

Evaluation of Depression and Anxiety in a Diverse Population With Thyroid Eye Disease Using the Nationwide NIH *All of Us* Database

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Purpose: To evaluate the prevalence of depression and anxiety among individuals with thyroid eye disease (TED) and identify sociodemographic risk factors using the NIH *All of Us* database.

Methods: Three hundred ninety eight cases with TED were compared with 1,592 controls with demographics matching the 2020 US Census. Primary outcomes were diagnosed depression or anxiety; Patient Health Questionnaire-9 (PHQ-9) scores and General Anxiety Disorder-7 (GAD-7) scores were included as secondary outcomes. We performed multivariable logistic regression to generate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between TED and depression and anxiety.

Results: Patients with TED were more likely to have depression (OR 2.72, 95% CI 2.08–3.56, $p < 0.001$) and anxiety (OR 2.82, 95% CI 2.16–3.70, $p < 0.001$) than controls. In patients with TED, female gender was an independent risk factor for both depression (OR 1.72; 95% CI 1.00–5.07, $p = 0.05$) and anxiety (OR 2.17, 95% CI 1.25–3.85, $p = 0.006$). Unemployment (OR 1.72, 95% CI 1.03–2.94, $p = 0.04$) and lower income (OR 0.88 for income as a continuous variable, 95% CI 0.79–0.99, $p = 0.03$) were risk factors for anxiety. Risk factors for more severe depression as assessed by PHQ-9 included lower income (OR 0.70, 95% CI 0.57–0.85, $p < 0.001$), and protective factors included Black race (OR 0.12, 95% CI 0.02–0.45, $p = 0.002$). Lower income was associated with more severe anxiety as assessed by GAD-7 (OR 0.77, 95% CI 0.64–0.94, $p = 0.009$).

Conclusions: Patients with TED were more likely to develop depression and anxiety compared with controls. This study highlights the psychosocial impact of TED and associated socioeconomic risk factors.

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Thyroid eye disease (TED) is associated with decreased quality of life due to associated proptosis, diplopia, eyelid retraction, and dry eye.^{1–9} In addition to physical symptoms such as orbital pain and double vision, individuals with TED also experience psychosocial sequelae including difficulty coping with disfigurement, inability to return to work, and changes in self-image and social interactions.^{7,10–12} In studies of physician-reported and patient-reported quality of life (QoL), patients with TED report worsened QoL and increased feelings of depression, anxiety, and stress.^{1,2,13–18} Moreover, given the rising prevalence of mental health issues secondary to the COVID-19 pandemic shed additional light on the importance of social support in combating psychological distress,^{19–25} individuals with TED are likely to be especially at risk given a greater baseline mental health burden and social isolation experienced even before the pandemic.¹¹

TED's impact on individuals is largely dependent on socioeconomic factors such as race and social deprivation

indices, which can affect both clinical presentation and how the disease is managed.^{26–28} Tingley et al. reported higher prevalence of proptosis, extraocular muscle restriction, and optic neuropathy on presentation in a primarily Black and Hispanic population compared with traditionally studied populations.²⁷ These studies highlight the importance of identifying varying socioeconomic factors among diverse populations to understand the real impact of TED.

The National Institutes of Health (NIH) *All of Us* (AoU) database is a nationwide data repository with more than 486,000 participants launched in 2018 with special emphasis on enrolling individuals from groups historically underrepresented in biomedical research including racial and ethnic minorities, sexual and gender minorities, individuals with income or education below a certain threshold, and individuals with disabilities.²⁹ The program protocol contains elements such as health questionnaires, physical measurements, analyzed biospecimens, and numerous domains of electronic health record (EHR) data, including diagnosed conditions, labs, procedures, and medications. The AoU database has demonstrated considerable usefulness in addressing questions such as the association of blood pressure with glaucoma and risks factors for enucleation, amongst others.^{30–34} As such, the primary aim of this study was to determine the prevalence and severity of depression and anxiety in a diverse population of TED patients compared with the general population using the NIH AoU database. A secondary aim of the study was to identify demographic and socioeconomic factors associated with depression and anxiety among patients with TED, which, to the authors' knowledge, has not been examined in prior studies.

