Association between Psychiatric Disorders and Glomerular Disease.

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Abstract

Background: Patients with chronic health conditions are at heightened risk for psychiatric disorders; yet, little is known about the occurrence of psychiatric disorders or associations with patient and disease characteristics in glomerular disease.

Methods: This study included patients with glomerular disease enrolled in the Kidney Research Network multisite patient registry. Registry data includes encounter, diagnoses, medication, lab, and vital signs data extracted from participants' electronic health records. ICD9/10 diagnosis codes were used to identify subset of psychiatric disorders focused on anxiety, mood, and behavioral disorders. Time-varying Cox proportional hazards models were used to analyze time from onset of kidney disease to diagnosis of psychiatric disorder. Models adjusted for age, sex, race, ethnicity, and time-varying treatment, estimated glomerular filtration rate (eGFR), and proteinuria. Analogous models examined diagnosis of psychiatric disorder as a predictor of time to end stage kidney disease (ESKD).

Results: Data were available for 943 participants with a median of 58 months of follow-up. 109 (12%) participants were ever diagnosed with a psychiatric disorder during follow up. Estimated risk of psychiatric diagnosis after kidney disease was 14.7 cases per 1,000 person-years, and was highest among adolescents. Adjusted analyses found adolescent age (vs. Adult, HR=2.03, CI=1.23-3.35), Asian race (vs. White, HR=0.34, 95% CI=0.16-0.70) and steroid therapy (HR=2.27, 95% CI=1.53-3.38) were associated with psychiatric diagnosis. Psychiatric diagnosis was also associated with progression to ESKD (HR=2.47, 95% CI=1.55-3.95) after adjusting for kidney diagnosis, eGFR at onset, proteinuria over time, and steroid therapy.

Discussion: Psychiatric disorders were documented in approximately one eighth of patients with glomerular disease and correlated with clinical disease characteristics.

Conclusions: These findings suggest mental health screening may be warranted in patients with glomerular disease.

Background

Improved outcomes in the treatment and management of chronic illness have led to an increase in the number of children and adults living with chronic medical conditions. Previous research into chronic diseases, such as diabetes, chronic obstructive pulmonary disease (COPD), asthma, and sickle cell disease, has shown that ongoing treatment demands and disease progression can contribute to emotional and behavioral problems. Studies have demonstrated that patients with chronic illnesses experience higher levels of depressive symptoms than their healthy peers.[1–5] In addition, psychological distress in a chronically ill population has been consistently associated with poor health outcomes and an increase in somatic complaints across various diseases including diabetes, COPD, and sickle cell disease. [4, 6–10]

Disease-specific differences have been reported across the age spectrum. For instance, youth with poorly controlled asthma have significantly higher odds than those with mild or well-controlled asthma of experiencing affective and anxiety problems as well as more frequent conduct disorders. [11, 12] Likewise, asthma research has shown that when compared to healthy peers, children and adolescents show a higher incidence of internalizing as well as externalizing behaviors [6, 7], while adults consistently express higher levels of anxiety (specifically panic disorder) and depressive disorders. [13–16] In cystic fibrosis, depression has been documented in 8–29% of children and adolescents and 13–33% of adults. Similarly, the proportion of children and adults with cystic fibrosis and anxiety ranges between 30 and 33%. As a comparison, healthy cohort data support an expected frequency of depression in 3% of children and adolescents and 7% of adults and of anxiety in 7% of children and 19% of adults. [17–21]

The impact of disease-specific psychological stressors has been a focus in the diabetes literature across the lifespan. High levels of diabetes-related stress had a significant impact on metabolic control and adherence and led to worse outcomes for patients. [22–24] Additionally, diabetes has consistently been linked to a 25% increase in the rate of depression across the lifespan. [25, 26]

