The prevalence of anxiety symptoms and disorders among ophthalmic disease patients

Zulvikar Syambani Ulhaq (iD)**, Gita Vita Soraya, Nadia Artha Dewi and Lely Retno Wulandari**

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

Correspondence to:
Zulvikar Syambani Ulhaq
Research Center for Pre-Clinical and Clinical Medicine, National Research and Innovation Agency Republic of Indonesia, Cibinong, Indonesia

Faculty of Medicine and Health Sciences, Maulana Malik Ibrahim State Islamic University of Malang, Malang 65151, East Java, Indonesia
zulvikar.syambani.ulhaq@brin.go.id; zulhaq@kedokteran.uin-malang.ac.id

Gita Vita Soraya
Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

Nadia Artha Dewi
Lely Retno Wulandari
Department of Ophthalmology, Faculty of Medicine, Brawijaya University, Malang, Indonesia

Introduction

Anxiety disorders are highly prevalent, affecting about 7.3% (4.8%–10.9%) of the population,[1] with higher incidence among females relative to males.[2] Among them, specific phobias are the most common type of anxiety disorder, followed by panic disorder, social anxiety disorder, and generalized anxiety disorder.[2,3] Anxiety disorders are also highly comorbid with other mental disorders, especially depressive disorders.[2,4] These implicate that patients with anxiety and depressive disorders may often have poorer outcomes and require specific psychopharmacological adjustments.

Chronically ill patients are at high risk of experiencing anxiety disorders as a result of the psychoemotional disturbances implicated by physical

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.[5] Several studies have shown the association between anxiety symptoms and ocular diseases.[6–8] However, the reported prevalence of anxiety symptoms and disorders in patients with ocular diseases remains highly varied, ranging from 2.4% to 78%[6,9] and 6.3% to 73%, respectively.[10,11]

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.[12] 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.[13] 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.[14] 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/ophthalmology 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.[15] The maximum score for each study is 9. Studies scoring less than 5 were judged to be at a high risk of bias.[16]

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.[17–22] Meta-analysis was performed utilizing Open Meta-Analyst software package.[23] The value of 0.05 was indicative of statistical significance.

Results
Ninety-five studies were included in this meta-analysis,[6–11,24–98] 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 6.5% to 77.5%, respectively. The random-effect model was used because heterogeneity existed ($I^2 > 50\%$). The overall pooled prevalences of
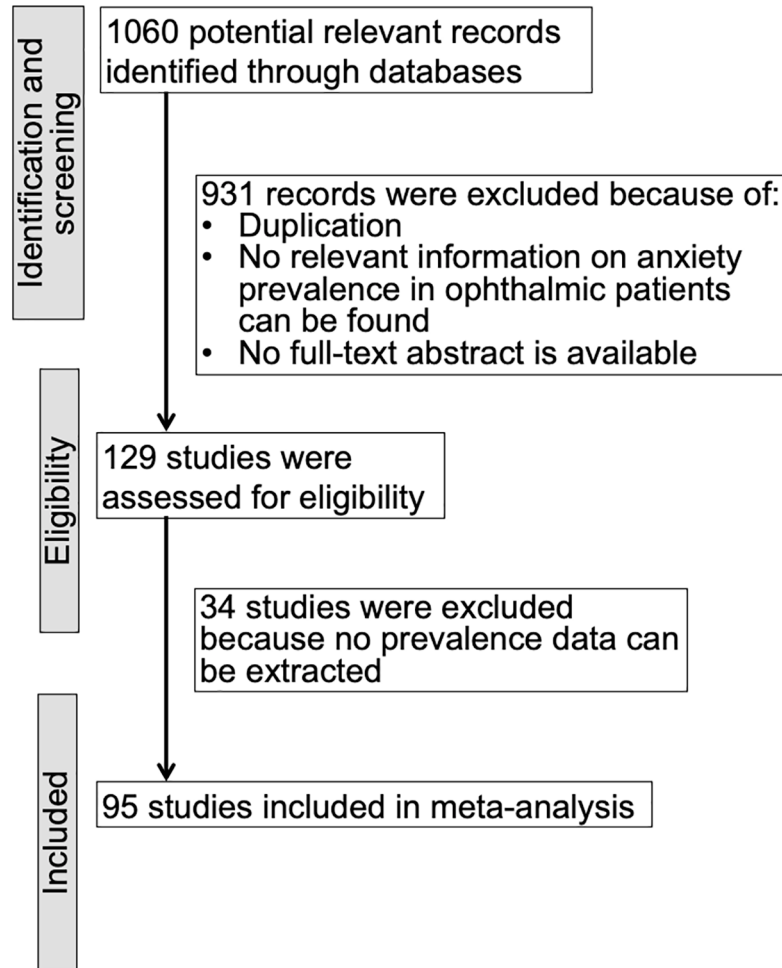
Figure 1. Flow diagram of the study selection process.