METHODS

Selection of Cases and Controls. The NIH AoU database contained 486,000 participants at the time of analysis in May 2022. Participant data contained linked demographics, medical conditions, procedures, drug exposures, and patient surveys. All patient information was deidentified with suppression of highly identifiable data. The All of Us Registered Tier Curated Data Repository Data Dictionary contains formal documentation on privacy implementation and creation of the data repository.²⁹ Secondary analyses of deidentified data included in *All of Us*, such as that presented here, are considered nonhuman subjects research, which was confirmed by the University of California San Diego Institutional Review Board. Data collection was approved by the AoU Institutional Review Board; this study was HIPAA-compliant and adhered to the Declaration of Helsinki.

In this case-control study, 398 patients with condition codes relating to TED (cases) were sampled from the NIH AoU database, version 5 (Fig. 1). These included participants with codes directly related to TED (e.g., Graves' orbitopathy) and individuals with concomitant diagnosis codes of a thyroid disorder and either proptosis or eyelid retraction. Individuals with bipolar disorder and personality disorders were excluded. Using a 4:1 case-to-control ratio, controls (n = 1,592) were generated with demographics matching the 2020 US Census using the R package *MatchIt*, as previously described.^{31,32,34} We sampled controls with demographics matching the 2020 US Census to enhance representativeness of the general population, given the known enrichment of underrepresented groups in AoU enrollment.

Primary and Secondary Outcomes. Primary outcomes were diagnosis codes of depression or anxiety. In patients with TED, depression and anxiety diagnoses were included only if initial diagnosis was concurrent with or followed the TED diagnosis temporally.

In a selection of the sampled cohort, Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder Questionnaire (GAD-7) scores from the COVID-19 Participant Experience (COPE) survey were

assessed as secondary outcomes indicating severity of depression and anxiety, respectively.^{35,36} The COPE survey is a longitudinal questionnaire contained with the AoU database aimed at assessing the impact of the COVID-19 pandemic on participants' mental and physical health. The PHQ-9 and GAD-7 questionnaires within the COPE survey are common screening questionnaires for depression and anxiety, respectively.^{35,36} We utilized these questionnaire scores as measures of depression and anxiety severity. Because responses to the COPE Survey were available in only approximately one-fourth of the cohort, these outcomes were analyzed in a separate model.

Predictor Variables and Covariates. For the study's primary analysis, TED diagnosis was utilized as the primary predictor variable while controlling for age, self-reported gender identity (heretofore referred to as "gender"), race, employment, income, substance use, and disability. In the secondary analysis, socioeconomic and demographic variables (e.g., age, gender, race, income, and employment) were utilized as predictor variables in the TED population. Known risk factors for mood disorders including substance use and level of disability were utilized as covariates to control for potential confounding effects.^{37,38}

Concept sets were created for each of the following predictors, covariates, and outcomes: age, gender, race, ethnicity, income, employment, TED severity, substance use, disability, depression, anxiety, PHQ-9 score, and GAD-7 score. Severity of TED was estimated as the number of TED-associated diagnoses in each patient's chart, with TED-associated diagnoses defined as condition codes in 4 categories: (1) proptosis, (2) lagophthalmos or exposure keratopathy, (3) eyelid retraction, and (4) diplopia or strabismus. Additional information on the conditions included in the concept sets can be found in Table (Supplemental Digital Content 1, available at <http://links.lww.com/IOP/A350>).

For each of the models, we performed bivariate analyses and multivariable logistic regression to generate odds ratios (ORs) and 95% confidence intervals (CIs). *P* values were considered statistically significant at the $\alpha = 0.05$ level. R programming was used for all logistic regression modeling. The following R packages were used: *ggplot2*, *tibble*, *tidyr*, *readr*, *purrr*, *dplyr*, *stringr*, *forcats*.

RESULTS

The TED study group included 398 patients; 320 (80.4%) were female. Mean (standard deviation, SD) age was 64 (13.6) years. Two hundred thirteen (53.5%) identified as Caucasian, 114 (28.6%) as Black, <20 (<5.0%) Asian, and 64 (16.1%) other; 62 (15.6%) of the group identified as being of Hispanic/Latino ethnicity. One hundred fifty-nine (40%) patients with TED had associated diagnoses of eyelid retraction, 159 (40%) proptosis, 99 (25%) strabismus, and 243 (61%) exposure keratopathy or lagophthalmos. Additional patient characteristics are described in Table 1.