While there is a body of evidence demonstrating the negative effect of end stage kidney disease (ESKD) on overall mental health [27–29] studies focusing on patients with pre-ESKD chronic kidney disease (CKD) are more limited and conflicting. In community clinical settings and the Veteran Affairs Health System (VAHS) settings, studies have found that between 21 and 30% of individuals with pre-ESRD CKD have depression. [30, 31] However, a prior study using the National Health and Nutrition Examination Survey (NHANES) 2005–2006 found only 7% of participants with CKD to have depression. The Chronic Kidney Disease in Children (CKiD) cohort found approximately 7% of participating children either had elevated depressive symptoms or were being treated for depression, and further concluded that depression correlated with lower health-related quality of life (HRQoL). [32]

Clearly, patients with chronic conditions are at a heightened risk for psychiatric disorders and there are disease specific differences that may impact psychological distress and treatment outcomes. Like many chronic diseases, we hypothesized that glomerular disease has both a physical and psychological impact on patients. Therefore the goal of this study was to utilize the Kidney Research Network patient registry to explore the occurrence of psychiatric disorders in patients with glomerular disease, the potential associations between psychiatric diagnosis and demographic and clinical characteristics, and the relationship between psychiatric diagnosis and progression to ESKD.

Methods

Participants and data source

The Kidney Research Network (KRN) is an ongoing registry of patients with proteinuric kidney disease (glomerular disease) from seven clinical centers in the United States that began enrollment in August 2015. [33] Patients enrolled in KRN consented to share retrospective (prior to enrollment) and prospective

(monthly post-enrollment) data directly reported from study personnel as well as extracted from their electronic health records (EHR). The data collection has been previously described and includes demographics, diagnoses including provider confirmed primary kidney diagnosis, kidney biopsy reports, laboratory values, vital signs, medications, and hospitalizations.[33] Patients could consent to join the registry at any point in their kidney disease course, but retrospective data were available from the time the patient entered the local nephrology care EHR environment. The study protocol was reviewed and approved by the University of Michigan Institutional Review Board.

For this analysis, we excluded participants with ESKD prior to their first EHR data capture event in the KRN data registry as well as those with lupus classes I-IV, ANCA vasculitis, or HIV-associated nephropathy. Additionally, while six of the seven KRN sites provide EHR data extracts, as of this study analysis one site provided kidney disease-focused data via manual data entry alone. Participants [n = 136] from this site were excluded due to the unlikely capture of the primary outcome of interest. Participants with diagnosis of psychiatric disorder prior to onset of kidney disease were excluded from these analyses.

Outcomes

The primary outcome of interest was psychiatric disorder diagnosis. Psychiatric diagnoses were limited to anxiety (Adjustment Disorder, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Panic Disorder, Post-Traumatic Stress Disorder, other/unspecified anxiety disorder), mood disorders (Bipolar Disorder, Depressive Disorders, other/unspecified mood disorder) and behavioral disorders (Attention Deficit Hyperactivity Disorder, Conduct Disorder, Intermittent Explosive Disorder, Oppositional Defiant Disorder, other/unspecified behavioral disorder). Diagnosis was defined as the date of first occurrence of psychiatric disorder ICD-9/10 code (details in Table S1).

Secondary analyses examined diagnosis of psychiatric disorder during period of observation as a potential predictor of progression to ESKD, defined as initiation of chronic dialysis (≥ 60 days), kidney transplant, chronically low eGFR (eGFR < 15 for ≥ 60 days), or ICD-9/-10 codes of stage 5 CKD. eGFR was calculated using the creatinine-based modified CKiD formula in children and the CKD-EPI equation in adults. [34, 35]

Statistical analyses

The cohort was described using frequencies and percentages for categorical variables and medians with interquartile ranges for continuous variables. Stratified summary descriptions were provided by occurrence of psychiatric diagnosis after onset of kidney disease. P-values comparisons were made with chi-square tests for categorical and Kruskal-Wallis tests for continuous characteristics.

Kaplan-Meier plots were used to display the time from onset of kidney disease to diagnosis of psychiatric disorder by age, and subset analyses were repeated for (1) anxiety disorder, (2) mood disorder and (3) behavioral disorder. Risk of diagnosis was quantified using a person-time denominator.