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, 24.9%–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
Anxiety states										
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 (PACG + 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 (PACG + 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 (PACG)	NA	Cross-sectional study	HADS-A	>10	26.7% (16/60)	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	29.66% (78/263)	6
18	Zhan and Zhitan	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

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Table 1. (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
Anxiety states										
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	18–72[a]	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.* (b)	2021	China	Glaucoma (POAG)	56.6 (15.7)	Cross-sectional study	HADS-A	>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.* (b)	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-A	⩾8	17.3% (52/300)	6
30	Eramudugolla *et al.* (b)	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.* (b)	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% (24/96)	6

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Table 1. (Continued)

No	Study	Year	Country	Disease	Age [Mean (SD)]	Study design	Assessment tools	Cutoff	Prevalence (case/participants)	NOS
39	Na et al.	2015	Korea	DED	44.9 (0.8)	Population-based cross-sectional study	EQ-5D (EQ_5)	>1	17.5% (142/816)	7
40	Wen et al.	2012	China	DED	41 (15)	Cross-sectional study	SAS	>52	61.8%% (175/283)	6
41	Yilmaz et al.	2015	Turkey	DED	41[a]	Case-control study	DASS	>7	63.3% (77/121)	7
Anxiety states										
42	Wu et al. (b)	2019	China	DED	45.52 (12.8)	Case-control study	GAD-7	⩾5	39% (41/106)	7
43	Kitazawa et al.	2018	Japan	DED	61.3 (18.1)	Observational prospective study	HAM-A	⩾14	14.7% (5/34)	6
44	Bitar et al.	2019	USA	DED	65.5 (13.3)	Prospective study	GAD-7	>10	22.2% (10/45)	6
45	Zhang et al. (c)	2016	China	SSDE	46.8 (11.1)	Case-control study	SAS	>50	43.33% (13/30)	7
46	Ayaki et al. (c)	2018	Japan	Cataract	59.5 (19.9)	Cross-sectional study	HADS	⩾10	36.9% (59/159)	6
47	Eramudugolla et al. (c)	2013	Australia	Cataract	77.57 (4.5)	Population-based cross-sectional study	GADS	⩾4	10.8% (21/94)	7
48	Evans et al.	2007	UK	Cataract	84.7 (5.3)	Population-based cross-sectional study	GHQ-28	NA	8.2% (29/350)	7
49	Zhang et al. (d)	2018	China	Catracat	70.23 (9.78)	Cross-sectional study	HADS-A	⩾8	18% (18/100)	6
50	Onal et al.	2017	Turkey	Uveitis	36.09 (12.49)	Cross-sectional study	STAI-I	⩾40	52.5% (52/99)	6
51	Sittivarakul and Wongkot	2018	Thailand	Uveitis	43.5[a]	Descriptive study	HADS-A	⩾8	12.8% (11/86)	6
52	Eser-Öztürk et al. (a)	2021	Turkey	Behçet Uveitis	34.76 (11.14)	Cross-sectional study	STAI-I	⩾40	58.6% (34/58)	6
53	Eser-Öztürk et al. (b)	2021	Turkey	Behçet Uveitis	34.76 (11.14)	Cross-sectional study	STAI-II	⩾40	79.3% (46/58)	6
54	Silva et al.	2017	Brazil	Uveitis	42.8 (14.5)	Cross-sectional study	HADS	⩾8	65.1% (52/80)	6
55	Heindl et al.	2021	Germanuy	Unilateral anophthalmic	62.54 (16.77)	Cross-sectional study	GAD-7	⩾5	44.7% (132/295)	7
56	Ayaki et al. (d)	2016	Japan	Retinal disease	59.5 (19.9)	Cross-sectional study	HADS	⩾10	42.3% (51/120)	6
57	Ayaki et al. (e)	2017	Japan	IOL	59.5 (19.9)	Cross-sectional study	HADS	⩾10	28.4% (28/99)	6

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Table 1. (Continued)

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										
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	Kleinschmidt *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[a]	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.* (e)	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[a]	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[a]	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

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Table 1. (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[a]	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	Kabedi 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[a]	Cohort	PHQ-4-A	>3	27.2% (2063/7584)	7
Anxiety disorders										
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% (1461/22,482)	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% (1916/11,234)	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

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Table 1. (Continued)

No	Study	Year	Country	Disease	Age [Mean (SD)]	Study design	Assessment tools	Cutoff	Prevalence (case/participants)	NOS
13	Wang *et al.*	2021	USA	TED	49.4 (13.6)	Retrospective cohort study	Clinical diagnosis	NA	26% (188/714)	7
14	Dudani *et al.*	2021	India	Central serous chorioretinopathy	39.55 (8.33)	Prospective study	Clinical diagnosis	NA	77.5% (31/40)	6

AMD, age-related macular degeneration; BAI, Beck's Anxiety Inventory; DASS, Depression Anxiety Stress Scales; DED, dry eye disease; DME, diabetic macular edema; DR, diabetic retinopathy; EQ-5D; EuroQol-5D health-status descriptive system; GAD-7, Generalized Anxiety Disorder-7 Scale; GAD, Goldberg Anxiety and Depression; GAI, Geriatric Anxiety Inventory; GHQ-28, Anxiety subscale of the General Health Questionnaire; GO, Graves ophthalmopathy; HADS, Hospital Anxiety and Depression Scale; HADS-A, HDSA-Anxiety, HADS-P, Hospital Anxiety and Depression Scale (The Filipino version); HAM-A, Hamilton Anxiety Rating Scale; HARS, Hamilton Anxiety Rating Scale; NA, not available; NOS, the Newcastle-Ottawa Scale; MINI, Mini-International Neuropsychiatric Interview; PXG, pseudoexfoliative glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; PCV, polypoidal choroidal vasculopathy; PHQ-4, The Patient Health Questionnaire for Depression and Anxiety; RP, retinitis pigmentosa; SAS, The Zung Self-rating Anxiety Scale; SD, standard deviation; SSDE, Sjögren syndrome dry eye; STAI, The State–Trait Anxiety Inventory; STAIC, The State–Trait Anxiety Inventory for Children; TED, Thyroid Eye Disease. Gray shading indicates children group.
aAge presented as mean/median/range.

