Impact of anxiety and depression on progression to glaucoma among glaucoma suspects

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ABSTRACT

Aims To assess the impact of anxiety and depression in the risk of converting to glaucoma in a cohort of glaucoma suspects followed over time.

Methods The study included a retrospective cohort of subjects with diagnosis of glaucoma suspect at baseline, extracted from the Duke Glaucoma Registry. The presence of anxiety and depression was defined based on electronic health records billing codes, medical history and problem list. Univariable and multivariable Cox proportional hazards models were used to obtain HRs for the risk of converting to glaucoma over time. Multivariable models were adjusted for age, gender, race, intraocular pressure measurements over time and disease severity at baseline.

Results A total of 3259 glaucoma suspects followed for an average of 3.60 (2.05) years were included in our cohort, of which 911 (28%) were diagnosed with glaucoma during follow-up. Prevalence of anxiety and depression were 32% and 33%, respectively. Diagnoses of anxiety, or concomitant anxiety and depression were significantly associated with risk of converting to glaucoma over time, with adjusted HRs (95% CI) of 1.16 (1.01, 1.33) and 1.27 (1.07, 1.50), respectively.

Conclusion A history of anxiety or both anxiety and depression in glaucoma suspects was associated with developing glaucoma during follow-up.

INTRODUCTION

Glaucoma is the leading cause of irreversible vision loss worldwide,[1] and due to its chronic, progressive nature, it often imposes a psychological burden on patients.[2 3] Upon a glaucoma diagnosis, patients often fear going blind and are overcome with negative emotions[4] and furthermore have increased odds of inpatient hospitalisation, higher annual cost of care, falls and driving accidents.[5]

Numerous population-based studies have shown an association between glaucoma and psychiatric disorders, most often depression and anxiety.[6–12] Among studies of primary open-angle glaucoma patients, the prevalence of depression and anxiety ranges from 13% to 30% and from 6% to 25%, respectively.[12] In a National Health and Nutrition Examination Survey sample, glaucoma was significantly associated with depression after adjustment for demographics,[13] and in a study of a large health system, glaucoma patients were 10.6 and 12.3 times more likely to have depression and anxiety symptoms, respectively.[12] In glaucoma patients, older age, unmarried status and increased medical comorbidity were associated with depression, and younger age, female sex and lower socioeconomic status were associated with anxiety.[10 14] Longer follow-up and worse disease severity have been shown to be associated with depression,[15] and in a longitudinal study, faster visual field progression was associated with the occurrence of depressive symptoms.[11]

While there is substantial evidence, the role of psychiatric disorders in glaucoma remains complicated. Although they may certainly be a consequence of visual loss and glaucoma diagnosis, they may also contribute to disease progression over time. To this end, it has been shown that depression decreases glaucoma medication adherence,[16] which is known to be associated with faster visual field progression.[17] In addition, recent evidence has shown in non-human primates that intraocular pressure (IOP) increases with stress,[18] a finding that may have important ramifications in the relationship between anxiety and glaucoma.

In this study, we investigated a large cohort of glaucoma suspects to better understand the effect of anxiety and depression on progression to a diagnosis of glaucoma. The study cohort is curated from electronic health records (EHR), leveraging systemic data to observe clinical processes at a large scale. We hypothesised that the presence of anxiety and depression upon a glaucoma suspect diagnosis would be associated with an increased risk of developing glaucoma during follow-up.

MATERIALS AND METHODS

This was a retrospective cohort study of patients from the Duke Glaucoma Registry which consisted of adults at least 18 years of age with glaucoma or glaucoma suspect diagnoses who were evaluated at the Duke Eye Center or its satellite clinics from 2012 to 2019. The Duke University Institutional Review Board approved this study with a waiver of informed consent due to the retrospective nature of this work. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects and were conducted in accordance with regulations of the Health Insurance Portability and Accountability Act.