Two hundred one (50.5%) of patients with TED had diagnosed depression compared with 438 (27.5%) in the control group. Furthermore, 192 (48.2%) of patients with TED had diagnosed anxiety compared with 365 (22.9%) in the control group (Fig. 2). In multivariable logistic regression, patients with TED were significantly more likely to have clinically diagnosed depression (OR 2.72, 95% CI 2.08–3.56, $p < 0.001$) and anxiety (OR 2.82, 95% CI 2.16–3.70, $p < 0.001$) compared with controls. Among patients with TED, female gender was an independent risk factor for both depression (OR 1.72, 95% CI 1.00–5.07, $p = 0.05$) and anxiety (OR 2.17, 95% CI 1.25–3.85, $p = 0.006$) (Table 2). Unemployment (OR 1.72, 95% CI 1.03–2.94, $p = 0.04$) and lower income (OR 0.88 for income as a continuous variable, 95% CI 0.79–0.99, $p = 0.03$) were additional risk factors for anxiety in TED. In TED patients, lower income was associated with more severe depression as assessed by PHQ-9 score (OR 0.70 for income as a continuous variable, 95% CI 0.57–0.85, $p < 0.001$), while Black race was associated with lower PHQ-9 score (OR 0.12, 95% CI 0.02–0.45, $p = 0.002$) (Table 3). Lower income was also associated with higher GAD-7

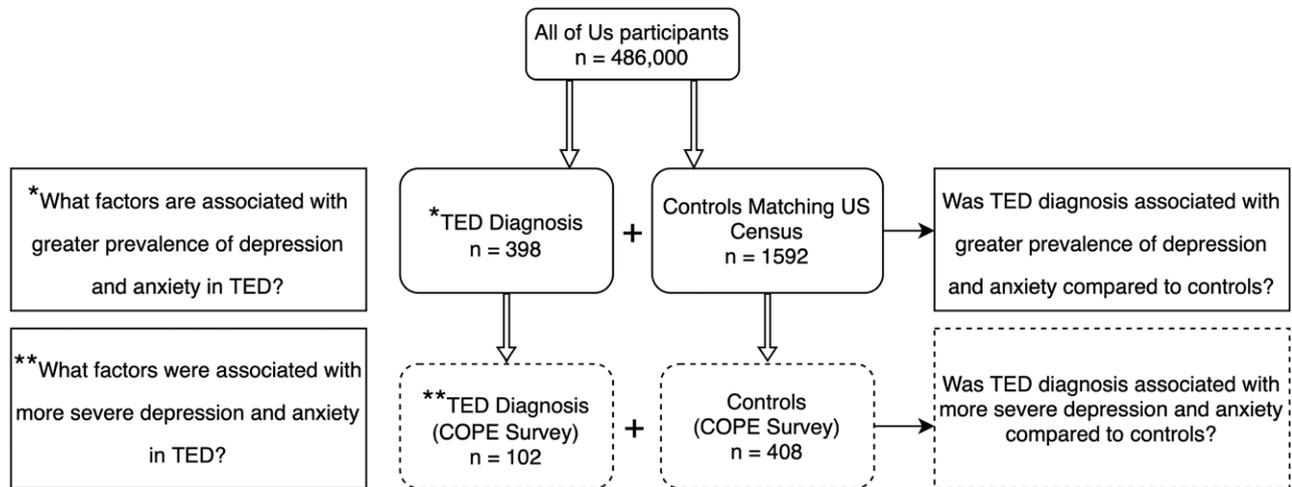


FIG. 1. Study design. The above questions were evaluated in this study. Cases with condition codes relating to TED were compared with controls with demographics matching the 2020 US Census to assess prevalence of depression and anxiety in TED patients compared with controls. In a selection of the sampled cohort, PHQ-9 scores and GAD-7 scores were included as secondary outcomes to evaluate for severity of depression and anxiety, respectively, in TED patients compared with controls. Social determinants of depression and anxiety were further analyzed within the TED cohorts. GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; TED, thyroid eye disease.