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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)).

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.[1,99] 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, DR, 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
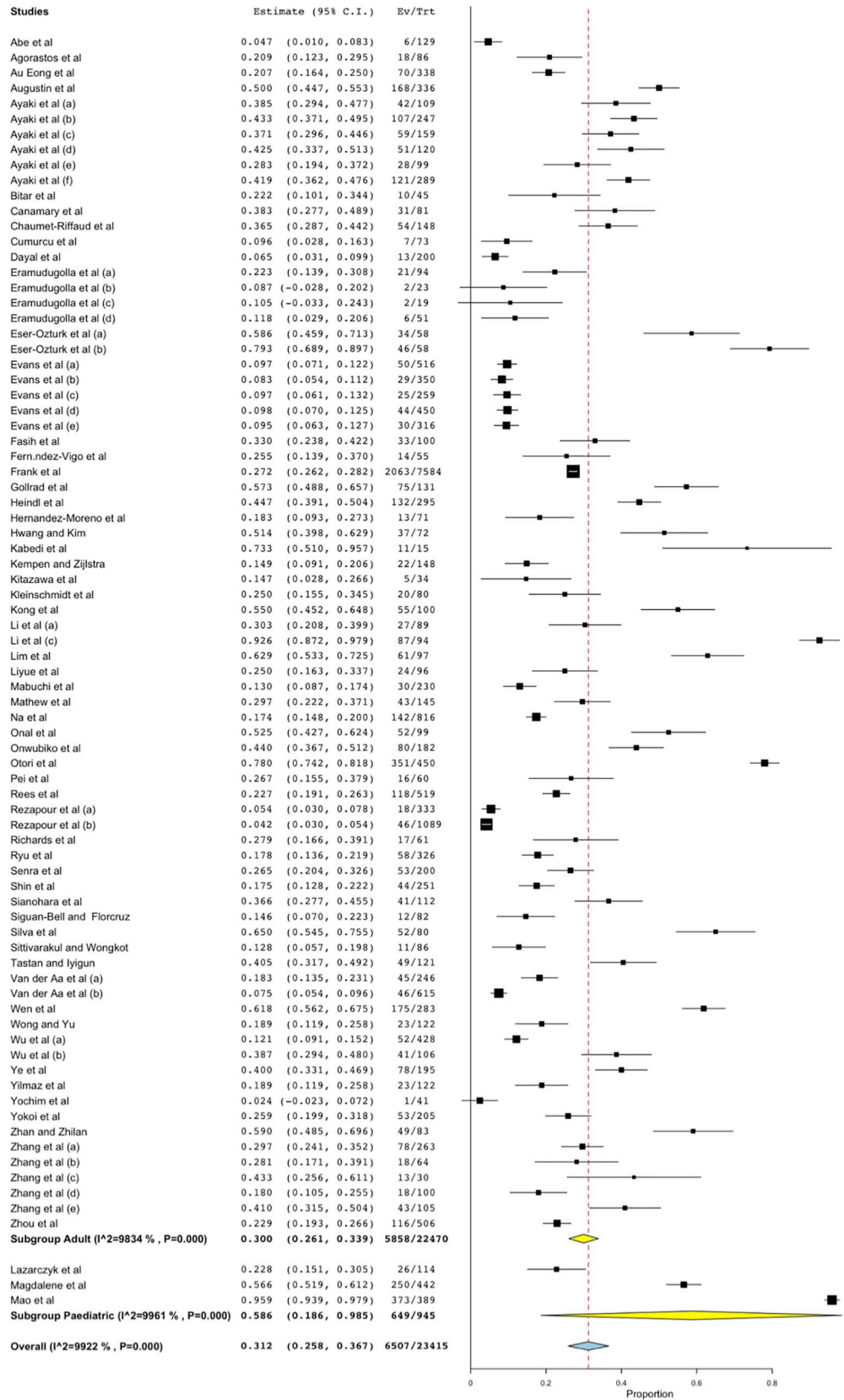
Studies	Estimate (95% C.I.)	Ev/Trt
Abe et al	0.047 (0.010, 0.083)	6/129
Agorastos et al	0.209 (0.123, 0.295)	18/86
Au Eong et al	0.207 (0.164, 0.250)	70/338
Augustin et al	0.500 (0.447, 0.553)	168/336
Ayaki et al (a)	0.385 (0.294, 0.477)	42/109
Ayaki et al (b)	0.433 (0.371, 0.495)	107/247
Ayaki et al (c)	0.371 (0.296, 0.446)	59/159
Ayaki et al (d)	0.425 (0.337, 0.513)	51/120
Ayaki et al (e)	0.283 (0.194, 0.372)	28/99
Ayaki et al (f)	0.419 (0.362, 0.476)	121/289
Bitar et al	0.222 (0.101, 0.344)	10/45
Canamary et al	0.383 (0.277, 0.489)	31/81
Chaumet-Riffaud et al	0.365 (0.287, 0.442)	54/148
Cumurcu et al	0.096 (0.028, 0.163)	7/73
Dayal et al	0.065 (0.031, 0.099)	13/200
Eramudugolla et al (a)	0.223 (0.139, 0.308)	21/94
Eramudugolla et al (b)	0.087 (−0.028, 0.202)	2/23
Eramudugolla et al (c)	0.105 (−0.033, 0.243)	2/19
Eramudugolla et al (d)	0.118 (0.029, 0.206)	6/51
Eser-Ozturk et al (a)	0.586 (0.459, 0.713)	34/58
Eser-Ozturk et al (b)	0.793 (0.689, 0.897)	46/58
Evans et al (a)	0.097 (0.071, 0.122)	50/516
Evans et al (b)	0.083 (0.054, 0.112)	29/350
Evans et al (c)	0.097 (0.061, 0.132)	25/259
Evans et al (d)	0.098 (0.070, 0.125)	44/450
Evans et al (e)	0.095 (0.063, 0.127)	30/316
Fasih et al	0.330 (0.238, 0.422)	33/100
Fern.ndez-Vigo et al	0.255 (0.139, 0.370)	14/55
Frank et al	0.272 (0.262, 0.282)	2063/7584
Gollrad et al	0.573 (0.488, 0.657)	75/131
Heindl et al	0.447 (0.391, 0.504)	132/295
Hernandez-Moreno et al	0.183 (0.093, 0.273)	13/71
Hwang and Kim	0.514 (0.398, 0.629)	37/72
Kabedi et al	0.733 (0.510, 0.957)	11/15
Kempen and Zijlstra	0.149 (0.091, 0.206)	22/148
Kitazawa et al	0.147 (0.028, 0.266)	5/34
Kleinschmidt et al	0.250 (0.155, 0.345)	20/80
Kong et al	0.550 (0.452, 0.648)	55/100