Information on comprehensive ophthalmic examinations from baseline and follow-up visits were collected including patient diagnosis codes (International Classification of Diseases (ICD)), procedures (Current Procedural Terminology

(CPT)), medical history and problem list. IOP was measured using the Goldmann applanation tonometry (Haag-Streit, Konig, Switzerland) and the Tono-Pen (Reichert, Depew, New York, USA). Standard automated perimetry (SAP) tests were acquired with the Humphrey Field Analyser (HFA, Carl Zeiss Meditec, Dublin, California, USA) during the study period. Only 24-2 and 30-2 Swedish Interactive Threshold Algorithm or full threshold tests of the HFA with size III white stimulus were exported from the database. Visual fields were excluded if they had >33% fixation losses or >15% false-positive or false-negative errors.

Patients were included in the study if they had a glaucoma suspect diagnosis, based on ICD codes version 9 or 10 (online supplemental etable 1), at baseline. We excluded patients if they had any ICD code indicative of diagnosis of glaucoma prior to the glaucoma suspect diagnosis. In addition, patients were excluded if they had procedures or diseases that could confound SAP results. These included treatment with pan-photocoagulation according to CPT codes, any diagnosis of retinal detachment, retinal or choroidal tumours, disorders of the optical nerve and visual pathways, inflammations including endophthalmitis, uveitis, focal chorioretinitis, and iridocyclitis, amblyopia and venous or arterial retinal occlusion according to ICD codes (online sup plemental etable 1). Finally, to be included in the cohort, patients were required to have a baseline visual field and IOP measurement within 1 year of the baseline suspect diagnosis and prior to any glaucoma diagnosis.

Glaucoma outcome

A diagnosis of glaucoma during follow-up was defined at the patient level based on ICD codes (online supplemental table 1). If a diagnosis of glaucoma did not occur during the study period, patients were considered censored. The follow-up stopped at the end of 2019, so all patients without a glaucoma diagnosis at the end of follow-up were censored on January 1, 2020. Since we are interested in a time-to-event analysis, we recorded the time from a baseline glaucoma suspect diagnosis until the first appearance of a diagnosis of glaucoma in the chart, in years from baseline.

Psychiatric measures

Patients were categorised into psychiatric diagnoses based on billing data, including ICD codes, medical history and problem list based on validated algorithms for identifying anxiety[19 20] and depression.[21] To be classified as having anxiety or depression, at least one of the indications had to be present in a patient's EHR data in the 5 years prior to the baseline glaucoma suspect diagnosis (online supplemental etable 2). Throughout the manuscript, we analyse three definitions of the psychiatric diagnoses: (1) anxiety versus no anxiety, (2) depression versus no depression and (3) no psychiatric diagnoses, anxiety only, depression only, and both anxiety and depression. The first two are binary indicators, and the last is a mutually exclusive four-level categorical variable.

Statistical analysis

We investigated the impact of diagnoses of anxiety, depression or both on the risk of developing glaucoma during follow-up. To assess the impact of baseline risk factors on an eventual diagnosis of glaucoma, standard time-to-event techniques were employed. In particular, we estimated HRs, which represent an instantaneous risk of an event occurring at a particular time in the follow-up period. Cumulative HR curves are presented using Kaplan-Meier curves, with CIs calculated on the logarithmic scale using Greenwood's formula and p values obtained from the log-rank test.[22 23] Furthermore, both univariable and multivariable Cox regression models were used. Multivariable models were adjusted for potential confounding factors, including age, gender, race, IOP measurements over time and baseline disease severity, as measured by SAP mean deviation (MD). For the eye-specific variables IOP and MD, we averaged measurements from both eyes. Adjusted HRs were obtained from the multivariable models, with IOP encoded as a time-dependent covariate.[24] To allow meaningful comparison and interpretation of HRs, all continuous variables were standardised.

Summaries are presented across psychiatric groups at baseline. Continuous baseline variables are presented as mean and SD and categorical variables are presented as counts and percentages. In addition to baseline variables, we also presented summaries of IOP throughout follow-up and among patients ultimately diagnosed with glaucoma, and SAP MD at the time of event. IOP measures throughout follow-up were summarised as mean, peak and fluctuation IOP. Fluctuation IOP was defined as the range of IOP across follow-up.[25] All analyses were performed using the R programming language (Version 3.5.1, R Core Team, Vienna, Austria) within the Protected Analytics Computing Environment, a highly protected virtual network space developed by Duke University for analysis of identifiable protected health information. The type 1 error was set at 0.05.