Time-varying cox proportional hazards models were used to test for predictors of psychiatric diagnosis. Predictors of interest included age, sex, race, ethnicity, kidney diagnosis (focal segmental glomerulosclerosis (FSGS) vs. minimal change disease (MCD) vs. membranous nephropathy (MN) vs. nephrotic syndrome (NS)-not biopsied vs. IgA nephropathy vs. Other), eGFR, urine protein: creatinine ratio (UPCR), and immunosuppressive therapy (IST). Participants with C1q nephropathy (n = 11) were reclassified as FSGS; participants with mesangial proliferative glomerulonephritis (n = 6) or IgM nephropathy (n = 17) were reclassified as MCD. Analyses were censored at onset of ESKD. Hazard ratios (HR) and 95% confidence intervals (CI) are reported. All variables were initially tested as unadjusted, univariate predictors of psychiatric diagnosis. Any variable significant with $p < 0.20$ was included in a backwards multivariable model selection. Non-significant variables were removed in reverse order of p-value until all remaining variables in the model were significant at $p < 0.05$. Analogous time-varying cox proportional models were fit modeling time from onset of kidney disease to ESKD. In these models, diagnosis of psychiatric disorder was included as a covariate to test for an association between psychiatric disorders and progression to ESKD. Analyses were completed in SAS® (version 9.4; SAS Institute Inc, Cary, NC).

Results

Sample

As of October 2019, there were 1,199 participants enrolled in the KRN registry. After excluding subjects not fully enrolled or meeting other exclusion criteria, 943 participants contributed to this analysis sample (Fig. 1).

Characteristics of the sample are provided in Table 1. Half of participants had onset of kidney disease prior to age 18 and 43% were female. FSGS was the most common diagnosis (28%), the median eGFR closest to kidney disease onset was 86 ml/min/1.73 m², and median UPCR was 2.1 g/g. Seventy-eight percent of participants had ever been treated with steroids and 67% had ever been treated with any other IST. With a median 58 months of follow-up, 109 of 943 participants (12%) had a diagnosis of psychiatric disorder during follow-up, including non-exclusive categories of 74 (7.8%) anxiety disorder, 56 (5.9%) mood disorder and 12 (2.2%) behavior disorder.

Table 1

Descriptive statistics of participants by diagnosis of psychiatric disorder in the Kidney Research Network registry analysis sample (n = 943)

Characteristic	All patients (n = 943)	Ever had psychiatric disorder (n = 109)	Never had psychiatric disorder (n = 834)	p-value
Age at kidney disease onset (years), median (IQR)	18 (4, 40)	15 (5, 35)	19 (4, 41)	0.004
Children (0–12 years), n (%)	395 (42)	46 (42)	349 (42)	
Adolescents (13–17 years), n (%)	74 (8)	17 (16)	57 (7)	
Adults (18 + years), n (%)	474 (50)	46 (42)	428 (51)	
Female, n (%)	403 (43)	54 (50)	349 (42)	0.13
Race, n (%)				0.02
White	522 (55)	75 (69)	447 (54)	
Black	103 (11)	10 (9)	93 (11)	
Asian	154 (16)	8 (7)	146 (18)	
Other	137 (15)	15 (14)	122 (15)	
Unknown/missing	27 (3)	1 (1)	26 (3)	
Hispanic Ethnicity, n (%)	180 (19)	16 (15)	164 (20)	0.14
Diagnosis, n (%)				0.003
FSGS	264 (28)	31 (28)	233 (28)	
Minimal Change	161 (17)	32 (29)	129 (15)	
Membranous Nephropathy	93 (10)	10 (9)	83 (10)	
NS-not biopsied	143 (15)	9 (8)	134 (16)	
IgA Nephropathy	156 (17)	11 (10)	145 (17)	
Other	126 (13)	16 (15)	110 (13)	
eGFR closest to kidney disease onset (ml/min/1.73 m ²), median (IQR)	86 (43, 121)	103 (63, 133)	82 (39, 120)	< 0.001

p-values from chi-square tests for categorical and Kruskal-Wallis tests for continuous characteristics.