Li et al (a)	0.303 (0.208, 0.399)	27/89
Li et al (c)	0.926 (0.872, 0.979)	87/94
Lim et al	0.629 (0.533, 0.725)	61/97
Liyue et al	0.250 (0.163, 0.337)	24/96
Mabuchi et al	0.130 (0.087, 0.174)	30/230
Mathew et al	0.297 (0.222, 0.371)	43/145
Na et al	0.174 (0.148, 0.200)	142/816
Onal et al	0.525 (0.427, 0.624)	52/99
Onwubiko et al	0.440 (0.367, 0.512)	80/182
Otori et al	0.780 (0.742, 0.818)	351/450
Pei et al	0.267 (0.155, 0.379)	16/60
Rees et al	0.227 (0.191, 0.263)	118/519
Rezapour et al (a)	0.054 (0.030, 0.078)	18/333
Rezapour et al (b)	0.042 (0.030, 0.054)	46/1089
Richards et al	0.279 (0.166, 0.391)	17/61
Ryu et al	0.178 (0.136, 0.219)	58/326
Senra et al	0.265 (0.204, 0.326)	53/200
Shin et al	0.175 (0.128, 0.222)	44/251
Sianohara et al	0.366 (0.277, 0.455)	41/112
Siguan-Bell and Florcruz	0.146 (0.070, 0.223)	12/82
Silva et al	0.650 (0.545, 0.755)	52/80
Sittivarakul and Wongkot	0.128 (0.057, 0.198)	11/86
Tastan and Iyigun	0.405 (0.317, 0.492)	49/121
Van der Aa et al (a)	0.183 (0.135, 0.231)	45/246
Van der Aa et al (b)	0.075 (0.054, 0.096)	46/615
Wen et al	0.618 (0.562, 0.675)	175/283
Wong and Yu	0.189 (0.119, 0.258)	23/122
Wu et al (a)	0.121 (0.091, 0.152)	52/428
Wu et al (b)	0.387 (0.294, 0.480)	41/106
Ye et al	0.400 (0.331, 0.469)	78/195
Yilmaz et al	0.189 (0.119, 0.258)	23/122
Yochim et al	0.024 (−0.023, 0.072)	1/41
Yokoi et al	0.259 (0.199, 0.318)	53/205
Zhan and Zhilan	0.590 (0.485, 0.696)	49/83
Zhang et al (a)	0.297 (0.241, 0.352)	78/263
Zhang et al (b)	0.281 (0.171, 0.391)	18/64
Zhang et al (c)	0.433 (0.256, 0.611)	13/30
Zhang et al (d)	0.180 (0.105, 0.255)	18/100
Zhang et al (e)	0.410 (0.315, 0.504)	43/105
Zhou et al	0.229 (0.193, 0.266)	116/506
Subgroup Adult (I^2=9834 % , P=0.000)	0.300 (0.261, 0.339)	5858/22470
Lazarczyk et al	0.228 (0.151, 0.305)	26/114
Magdalene et al	0.566 (0.519, 0.612)	250/442
Mao et al	0.959 (0.939, 0.979)	373/389
Subgroup Paediatric (I^2=9961 % , P=0.000)	0.586 (0.186, 0.985)	649/945
Overall (I^2=9922 % , P=0.000)	0.312 (0.258, 0.367)	6507/23415