RESULTS

The cohort consisted of 3259 patients with diagnosis of glaucoma suspect at baseline and followed for an average of 3.60 (2.05) years. Table 1 presents clinical and demographic characteristics at baseline across psychiatric groups. Overall in our cohort, the mean (SD) age at baseline was 60.0 (14.2) years, 58% were women and 57% self-identified themselves as Caucasian, while 34% self-identifie as African American. Of the 3259 patients, 1015 (32%) patients had anxiety and 1057 (33%) had a diagnosis of depression. A total of 1465 (46%) patients had either depression or anxiety, while 607 (19%) had both anxiety and depression.

From the 3259 patients, 911 subjects (28%) received a diagnosis of glaucoma during follow-up. There was an association between a glaucoma diagnosis and psychiatric diagnosis groups at baseline ($p=0.013$). Of note, 33% of patients with both anxiety and depression would eventually receive a glaucoma diagnosis. This p value should be interpreted with care, because it does not account for the time-to-event nature of the data. In addition to glaucoma event status, we found that female and Caucasian patients had an increased risk of having a psychiatric diagnosis at baseline (both $p<0.001$). Furthermore, in our cohort, there was a significant association between baseline MD and psychiatric group ($p<0.001$), with worse levels of MD for patients with a psychiatric diagnosis.

Figure 1 shows Kaplan-Meier survival curves for risk of developing glaucoma during follow-up for subjects with anxiety or depression. Table 2 shows univariable HRs for each putative factor for predicting risk of glaucoma over time. Glaucoma suspects with a diagnosis of anxiety at baseline carried a 20% increased risk of developing glaucoma (HR: 1.20; 95% CI 1.04 to 1.37; $p=0.010$), while subjects diagnosed with depression had a 15% increased risk (HR: 1.15; 95% CI 1.01 to 1.32). Other factors significantly associated with development of glaucoma

Table 1 Summary statistics for study cohort presented across mutually exclusive psychiatric diagnosis groups (none=no psychiatric diagnosis, anxiety=anxiety only, depression=depression only, both=anxiety and depression)

Variable	None	Anxiety	Depression	Both	P value
n	1794 (55%)	408 (13%)	450 (14%)	607 (19%)	
Glaucoma diagnosis (%)					0.013*
Censored	1318 (73%)	295 (72%)	330 (73%)	405 (67%)	
Glaucoma	476 (27%)	113 (28%)	120 (27%)	202 (33%)	
Baseline age (years)	59.61 (14.56)	61.2 (13.69)	60.1 (14.01)	60.32 (13.73)	0.209†
Gender (%)					<0.001*
Men	866 (48%)	174 (43%)	157 (35%)	177 (29%)	
Women	928 (52%)	234 (57%)	293 (65%)	430 (71%)	
Race (%)					<0.001*
Caucasian	981 (55%)	242 (59%)	264 (59%)	385 (63%)	
African American	634 (35%)	139 (34%)	155 (34%)	192 (32%)	
Asian	117 (7%)	13 (3%)	16 (4%)	8 (1%)	
Multiracial	34 (2%)	7 (2%)	6 (1%)	10 (2%)	
Other	28 (2%)	7 (2%)	9 (2%)	12 (2%)	
Ethnicity (%)					0.081*
Not Hispanic/Latino	1762 (98%)	403 (99%)	435 (97%)	598 (99%)	
Hispanic/Latino	32 (2%)	5 (1%)	15 (3%)	9 (1%)	
Baseline IOP (mm Hg)	16.86 (4.36)	16.94 (4.15)	16.86 (3.98)	16.81 (3.89)	0.977†
Baseline MD (dB)	−2.96 (4.56)	−3.20 (5.41)	−3.69 (5.01)	−3.77 (5.27)	<0.001‡
Total follow-up (years)	3.64 (2.03)	3.61 (2.1)	3.68 (2.04)	3.43 (2.07)	0.108‡
IOP visits					0.039‡
Mean (SD)	4.16 (3.8)	4.76 (4.98)	4.61 (3.83)	4.34 (3.84)	
Median (min, max)	3 (1, 37)	3 (1, 42)	4 (1, 19)	3 (1, 37)	
Mean IOP (mm Hg)	16.69 (3.65)	16.74 (3.45)	16.57 (3.35)	16.58 (3.30)	0.817†
Peak IOP (mm Hg)	18.94 (5.24)	19.44 (5.46)	18.98 (4.75)	18.8 (4.45)	0.237†
Fluctuation IOP (mm Hg)	4.19 (4.77)	4.92 (5.34)	4.50 (4.64)	4.20 (4.16)	0.075 ‡
Time-of-event MD (dB)	−4.71 (4.94)	−4.98 (5.87)	−5.18 (5.47)	−5.19 (5.78)	0.958 ‡