TABLE 1. Patient characteristics

		TED group (n = 398)	Controls* (n = 1,592)
		Count (%)	Count (%)
Race	Caucasian	213 (53.5%)	1,214 (76.3%)
	Black	114 (28.6%)	213 (13.4%)
	Asian	<20 (<5.0%)	93 (5.8%)
	Other	64 (16.1%)	72 (4.5%)
Ethnicity	Hispanic or Latino	62 (15.6%)	294 (18.5%)
	Not Hispanic or Latino	336 (84.4%)	1,298 (81.5%)
Gender	Female	320 (80.4%)	808 (50.7%)
	Male	78 (19.6%)	784 (49.2%)
Annual Income	>\$200,000	<20 (<5.0%)	101 (7.8%)
	\$150,000–200,000	<20 (<5.0%)	68 (5.2%)
	\$100,000–150,000	39 (12.9%)	167 (12.8%)
	\$75,000–100,000	36 (11.9%)	129 (9.9%)
	\$50,000–75,000	45 (14.9%)	159 (12.2%)
	\$35,000–50,000	26 (6.5%)	139 (10.7%)
	\$25,000–35,000	24 (7.9%)	131 (10.1%)
	\$10,000–25,000	50 (16.6%)	197 (15.1%)
Employment	<\$10,000	49 (16.2%)	211 (16.2%)
	Employed for wages or self-employed	126 (32.3%)	530 (35.0%)
	Not currently employed for wages	264 (67.7%)	986 (65.0%)

Race, ethnicity, gender, income, and employment distributions for TED and control cohorts. Per the *All of Us* Research Program data sharing policies, cells with less than 20 individuals are suppressed.

*Created based on 2020 US Census population breakdown.

score (OR 0.77 for income as a continuous variable, 95% CI 0.64–0.94, $p = 0.009$).

TED diagnosis was not significantly associated with higher PHQ-9 score ($p = 0.789$) or GAD-7 score ($p = 0.133$) compared with controls. In addition, TED severity as estimated by the number of TED-associated diagnoses was not significantly associated with either prevalence or severity of depression or anxiety.

DISCUSSION

TED can be debilitating for affected individuals due to chronic disease burden and the psychosocial impact of disfigurement. Decreased quality of life and heightened emotional distress secondary to TED are well-documented in the existing

literature.^{1,5,7–9,17,18,39,40} Cockerham et al. noted a 34% prevalence of patient-reported depression and 28% prevalence of anxiety in patients with chronic TED.^{16,17} While depression and anxiety have been studied in populations with TED, the mixed demographic makeup of the studied populations has not been further analyzed.^{1,7,8,16} The data presented in this study draws from a diverse nationwide registry and represents the largest cohort of individuals studied to date to address this question.

In this study, we found that individuals from all races and ethnicities with a TED diagnosis were significantly more likely to develop clinically diagnosed depression (OR = 2.72) and anxiety (OR = 2.82) compared with controls when controlling for other factors. Qualitative studies have suggested that feelings of depression and anxiety occur as a result of psychosocial