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.
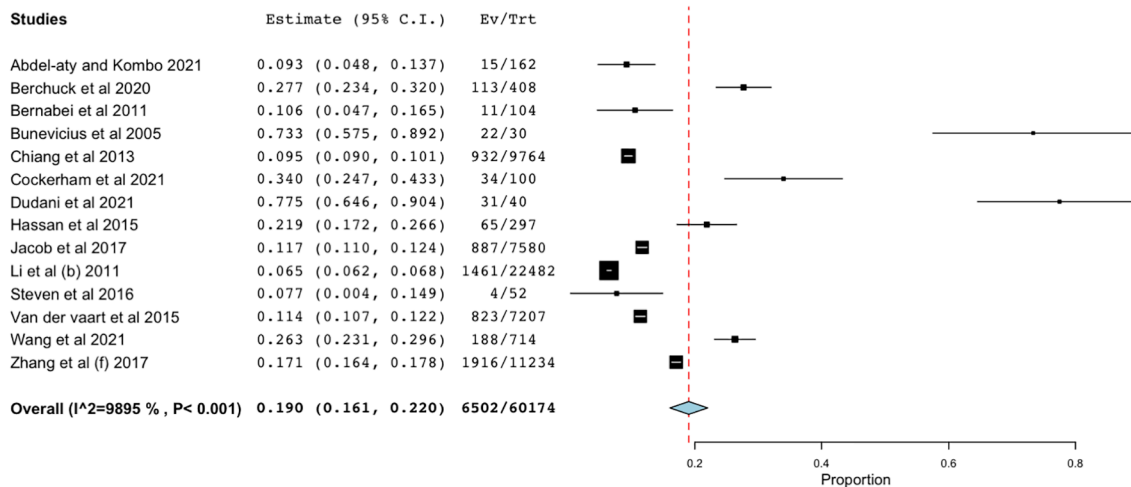
Figure 3. Forest plot of the 14 studies estimating the pooled prevalence of anxiety disorders among patients with ophthalmic disease.