*χ.
†ANOVA.
‡Kruskal-Wallis.
Summaries are mean and SD, unless otherwise noted. P values represent hypothesis tests across psychiatric groups, with categorical variables tested using a χ^2 test and continuous variables tested using ANOVA or Kruskal-Wallis, depending on normality.
IOP, intraocular pressure; MD, mean deviation.

during follow-up in univariable models included older age, male gender, higher IOP and worse disease severity at baseline. Asian race was a protective factor. In figure 2, these univariable HRs are presented as a forest plot.

Table 3 shows results from multivariable models adjusting for age, gender, race, IOP measurements over time and SAP MD at baseline (ie, the significant results from table 2). We present three multivariable models that each contain different forms of the psychiatric disorders: (1) anxiety main effect only, (2) depression main effect only and (3) a model with anxiety only, depression only, and both anxiety and depression. The effect of anxiety remained statistically significant in the multivariable model (Model 1), with HR (95% CI) of 1.16 (1.01, 1.33), while for depression it was no longer significant (Model 2). For patients with both anxiety and depression (Model 3), the effect was statistically significant, with HR (95% CI) of 1.27 (1.07, 1.50).

Finally, we compare the prevalence of anxiety and depression in our cohort from baseline to time of event/censor, for both glaucoma and censored patients. Anxiety prevalence increases 13% among censored patients, while there is no change among patients ultimately diagnosed with glaucoma. Depression prevalence increased in both cohorts, by 10% in censored patients and 9% in patients ultimately diagnosed with glaucoma.

DISCUSSION

In this study, we showed that the presence of anxiety or concomitant depression increased the risk of developing glaucoma in a cohort of glaucoma suspects followed over time. Our findings suggest that approaches targeted at screening patients for coexisting psychiatric disorders may have a role in improving outcomes in glaucoma.

The overall prevalence of anxiety and depression in our cohort were relatively high, at 32% and 33%, respectively. For anxiety, this prevalence is on the upper end of values in the literature for glaucoma patients, most similar to a value of 30% reported in a cross-sectional study of Singaporean glaucoma patients.[26] In a similar EHR study that used ICD codes to define diagnoses, Zhang *et al* reported a prevalence of 17% for anxiety and 22% for depression.[12] Our higher prevalence is likely due to the inclusion of the problem list and medical history for anxiety phenotyping, which is known to increase sensitivity.[21] Differences in prevalence of psychiatric conditions may also largely differ among populations and our numbers may reflect those of a population followed at a tertiary care clinic. Of note, our study uniquely assessed the prevalence of these conditions in a cohort of glaucoma suspect patients followed over time, while past work has largely been limited to examining their prevalence