Abbreviations: eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; IST, immunosuppressive therapy; NS, nephrotic syndrome; UPCR, urine protein: creatinine ratio

Characteristic	All patients (n = 943)	Ever had psychiatric disorder (n = 109)	Never had psychiatric disorder (n = 834)	p-value
UPCR closest to kidney disease onset (g/g), median (IQR)	2.1 (0.6, 6.2)	2.8 (0.5, 6.8)	2.1 (0.6, 6.2)	0.40
Ever treated with steroids, n (%)	737 (78)	85 (78)	652 (78)	0.66
Ever treated with other ISTs, n (%)	635 (67)	65 (60)	570 (68)	0.07
Observation duration (months) median (IQR)	58 (26, 99)	86 (51, 122)	57 (23, 93)	< 0.001
p-values from chi-square tests for categorical and Kruskal-Wallis tests for continuous characteristics.				
Abbreviations: eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; IST, immunosuppressive therapy; NS, nephrotic syndrome; UPCR, urine protein: creatinine ratio				

Psychiatric Disorders

The estimated risk of diagnosis was 14.7 cases per 1,000 person-years. Time to diagnosis of any psychiatric disorder is shown as a Kaplan-Meier plot in Fig. 2. Adolescent participants were more likely to be diagnosed with a psychiatric disorder (31.9 cases per 1,000 person-years) compared to children (13.3 cases per 1,000 person-years) or adults (13.5 cases per 1,000 person-years).

Analyses were repeated for time to diagnosis in each disorder subcategory: anxiety (Fig. 3), mood (Fig. 4), and behavioral (Figure S1) disorders. Adolescents had a significantly higher rate of anxiety diagnosis compared to children and adults (children = 8.5 vs. adolescents = 20.2 vs. adults = 9.5 cases per 1,000 person-years respectively, *Logrank p* = 0.02). There was no difference in risk of mood diagnosis by age (children = 5.3 vs. adolescents = 12.6 vs. adults = 8.6 cases per 1,000 person-years, *Logrank p* = 0.10). Children and adolescents had higher rates of behavioral diagnosis, though this was based on a small (n = 21) number of events (children = 4.2 vs. adolescents = 3.5 vs. adults = 1.1 cases per 1,000 person-years respectively, *Logrank p* = 0.02).

Results of unadjusted cox proportional hazards models are reported in Table S2. As shown in the Kaplan-Meier plot (Fig. 2), adolescent age was associated with increased likelihood of psychiatric diagnosis. By race, Asians were less likely to be diagnosed with a psychiatric disorder compared with Whites (HR = 0.38, 95% CI = 0.18 to 0.79). Patients with MCD had an increased hazard of psychiatric diagnosis relative to NS-not biopsied (HR = 2.41, 95% CI = 1.15 to 5.05), which was consistent with the differences by age. Onset of steroid treatment was also associated with diagnosis of psychiatric disorder (HR = 1.97, 95% CI = 1.34 to 2.90). A similar relationship was found for rituximab treatment initiation (HR = 2.39, 95% CI = 1.10 to 5.19), and number of immunosuppressive treatments (HR per medication = 1.17, 95% CI = 1.03 to 1.34). Kaplan-Meier plots are shown with unadjusted analysis of anxiety, mood and behavior outcomes by age in Figs. 3, 4 and S1, respectively.

