk of severe bilateral visual impairment. In parallel, Dawson et al. showed that the prevalence estimate of anxiety symptoms in people with AMD ranges from 9.6% to 30.1%, and interestingly, we found that patients with wet AMD had slightly higher anxiety symptoms than previously reported. Although both glaucoma and AMD are considered slow-progressing eye diseases, acute onset of vision loss often occurs in wet AMD. Therefore, patients usually seek a rapid referral and treatment. On the other hand, the lives of people with glaucoma are largely unaffected while the disease progresses silently, which may have a long-term negative impact on their quality of life. Thus, according to our findings, it is possible to hypothesize that the chronicity of glaucoma may be closely associated with the development of anxiety symptoms and disorders.

Patients with TED often have a problem with the disfigurement of the eye. This can change the appearance of the eyes and lead to affected individuals looking tired all the time. These cosmetic issues can have a significant impact on emotional well-being and may be correlated with the development of anxiety disorders, because patients may face exclusion more often due to their facial appearance. Together, our study suggests that anxiety symptoms and disorders are common problems associated in patients with ophthalmic disease.

Anxiety symptoms and disorders that occur in ophthalmic disease patients may be due to several factors, such as a feeling of hopelessness and failing to cope, as a consequence of the untreatable and unpredictable losses of the visual field and losing of the driving license. The anxiety may
also be elicited by socioeconomic aspects, including increased costs from doctor and hospital visits, medications, and health care. From a biochemical standpoint, low serotonin levels (5-HT) have been associated with anxious behavior. Indeed, the reduction of serum 5-HT levels is observed in patients with glaucoma and chronic central serous chorioretinopathy. Interestingly, the administration of selective serotonin reuptake inhibitors (SSRIs) as well as anti-anxiety has been shown to not only improve anxiety symptoms but also suppressed the intraocular pressure (IOP) in glaucomatous patients, thereby implying that 5-HT may involve in glaucoma pathogenesis. Nevertheless, comprehensive and appropriate treatments are necessary for treating anxiety disorders among ophthalmic disease patients, which may help to

Figure 4. Forest plot of the pooled prevalence of anxiety symptoms in the different types of patients with ophthalmic disease: (a) uveitis; (b) dry eye disease (DED); (c) retinitis pigmentosa (RP); (d) Diabetic retinopathy (DR).
Figure 5. Forest plot of the pooled prevalence of anxiety symptoms in the different types of patients with ophthalmic disease: (a) glaucoma; (b) myopia; (c) age-related macular degeneration (AMD); (d) cataract.
reduce the cost of treatment. Moreover, cooperation between ophthalmologists and psychiatrists is essential to support complete eye treatment and to improve mental health conditions.

One of the strengths of this study is that it represents a comprehensive and updated evaluation on the prevalence of anxiety symptoms and disorders in all patients with ocular disease, while a previous study by Zheng et al.\textsuperscript{115} only specifically evaluated depression and depressive symptoms. Moreover, in the previous studies,\textsuperscript{68,115} they combine both symptoms and disorders as a single entity, but in fact, anxiety symptoms and disorders are two different entities. In addition, the strengths of the study included the in-depth analysis of anxiety symptoms in the pediatric group, which was not previously examined.

Some limitations should be noted when interpreting these findings. (1) Because anxiety is often comorbid with depression, the inclusion of studies that report a mixed prevalence of anxiety and depression may have influenced the prevalence estimate in this study. (2) Because the instruments for examining the anxiety symptoms or states are not uniform, this possibly contributes to the observed heterogeneity in this meta-analysis. (3) The uneven number of studies on glaucoma, DED, and AMD could be the other possible source of bias. (4) Because most of the included studies were designed as cross-sectional studies, the causal relationship between anxiety symptoms/disorders and ocular diseases can not be determined. (5) Included studies in the pediatric population are limited, thus the current finding may not be precise and further studies are still required.

In conclusion, our study implies that anxiety symptoms and disorders are common among ophthalmic disease patients. Therefore, a comprehensive and collaborative approach is essential\textsuperscript{116,117} to quickly identify and effectively care for ophthalmic

\textbf{Figure 6.} Forest plot of the pooled prevalence of anxiety disorders in the different types of patients with ophthalmic disease: (a) thyroid eye disease (TED); (b) glaucoma; (c) dry eye disease (DED).
Figure 7. Forest plot of the pooled prevalence of anxiety symptoms in patients with ophthalmic disease and control subjects: (a) overall; (b) dry eye disease (DED) group; (c) glaucoma.
disease patients with anxiety symptoms or disorders. Since more studies are expected to be available, additional accurate estimations can be performed to verify this conclusion.

Author contributions
Zulvikar Syambani Ulhaq: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Gita Vita Soraya: Data curation; Formal analysis; Investigation; Writing – original draft.

Nadia Artha Dewi: Supervision.

Lely Retno Wulandari: Supervision.

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