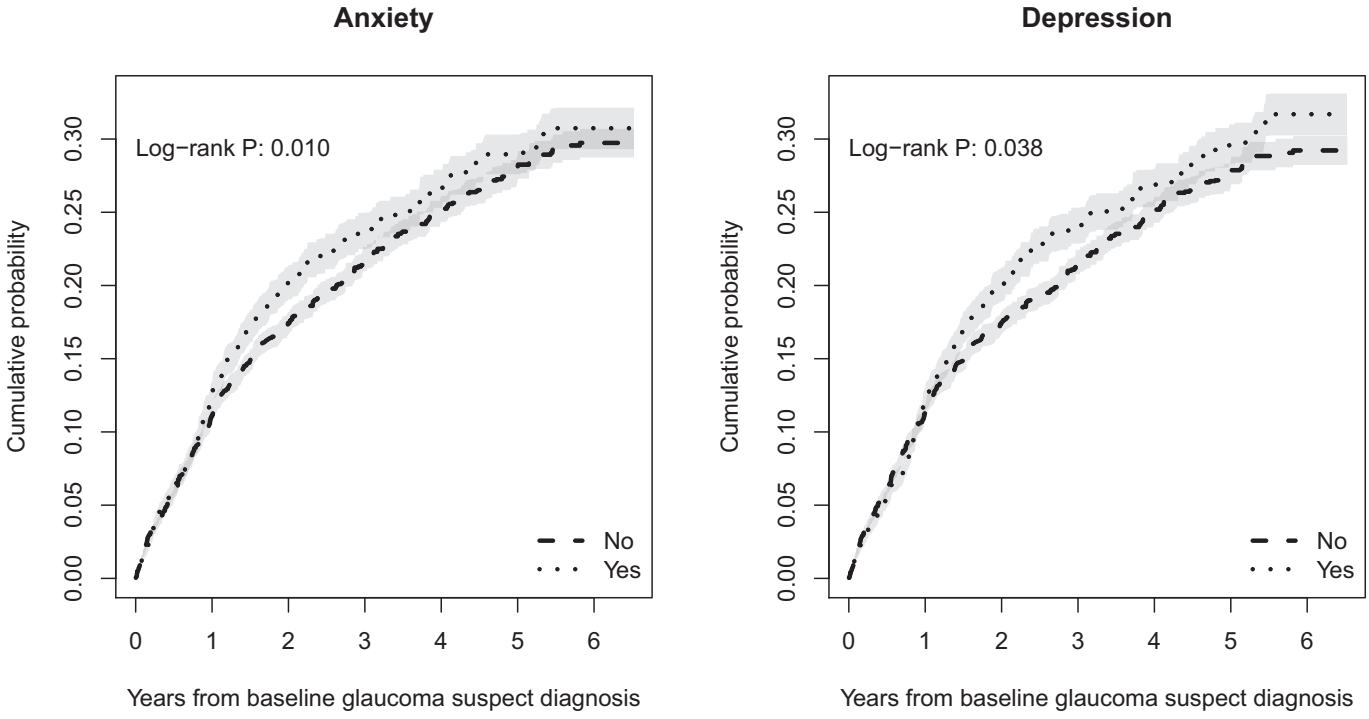

Figure 1 Kaplan-Meier cumulative probability estimates for a diagnosis of glaucoma for patients with anxiety and depression.

Table 2 Univariable Cox proportional hazards regressions for each risk factor individually (all HRs for continuous risk factors are for a 1 SD increase or decrease to put them on the same scale)

Variable	HR (95% CI)	P value
IOP (per SD higher)	1.38 (1.29, 1.48)	<0.001
Age (per SD higher)	1.47 (1.37, 1.57)	<0.001
Male gender	1.15 (1.01, 1.32)	0.031
Race (baseline: Caucasian)		
African American	0.99 (0.86, 1.14)	0.892
Asian	0.64 (0.44, 0.92)	0.017
Multiracial	0.64 (0.35, 1.16)	0.142
Other	0.87 (0.52, 1.45)	0.591
Ethnicity: Hispanic/Latino	1.16 (0.74, 1.83)	0.631
Anxiety: yes	1.20 (1.04, 1.37)	0.010
Depression: yes	1.15 (1.01, 1.32)	0.039
Baseline SAP MD (per SD lower)	1.36 (1.30, 1.42)	<0.001

IOP, Intraocular pressure; MD, mean deviation; SAP, standard automated perimetry.

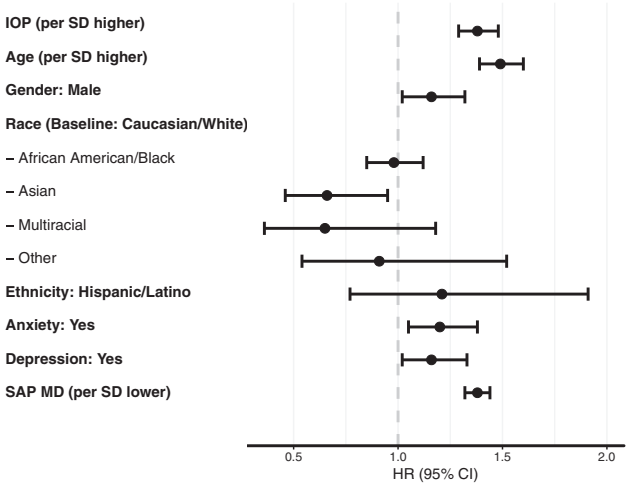

Figure 2 Forest plot of HRs and 95% CIs from models in table 2. IOP, intraocular pressure; MD, mean deviation; SAP, standard automated perimetry.