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.[100] 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.[101] It is notable that in 2017, a meta-analysis performed by Wan *et al.*[68] indicates that DED is associated with nearly a three times increase in the prevalence of anxiety. Recently, Basilious *et al.*[102] indicated possible interrelationships between DED severity with anxiety symptoms. In agreement with this finding, Zhang *et al.*[42] 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 threefold increased risk of severe bilateral visual impairment.[103] In parallel, Dawson *et al.*[104] 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.[104] 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.[105] 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.[106] 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[107] and losing of the driving license.[108] The anxiety may
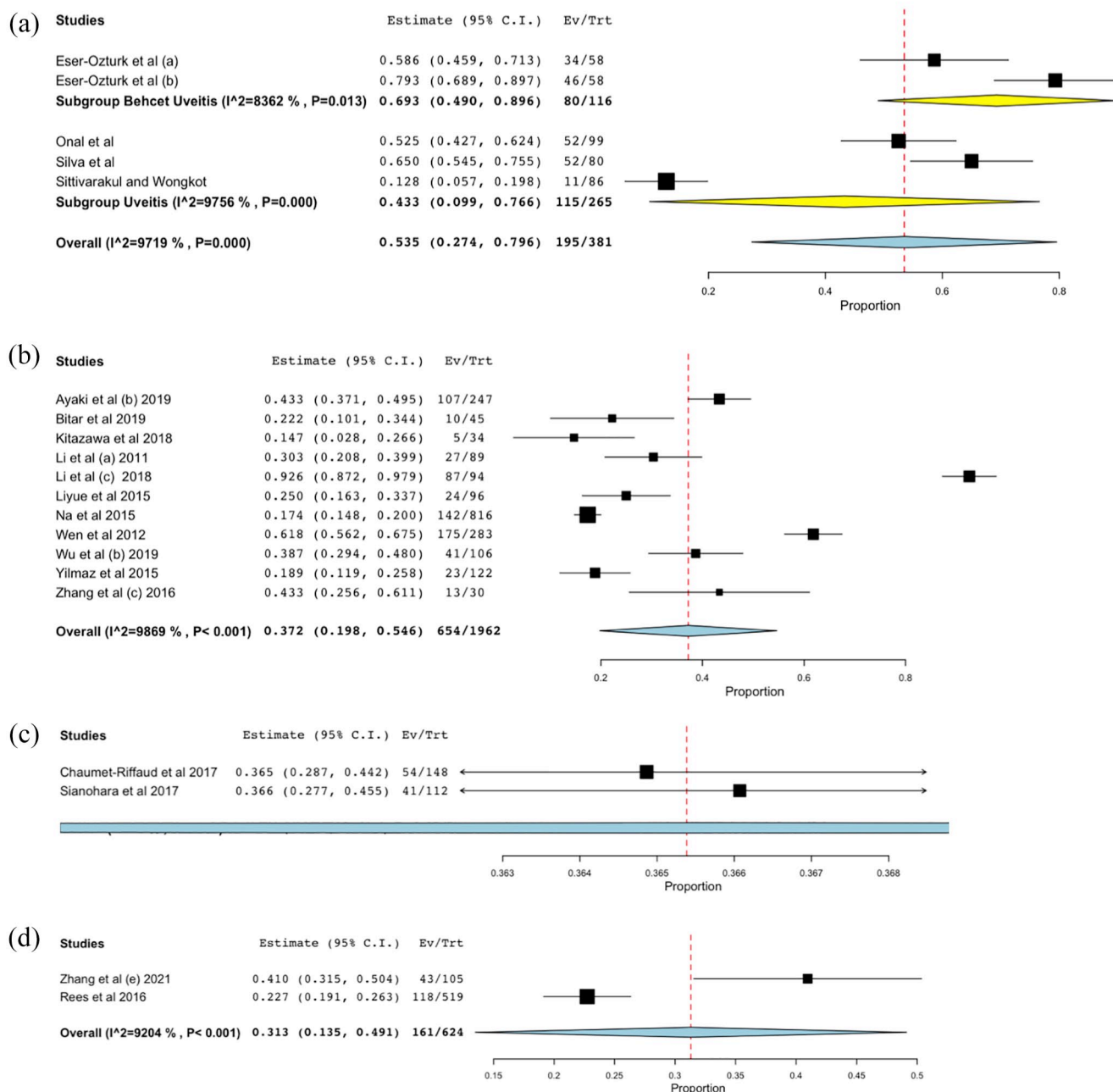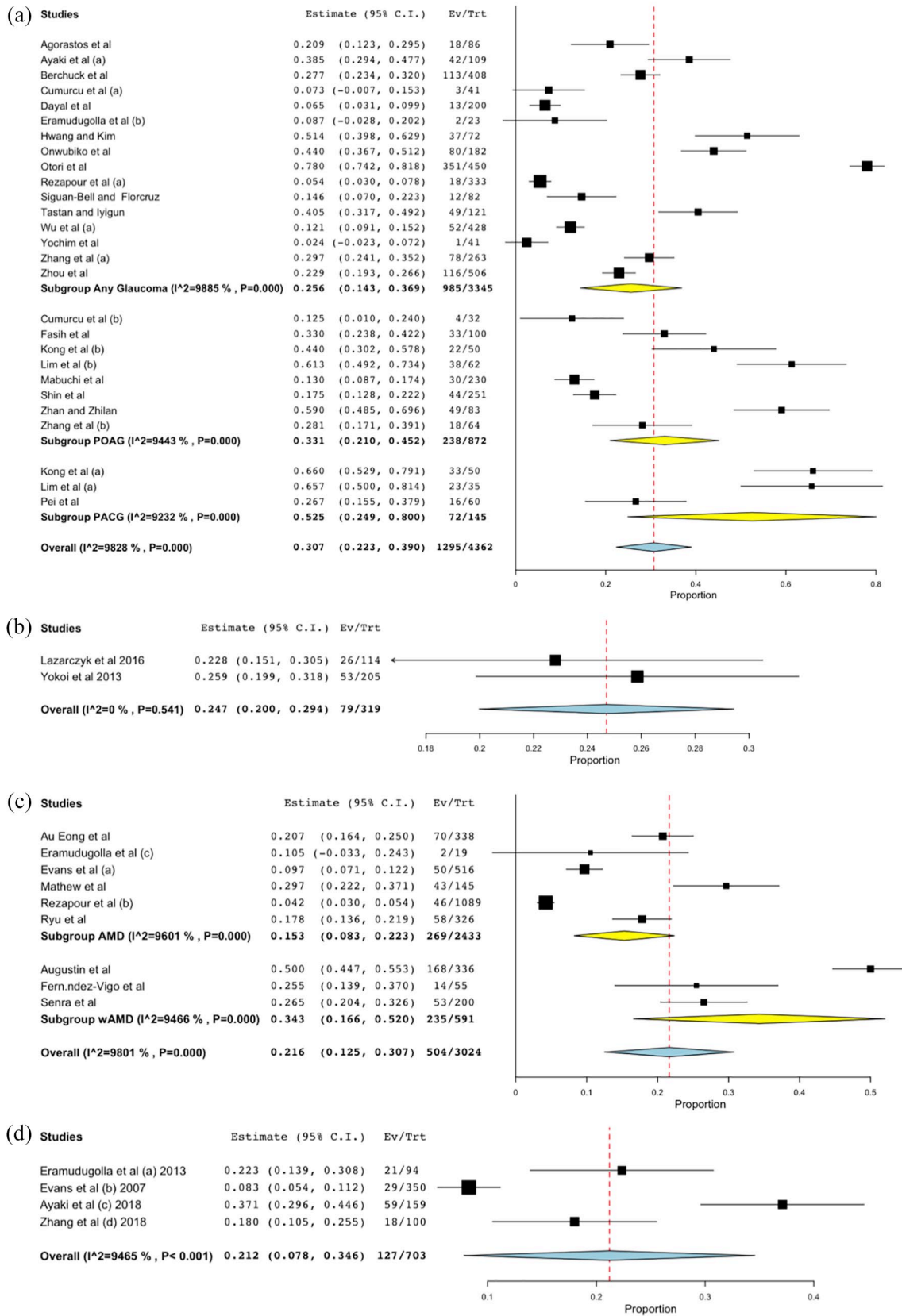
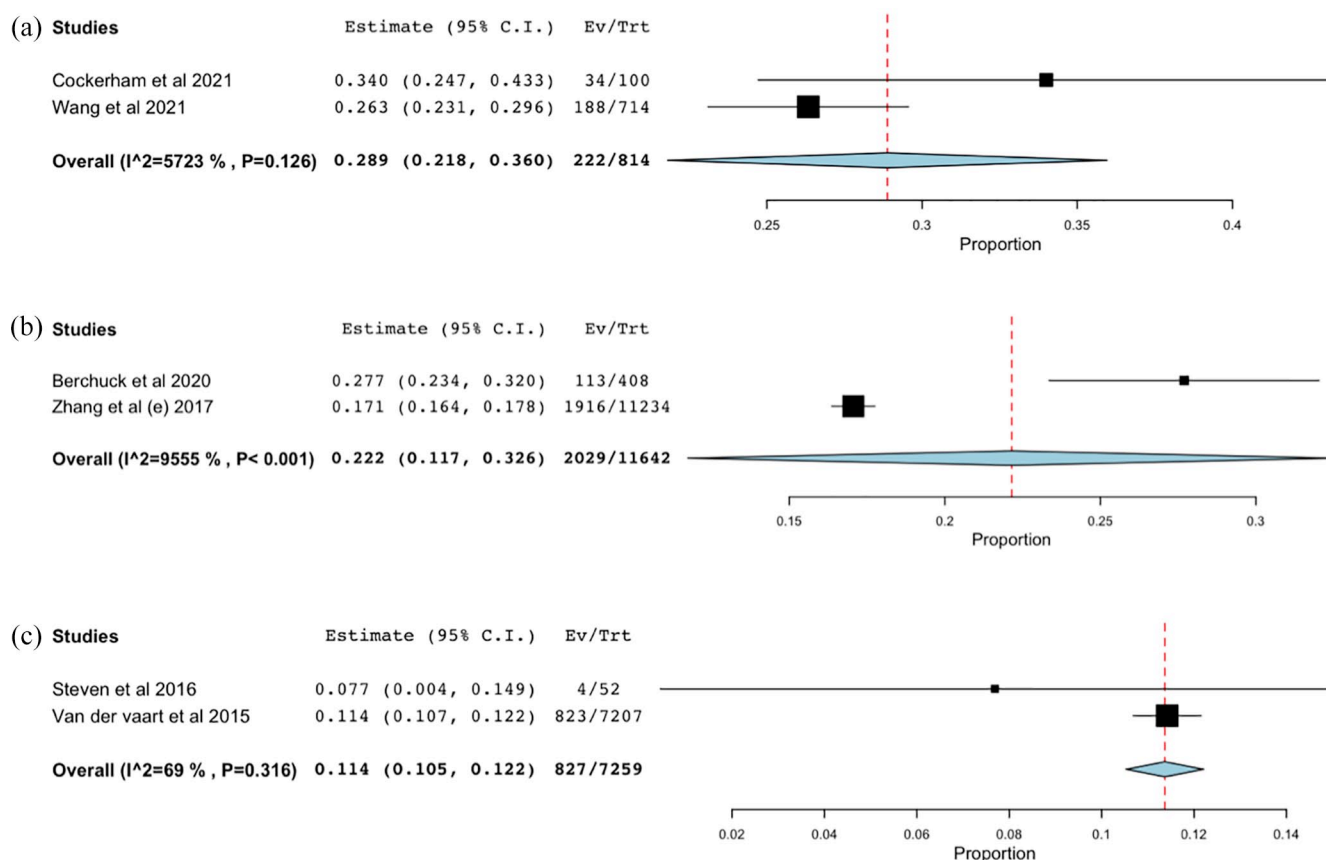**Figure 4.** Forest plot of the pooled prevalence of anxiety symptoms in the different types of patients with ophthalmic disease: (a) uveitis; (b) dry eye disease (DED); (c) retinitis pigmentosa (RP); (d) Diabetic retinopathy (DR).