The final multivariable model was generated using backwards selection for time to diagnosis of psychiatric disorder and results are shown in Table 2. Children were less likely (HR = 0.58, 95% CI = 0.35 to 0.96) and adolescents were more likely (HR = 2.03, 95% CI = 1.23 to 3.35) than adults to be diagnosed with psychiatric disorders. The differences by race persisted in this model, where Asians appeared to be at the lowest risk when White was used as the reference (HR 0.34, 95% CI = 0.16 to 0.70). Onset of steroid therapy was associated with a greater than two-fold risk of diagnosis of psychiatric disorder (HR = 2.27, 95% CI = 1.53 to 3.37).

Table 2

Adjusted model results assessing the relationship between demographic and clinical characteristics and psychiatric diagnosis outcome. Analysis method: adjusted time-varying cox-proportional hazards model (n = 943 participants; n = 109 events)

Adjusted model	Psychiatric Disorder Hazard ratio	95% confidence interval	p-value
Age			< 0.001
Children (0–12 years)	0.58	0.35 to 0.96	0.04
Adolescents (13–17 years)	2.03	1.23 to 3.35	0.01
Adults (18 + years)	REF	REF	REF
Race			0.03
White	REF	REF	REF
Black	0.77	0.39 to 1.48	0.43
Asian	0.34	0.16 to 0.70	0.004
Other	0.80	0.46 to 1.40	0.43
Steroid treatment	2.27	1.53 to 3.37	< 0.001

Unadjusted and adjusted results of time to ESKD, including 329 ESKD events, are found in Table S3 and Table 3 respectively. Children were less likely to progress to ESKD (vs. adults, HR = 0.46, 95% CI = 0.35 to 0.59), as were those with higher eGFR at onset (HR per 30 ml/min/1.73 m² = 0.59, 95% CI = 0.54 to 0.64). FSGS had the highest hazard of progression relative to NS-not biopsied (HR = 6.05, 95% CI = 3.24 to 11.30), followed by IgA (HR = 4.70, 95% CI = 2.46 to 8.97). After adjustment for diagnosis, eGFR at onset, UPCR over time, and onset of steroid therapy, onset of psychiatric disorder was associated with progression to ESKD (HR = 2.47, 95% CI = 1.55 to 3.95).

Table 3

Adjusted model results assessing the relationship between psychiatric diagnosis and ESKD outcome. Analysis method: adjusted time-varying cox-proportional hazards model (n = 943 participants; n = 329 events)

Adjusted model	ESKD Hazard ratio	95% confidence interval	p-value
Onset of psychiatric disorder	2.47	1.55 to 3.95	< 0.001
Diagnosis			0.008
FSGS	3.26	1.63 to 6.50	0.001
Minimal Change	2.13	0.99 to 4.62	0.05
Membranous Nephropathy	2.27	1.03 to 4.97	0.04
NS-not biopsied	REF	REF	REF
IgA Nephropathy	2.33	1.13 to 4.76	0.02
Other	2.65	1.27 to 5.53	0.01
eGFR at onset per 30 ml/min/1.73 m ²	0.64	0.58 to 0.70	< 0.001
UPCR over time per 1 log increase	1.10	1.05 to 1.16	< 0.001
Steroid treatment	0.61	0.46 to 0.80	< 0.001
Abbreviations: ESKD, end stage kidney disease; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; NS, nephrotic syndrome; UPCR, urine protein: creatinine ratio			

Discussion

The goals of this study were to describe psychiatric diagnoses based on EHR data among patients with glomerular disease and to identify relevant demographic and kidney disease related associations. We found approximately 1 in 8 patients were diagnosed with a psychiatric disorder after the onset of kidney disease and the risk was highest among the adolescent population (Table 1). The use of steroids was associated with two times the risk of a psychiatric diagnosis (HR = 2.27, 95% CI 1.53 to 3.37). The hazard of ESKD was greater following a psychiatric diagnosis, after adjusting for demographic and clinical characteristics (HR = 2.11, 95% CI 1.31–3.39).