in samples that were already diagnosed with glaucoma. Finally, from baseline, the prevalence of depression in our cohort increased by 10% and 9% in patients who were censored and eventually diagnosed with glaucoma, respectively. While for anxiety, prevalence increased by 13% among censored patients, with no change observed in patients eventually diagnosed with glaucoma. The increase in depression prevalence is likely due to the known association between depression and older age among patients with glaucoma,[14] while the discordant changes in anxiety prevalence across censored and diagnosed patients are less clear and need to be studied further.

Our study indicates that a history of anxiety upon a glaucoma suspect diagnosis is significantly associated with a future diagnosis of glaucoma, with a multivariable adjusted HR (95% CI) of 1.16 (1.01, 1.33). While depression was associated with an increased risk of glaucoma in univariable models, 1.15 (1.01, 1.32), this association was no longer significant when controlling for baseline clinical measures. In multivariable models, the only significant association of depression occurred concomitantly with anxiety, 1.27 (1.07, 1.50).

Given that a diagnosis of anxiety or depression in our study occurred before an eventual diagnosis of glaucoma, our findings may suggest that anxiety is a predictive factor in developing glaucoma, not only a consequence of glaucoma. The reason why anxiety would be associated with worse outcomes in suspects is unclear. In our study, baseline IOP was not associated with a psychiatric diagnosis (table 1, p=0.977). However, when comparing IOP summaries during follow-up, fluctuation IOP was

Table 3 Multivariable Cox proportional hazards regressions for significant variables from univariable analysis (as before, IOP is treated as a time-dependent covariate, to control for medication during follow-up)

Variable	Model 1	Model 2	Model 3
IOP (per SD higher)	**1.42 (1.33, 1.52)**	**1.42 (1.33, 1.52)**	**1.42 (1.33, 1.52)**
Anxiety: yes	**1.16 (1.01, 1.33)**	–	–
Depression: yes	–	1.14 (0.99, 1.31)	–
Psychiatric disorder (baseline: none)			
Anxiety: only	–	–	0.98 (0.80, 1.20)
Depression: only	–	–	0.96 (0.79, 1.18)
Both	–	–	**1.27 (1.07, 1.50)**
Age (per SD higher)	**1.42 (1.33, 1.53)**	**1.43 (1.33, 1.53)**	**1.42 (1.33, 1.53)**
Male gender	1.14 (1.00, 1.30)	1.14 (1.00, 1.30)	**1.14 (1.00, 1.31)**
Race (baseline: Caucasian)	–	–	–
African American	1.09 (0.94, 1.26)	1.09 (0.95, 1.26)	1.09 (0.95, 1.26)
Asian	0.90 (0.62, 1.30)	0.90 (0.62, 1.30)	0.91 (0.62, 1.31)
Multiracial	0.73 (0.40, 1.33)	0.74 (0.40, 1.34)	0.74 (0.40, 1.35)
Other	1.10 (0.66, 1.85)	1.12 (0.66, 1.87)	1.11 (0.66, 1.86)
Baseline SAP MD (per SD lower)	**1.34 (1.28, 1.41)**	**1.34 (1.28, 1.41)**	**1.34 (1.28, 1.41)**

Models are presented with various forms of the psychiatric disorders. Each summary is a HR with 95% CI, where bold entries are significant.
IOP, intraocular pressure; MD, mean deviation; SAP, standard automated perimetry.

weakly associated with a psychiatric diagnosis (table 1, p=0.075), with anxiety patients having the largest fluctuation in IOP. Therefore, it is possible that the effect of anxiety may be explained through the impact of stress on IOP. Several studies have indicated that psychiatric stress is associated with elevation of IOP,[27–29] and this has been confirmed recently in a study of non-human primates.[18] More research is needed in this field, as these studies have looked primarily at acute stress which is likely different than stress attributed to chronic anxiety disorders. Nonetheless, the impact of stress on IOP is a likely biological pathway that may explain the significant association found in our study. To formally determine causation, however, would require a randomised clinical trial.