also be elicited by socioeconomic aspects, including increased costs from doctor and hospital visits, medications, and health care.[109,110] From a biochemical standpoint, low serotonin levels (5-HT) have been associated with anxious behavior.[111] Indeed, the reduction of serum 5-HT levels is observed in patients with glaucoma and chronic central serous chorioretinopathy.[112,113] 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,[114] 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 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.

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).

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.*[115] only specifically evaluated depression and depressive symptoms. Moreover, in the previous studies,[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[116,117] to quickly identify and effectively care for ophthalmic
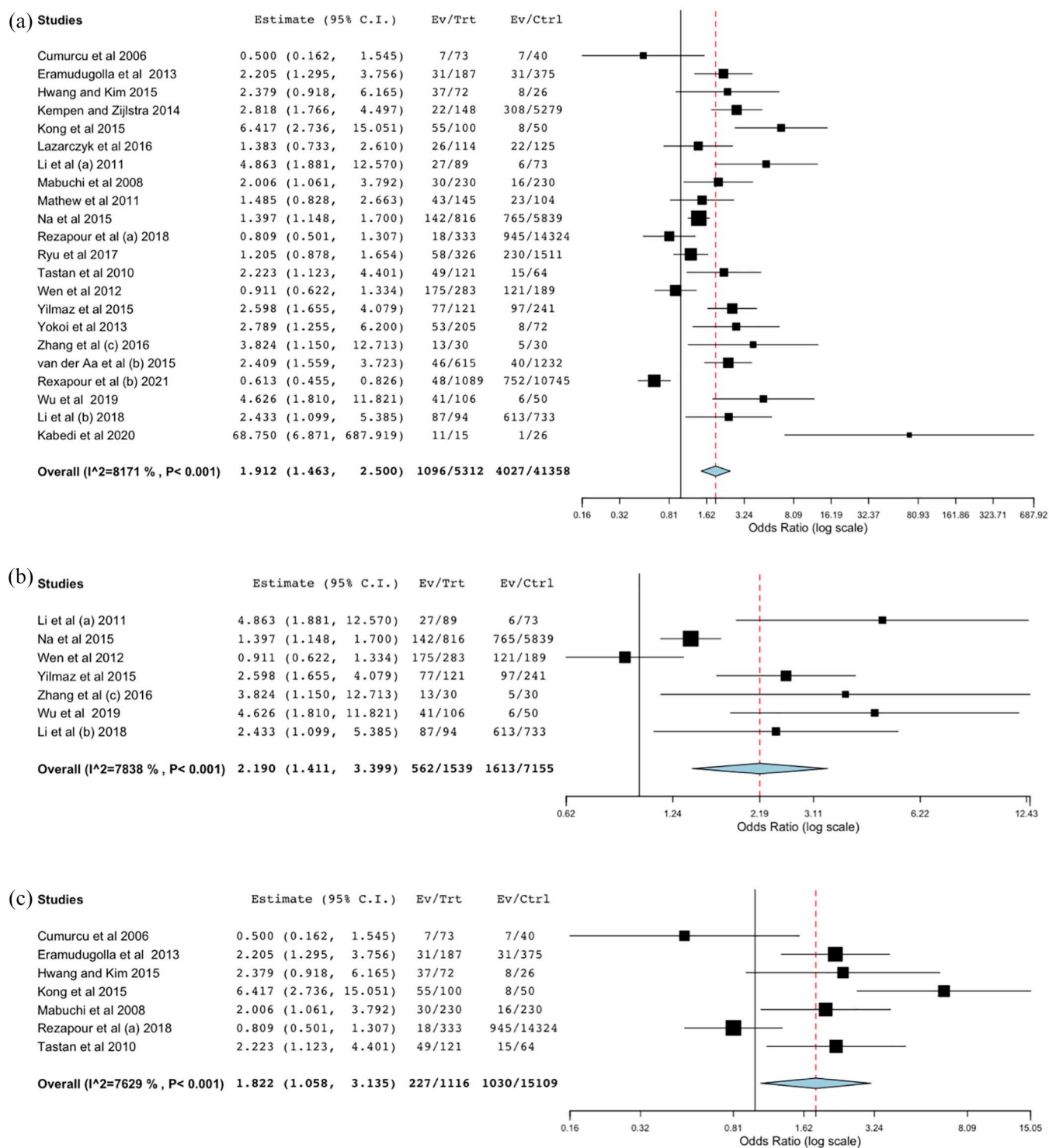
Figure 7. Forest plot of the pooled prevalence of anxiety symptoms in patients with ophthalmic disease and control subjects: (a) overall; (b) dry eye disease (DED) group; (c) glaucoma.
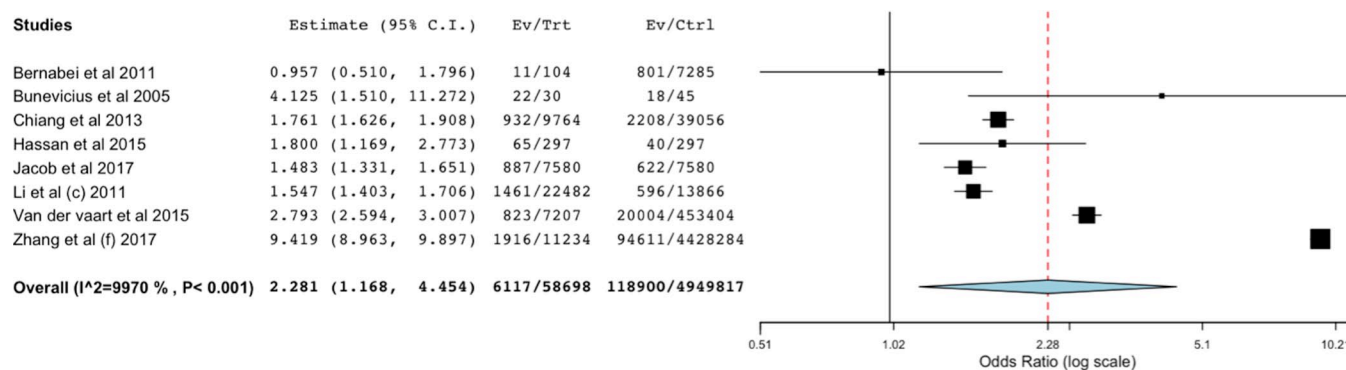
Figure 8. Forest plot of the pooled prevalence of anxiety disorders in patients with ophthalmic disease and control subjects.

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.

ORCID iD
Zulvikar Syambani Ulhaq (iD) https://orcid.org/0000-0002-2659-1940

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