To the best of our knowledge, this study represents the first investigation into the incidence psychiatric disorders among patients with non-diabetic glomerular diseases. The 12-month point prevalence of mood disorders is 9.5% in the US for ages 18 and older as reported by the National Comorbidity Survey Replication (NCS-R).[36] Based on a previous systematic review and meta-analysis of interview-based depression diagnosis with a combined sample of roughly 56,000 participants,[37] the prevalence of depression in advanced CKD stage 5 is approximately 22.8%. Depression and chronic kidney disease has

been associated with poor outcomes including lower quality of life and death. [29, 38] Previous population studies of patients with other chronic illnesses, including asthma and sickle cell disease have found an increased prevalence of psychiatric disorders compared to the general population.[39, 40].

In the current study, adolescents were at the highest risk of psychiatric disorder: 31.9 cases per 1,000 person-years compared with other age groups [children 13.3 and adults 13.5 cases per 1,000 person-years] (Fig. 2). The increased prevalence of psychiatric disorders among adolescents is seen in the general population, as the lifetime prevalence of mood disorders in the adolescent population is 14.3% among adolescents age 13–18 as reported by the NCS-R-Adolescent supplement.[41] Population studies of adolescents with asthma have found increased likelihood of major depression (OR 1.7 95% CI 1.3–2.3), and anxiety disorders (OR 1.6 95% CI 1.2–2.2) compared to adolescents in the general community, which were postulated to be, in part, attributable to childhood adversity or unexamined familial factors. [42] These findings support mental health screening as part of chronic disease management, particularly among adolescents.

Steroid exposure was associated with more than a doubling in risk for the onset of a psychiatric disorder. We attribute this to the adverse side effects of steroid therapy, but also recognize that this could be confounded by disease type, as patients with relapsing/remitting disease may be more likely to experience anxiety related to the unpredictable nature of the disease. It is important to note that our multivariable model assessed markers of kidney disease severity (diagnosis, eGFR, UPCR, and other ISTs), but these markers were not associated with psychiatric diagnosis. The use of steroids has previously been shown to adversely affect mood, as has been seen in with increase in manic symptoms in asthmatic patients treated with a short duration (7 days) of steroids. [43] In adults, the use of steroids has been shown to induce euphoria and hypomania in the short term, however long term the effects of steroid treatment tend to skew more towards depressive symptoms. [44] Furthermore, steroid dosage seems to directly correlate with the incidence, but not severity, of psychiatric episodes in adults. Literature detailing child and adolescent psychiatric syndromes as a result of steroid use is not as robust as adult literature. However, children and adolescents tend to express symptoms in the realm of an increase in externalizing behaviors such as conduct disorders and aggression.

Our time-varying analyses of time to ESKD found that the onset of a psychiatric disorder was associated with an increased likelihood of ESKD. Previous literature has reported the presence of major depressive episodes in patients with progression to ESKD, as well as associated with more frequent hospitalizations in CKD populations.[29]

This study is not without limitations, namely the reliance on EHR data from the KRN nephrology sites. Patients with a diagnosis of a psychiatric disorder that was not entered into the KRN-associated site EHR will not be recognized as a case in this study. Similarly, patients with an undiagnosed psychiatric disease would not be classified as a case in this study. Our data collection relied on coded diagnoses and is certainly an underrepresentation of the true prevalence of mood disorders in our population. Another limitation is that psychiatric diagnosis are less common in young children, however very few of our

patients are in a developmental age range that would be less likely to be diagnosed with a psychiatric disorder. Finally, our aim was to investigate a possible association between glomerular disease and psychiatric disorders. We recognize that kidney disease is not the sole factor involved. Psychiatric disorders are complex and multifactorial in origin with both environmental and genetic influences.

Conclusions

Despite its limitations, this study suggests that diagnosed psychiatric illnesses are common in patients with glomerular disease. Future research and quality initiatives are recommended to systematically conduct mental health screening in patients with glomerular disease to define the true incidence and prevalence of psychiatric disorders in patients with glomerular disease and foster access clinical psychiatric support as indicated.