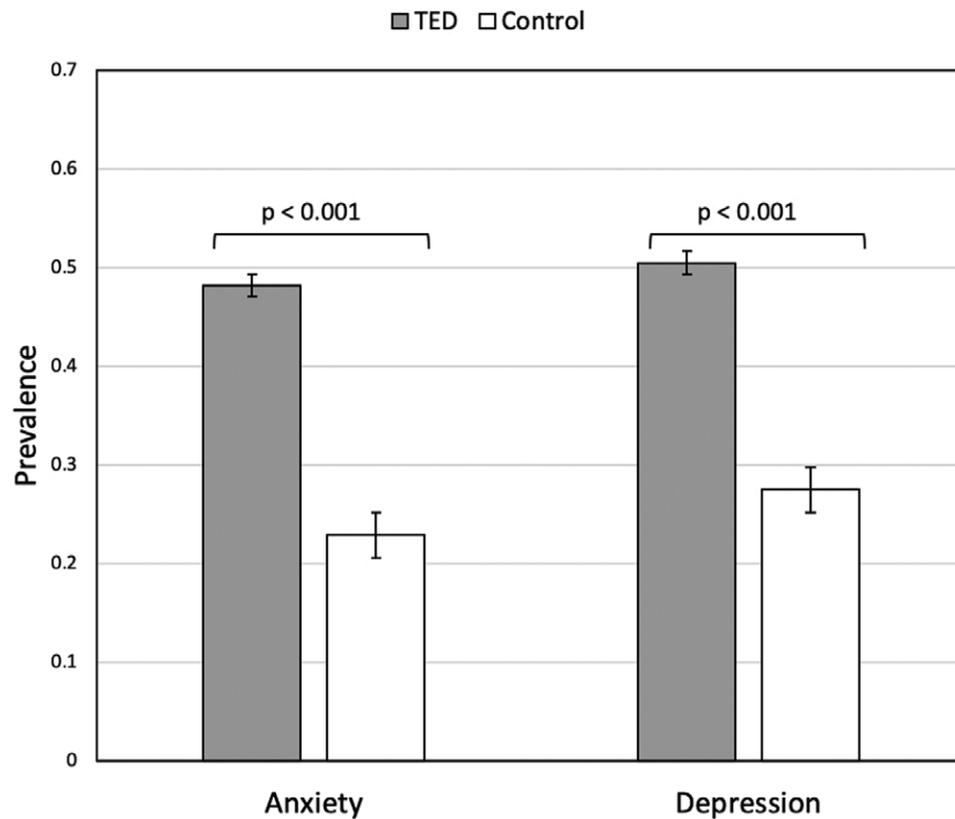


FIG. 2. Prevalence of anxiety and depression in TED patients compared with controls. TED, thyroid eye disease.

TABLE 2. Predictors of increased prevalence of depression and anxiety in TED

Predictor	Depression Prevalence			Anxiety Prevalence		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Race (Asian)	0.29	0.02–1.92	0.27	0.21	0.01–1.41	0.166
Race (Black)	1.15	0.67–2.00	0.63	0.79	0.46–1.37	0.411
Race (Other)	0.70	0.24–2.07	0.52	0.37	0.12–1.07	0.071
Gender (female)	1.72	1.00–2.94	0.05*	2.17	1.25–3.85	0.006*
Age	0.99	0.98–1.01	0.61	0.99	0.97–1.01	0.329
Unemployment	1.54	0.90–2.56	0.11	1.72	1.03–2.94	0.037*
TED severity (Number of TED-associated diagnoses)	1.03	0.82–1.30	0.81	1.21	0.96–1.53	0.115
Ethnicity (Hispanic/Latino)	1.17	0.31–4.49	0.82	1.09	0.30–4.17	0.899
Income	0.91	0.82–1.02	0.11	0.88	0.79–0.99	0.029*
Substance Use	2.43	1.57–3.79	<0.001*	1.71	1.11–2.65	0.016*
Disability	2.41	0.96–6.92	0.08*	1.24	0.53–3.02	0.622

Multivariable logistic regression with predictors of depression and anxiety in patients, with substance use and disability as covariates.

* indicates *p* value ≤ 0.05 .

changes patients experience due to disfigurement, changes in self-esteem, social avoidance, difficulty interacting with others, and inability to find or maintain employment.^{10–12} While depression and anxiety are common manifestations in patients with active thyroid disorders, TED has been shown to affect patients' quality of life well in the chronic phase; the increased prevalence of depression and anxiety is therefore unlikely due to thyroid dysregulation alone.^{14,16} Our TED cohort, which included both patients with active and chronic TED, reflects this increased overall prevalence. While the prevalence of depression (50.5%) and anxiety (48.2%) noted in our TED cohort was higher than in previous studies, this may be at least partially attributed to overall increased rates of depression and anxiety in the wake of the COVID-19 pandemic.^{16,17} According to the US

Census Bureau, depression was estimated to affect up to 23.5% of adults in 2020, compared with 6.6% prior to the pandemic.¹⁹ The prevalence of anxiety among adults in the US likewise increased from 8.2% in 2019 to 30.8% in 2020.¹⁹ The findings in our study indicate comparable rates of depression (33.3%) and anxiety (22.9%) among the 1,592 controls sampled from the AoU database.

In this study, we were unable to include history of TED treatment as a variable due to limitations of the database. It has been well-established in the literature that treatment for TED such as corticosteroids, orbital decompression, radiotherapy, and strabismus surgery may improve quality-of-life metrics, including measures of depression and anxiety, for patients with TED.^{41–51} With the advent of newer treatments for TED such as

TABLE 3. Predictors of increased severity of depression and anxiety in TED

Predictor	Depression Severity			Anxiety Severity		
	OR	95% CI	p	OR	95% CI	p
Race (Asian)	0.55	0.06–5.31	0.586	0.30	0.01–3.96	0.371
Race (Black)	0.116	0.03–0.45	0.002*	0.32	0.08–1.35	0.114
Race (Other)	0.63	0.07–4.84	0.658	0.43	0.06–2.63	0.366
Gender (female)	0.71	0.29–1.72	0.441	0.91	0.38–2.24	0.841
Age	0.98	0.95–1.01	0.180	0.97	0.94–1.00	0.083
Unemployment	0.79	0.33–1.90	0.594	0.86	0.36–2.03	0.726
TED severity (Number of TED-associated diagnoses)	0.90	0.64–1.27	0.553	0.96	0.69–1.32	0.783
Ethnicity (Hispanic/Latino)	0.31	0.01–39.67	0.610	0.25	0.01–21.43	0.482
Income	0.70	0.57–0.85	<0.001*	0.774	0.64–0.94	0.009*
Substance Use	1.85	0.89–3.87	0.101	1.45	0.69–3.08	0.324
Disability	1.30	0.15–11.23	0.806	0.81	0.10–6.86	0.839

Multivariable logistic regression with predictors of higher PHQ-9 and GAD-7 score in patients, with substance use and disability as co-variates. PHQ-9 and GAD-7 scores were assessed as part of the COPE survey in the AoU database.