Although our study did not show a direct association of depression on a diagnosis of glaucoma in multivariable models, patients with concomitant anxiety and depression were significantly more likely to receive a diagnosis. In this context, an impact of depression could possibly be explained through medication adherence, which is known to decrease in depressed patients. In particular, Friedman *et al* showed that patients with depression failed to take at least 75% of eyedrops.[16] Furthermore, it has been shown that depression is associated with worse glaucoma outcomes. In particular, Jampel *et al* and Diniz-Filho *et al* showed that depression is associated with worse vision-related quality of life and visual field progression, respectively.[2 11]

The relatively high prevalence of anxiety and depression and their significant relationship with risk of development of glaucoma found in our study suggest the need for an increased focus on understanding the coexistence of these conditions and their implications. In particular, our results support the suggestion of prior studies, including Zhang *et al*, that psychiatric assessment be routinely done in clinical care.[12] Also, they indicate the need for prospective studies specifically designed to elucidate the temporal relationship between these conditions.

Our study had limitations. While we used a large retrospective cohort, diagnoses were based on ICD codes extracted from EHR data. Such retrospective data may have missing values or be inaccurately coded. Coding was done by the attending physicians, without following prespecified guidelines other than general billing coding guidelines, and thus may differ from physician to physician. As such, many eyes classified as suspects at baseline may actually have had glaucomatous damage. Conversely, many eyes that were diagnosed as glaucoma during follow-up may have received such diagnosis based on factors not necessarily related to progression of structural and functional damage over time. Importantly, in patients who converted to glaucoma, the final SAP MD decreased to −4.71 dB, indicating a significant worsening during follow-up. Of note, ICD-9 codes are not eye-specific (ie, are at the patient level) and therefore we cannot be sure which eye a diagnosis code corresponds to without a full chart review. To remedy this limitation, we required that patients included in our cohort (ie, defined as a suspect at baseline) to not have any glaucoma diagnoses prior to the diagnosis of glaucoma suspect. By doing this we may be excluding eyes that are glaucoma suspects, where the patient's other eye has glaucoma. But, we are guaranteeing to the best of our ability that our patients do not have one suspect eye and the other glaucomatous.

In addition, it is possible that patients may have been followed for psychiatric conditions outside of the Duke healthcare system and such information may not have been available in the EHR. Using medications and problem list, as performed in our study, has been shown to improve phenotyping in psychiatric disorders; however, there is no substitute for a gold standard diagnostic test or patient-reported outcome survey.[30] Another consequence of using retrospective clinical data is that we do not have control over medical or surgical interventions during follow-up, which confounds inference. To account for the changing therapeutic routines, we used IOP as a proxy and treated IOP as a time-dependent covariate, which has been done before in glaucoma.[31 32] However, it should be noted that certain medications used to lower IOP, such as beta-blockers, may have an impact on mood disorders, although such an effect is likely to be small.[33]

In conclusion, our study demonstrated that the presence of anxiety or anxiety and depression upon a glaucoma suspect diagnosis is associated with a future diagnosis of glaucoma after controlling for known risk factors. These findings suggest that

approaches targeted at screening patients for coexisting psychiatric disorders may have a role in improving outcomes in glaucoma.

Contributors SB, SM and FAM conceived the research design. SB and AJ were involved in data acquisition and execution of the research. SB performed the data analysis and helped in interpreting the results by FAM and AJ. SB wrote and revised the manuscript in consultation with AJ, TS and FAM.

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Competing interests SB, AJ, SM and TS have nothing to disclose. FAM reports personal fees from Carl Zeiss Meditec, Heidelberg Engineering, Allergan, Reichert, Google, Aerie Pharmaceuticals, Novartis, Biogen, Galimedix, Annexon, Stealth Biotherapeutic, Biozeus and IDx and a patent from nGoggle.

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