Abbreviations

CI	Confidence interval
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children cohort
COPD	Chronic obstructive pulmonary disease
eGFR	Estimated glomerular filtration rate
EHR	Electronic health records
ESKD	End stage kidney disease
FSGS	Focal segmental glomerulosclerosis
HR	Hazard ratio
HRQoL	Health-related quality of life
IST	Immunosuppressive therapy
KRN	Kidney Research Network
MCD	Minimal change disease
MN	Membranous nephropathy
NCS-R	National Comorbidity Survey Replication
NHANES	National Health and Nutrition Examination Survey
NS	Nephrotic syndrome
OR	Odds ratio
UPCR	Urine protein: creatinine ratio
US	United States
VAHS	Veteran Affairs Health System

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of the University of Michigan. Informed consent was obtained following institutional policies from participants or legal guardians of minor participants before enrollment in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available at present but may be available from the corresponding author on reasonable request and with approval from the Kidney Research Network registry steering committee who governs its data use.

Competing interests

Though there are no conflicts of interest or disclosures related to these data, the authors would like to report the following financial relationships: JT research funding through the University of Michigan [UM] with Complexa Inc., Retrophin Inc. Goldfinch Bio, Vertex Pharmaceuticals and Pfizer Inc. DG has research funding through the UM with Complexa Inc., Retrophin Inc., Goldfinch Bio, and Reata Pharmaceuticals, and consults through UM with Vertex and AstraZeneca; EK has research funding from Pfizer and Complexa Inc., has served as a one-time consultant for Mallinckrodt, and serves on the Board of NephCure Kidney International. SM has research funding through Complexa and serves on the Retrophin Advisory Board.

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Author Contributions

KRN study design, conduct, enrollment of participants: HED, MM, AC, GJO, RL, MO, ME, SA, ESK, AP, DTS, PEG, NEC, DSG, SFM; conception of overall research question: HED; statistical analyses JPT; interpretation of results: all authors. All authors reviewed: revised: and approved the manuscript for submissions. Each author contributed important intellectual content during manuscript drafting and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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References

1. Fauman, K.R., et al., Predictors of depressive symptoms in parents of chronically ill children admitted to the pediatric intensive care unit. *Am J Hosp Palliat Care*, 2011. **28**(8): p. 556-63.
2. Piquart, M. and Y. Shen, Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. *J Pediatr Psychol*, 2011. **36**(4): p. 375-84.
3. Schneider, C., et al., COPD and the risk of depression. *Chest*, 2010. **137**(2): p. 341-7.
4. Atlantis, E., et al., Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. *Chest*, 2013. **144**(3): p. 766-777.
5. Jolles, M.P., et al., Mental Health Service Use for Adult Patients With Co-occurring Depression and Physical Chronic Health Care Needs, 2007–2010. *Medical Care*, 2015. **53**(8): p. 708-712.
6. Hilliard, M.E., et al., Resilience in Youth and Families Living With Pediatric Health and Developmental Conditions: Introduction to the Special Issue on Resilience. *J Pediatr Psychol*, 2015. **40**(9): p. 835-9.
7. Willgoss, T.G. and A.M. Yohannes, Anxiety disorders in patients with COPD: a systematic review. *Respir Care*, 2013. **58**(5): p. 858-66.
8. Balhara, Y.P., Diabetes and psychiatric disorders. *Indian J Endocrinol Metab*, 2011. **15**(4): p. 274-83.
9. Jonassaint, C.R., et al., A systematic review of the association between depression and health care utilization in children and adults with sickle cell disease. *Br J Haematol*, 2016. **174**(1): p. 136-47.
10. Sogutlu, A., et al., Somatic symptom burden in adults with sickle cell disease predicts pain, depression, anxiety, health care utilization, and quality of life: the PiSCES project. *Psychosomatics*, 2011. **52**(3): p. 272-9.
11. Goodwin, R.D., et al., Severity and persistence of asthma and mental health: a birth cohort study. *Psychol Med*, 2013. **43**(6): p. 1313-22.
12. Hijmans, C.T., et al., Behavioral and emotional problems in children with sickle cell disease and healthy siblings: Multiple informants, multiple measures. *Pediatr Blood Cancer*, 2009. **53**(7): p. 1277-83.
13. Barlow, J.H. and D.R. Ellard, The psychosocial well-being of children with chronic disease, their parents and siblings: an overview of the research evidence base. *Child Care Health Dev*, 2006. **32**(1): p. 19-31.