AoU, *All of Us*; COPE, COVID-19 participant experience; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9.

teprotumumab and other biologics, the importance of efficacious treatment for TED cannot be understated, especially in regards to its role in correcting the disproportionate depression and anxiety in TED patients.

In our analysis, income was assessed as a continuous variable; as higher income showed a decreased odds ratio and therefore a protective effect on several outcome variables, we interpreted this as lower income being a risk factor for those outcomes. Low income and unemployment were independent risk factors for anxiety in TED patients, and lower income was also associated with a higher (i.e., worse) PHQ-9 score for depression severity and GAD-7 score for anxiety severity. On the other hand, when adjusted for socioeconomic status, race, and ethnicity did not predict greater prevalence of depression or anxiety in patients with TED. In addition, female gender was associated with increased risk of depression and anxiety, consistent with previous reports in both TED and non-TED populations.^{37,40} Our data provide further evidence that socioeconomic factors contribute to the development and severity of the psychosocial aspect of TED, in addition to its clinical presentation.^{15,16,26–28} This highlights the importance of an interdisciplinary approach to treating TED, including adequate access to mental health resources and resources for financial assistance.

TED severity, estimated by number of TED-associated diagnoses, was not significantly associated with greater prevalence of depression or anxiety. To date, there remains little consensus on the correlation of TED disease severity with quality of life.^{17,41} Our findings echo a host of literature that found no correlation between disease severity and depression or anxiety.^{3,44,52,53} In contrast, several studies including Cockerham et al. previously found that patients with lower QoL measures were more likely to have more TED-associated diagnoses.¹⁶ Farid et al. found that proptosis, but not diplopia, was associated with higher emotional distress in TED patients.¹⁸ These mixed results may reflect interindividual variation in how disease severity affects perceived well-being.^{18,52} Another possibility is that given our TED cohort included both active and chronic TED patients, mood dysregulation associated with active thyroid disorders may also have influenced the lack of correlation seen between number of TED-associated diagnoses and depression or anxiety.

Additionally, the severity of depression and anxiety in patients, as evaluated in a subset who completed the COPE survey, was not significantly different between TED patients and controls. It is possible no association was noted due to the smaller sample size of patients for whom we assessed severity of depression and anxiety, as only a subset of patients completed

the COPE survey with PHQ-9 and GAD-7 questionnaires. Of note, on multivariable regression, Black race was associated with lower PHQ-9 depression severity scores in TED patients. It is currently unclear why this may be but is consistent with some studies where PHQ-9 scores were lower among Black race after controlling for socioeconomic status.⁵⁴ Further studies with greater sample sizes may be better able to expand on the significance of these findings.

Strengths of this study include the diverse population studied in the AoU database, which allow for a more thorough study of TED in groups historically underrepresented in scientific research. Due to inclusion of survey results and socioeconomic data such as income and employment status, the AoU database also allowed for analysis with information not available through standard electronic health records. To the extent of our knowledge, this is the first study to examine clinical and sociodemographic risk factors for worsened mental health in patients with TED. Limitations of the study include dependence on the quality of records and billing codes used in the AoU database. Clinical notes with visual acuity, proptosis measurements, and additional information on TED disease severity were also not directly examined and would be useful additions in future iterations of the database.

CONCLUSION

In this study, we found that patients with TED had significantly greater odds of developing clinically diagnosed depression and anxiety compared with studied controls. Among TED patients, female gender was a risk factor for both depression and anxiety, and lower income and unemployment were additional risk factors for anxiety. Lower income was also associated with more severe depression and anxiety. Overall, this study highlights the increased risk of psychiatric comorbidities among patients with TED and the socioeconomic disparities that exist in regards to mental health in TED. Clinicians should be acutely aware of the importance of psychosocial aspects of TED and address these issues by providing resources and referring to mental health professionals as appropriate.

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