14. Scott, K.M., et al., Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiatry*, 2007. **29**(2): p. 123-33.
15. Opolski, M. and I. Wilson, Asthma and depression: a pragmatic review of the literature and recommendations for future research. *Clin Pract Epidemiol Ment Health*, 2005. **1**: p. 18.
16. Kankaanranta, H., et al., Emerging Comorbidities in Adult Asthma: Risks, Clinical Associations, and Mechanisms. *Mediators Inflamm*, 2016. **2016**: p. 3690628.
17. Substance Abuse and Mental Health Services Administration., 2018 National Survey on Drug Use and Health: Methodological summary and definitions. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse, and Mental Health Services Administration. 2019.
18. Knudsen, K.B., et al., Associations between adherence, depressive symptoms and health-related quality of life in young adults with cystic fibrosis. *Springerplus*, 2016. **5**(1): p. 1216.
19. Yohannes, A.M., et al., Relationship between anxiety, depression, and quality of life in adult patients with cystic fibrosis. *Respir Care*, 2012. **57**(4): p. 550-6.
20. Riekert, K.A., et al., The association between depression, lung function, and health-related quality of life among adults with cystic fibrosis. *Chest*, 2007. **132**(1): p. 231-7.
21. Ghandour, R.M., et al., Prevalence and Treatment of Depression, Anxiety, and Conduct Problems in US Children. *J Pediatr*, 2019. **206**: p. 256-267.e3.
22. Malik, J.A. and H.M. Koot, Explaining the adjustment of adolescents with type 1 diabetes: role of diabetes-specific and psychosocial factors. *Diabetes Care*, 2009. **32**(5): p. 774-9.
23. Lin, E.H., et al., Mental disorders among persons with diabetes—results from the World Mental Health Surveys. *J Psychosom Res*, 2008. **65**(6): p. 571-80.
24. Ducat, L., L.H. Philipson, and B.J. Anderson, The mental health comorbidities of diabetes. *Jama*, 2014. **312**(7): p. 691-2.
25. Anderson, R.J., et al., The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*, 2001. **24**(6): p. 1069-78.
26. Nouwen, A., C.E. Lloyd, and F. Pouwer, Depression and type 2 diabetes over the lifespan: a meta-analysis. Response to Mezuk et al. *Diabetes Care*, 2009. **32**(5): p. e56; author reply e57.
27. Goh, Z.S. and K. Griva, Anxiety and depression in patients with end-stage renal disease: impact and management challenges - a narrative review. *Int J Nephrol Renovasc Dis*, 2018. **11**: p. 93-102.
28. Kimmel, P.L. and R.A. Peterson, Depression in patients with end-stage renal disease treated with dialysis: has the time to treat arrived? *Clin J Am Soc Nephrol*, 2006. **1**(3): p. 349-52.
29. Hedayati, S.S., et al., Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. *Jama*, 2010. **303**(19): p. 1946-53.
30. Hedayati, S.S., et al., Prevalence of major depressive episode in CKD. *Am J Kidney Dis*, 2009. **54**(3): p. 424-32.
31. Cukor, D., et al., A preliminary investigation of depression and kidney functioning in patients with chronic kidney disease. *Nephron Clin Pract*, 2012. **122**(3-4): p. 139-45.

32. Kogon, A.J., et al., Depressive Symptoms in Children with Chronic Kidney Disease. *J Pediatr*, 2016. **168**: p. 164-70.e1.
33. Gipson, D.S., et al., NephCure Accelerating Cures Institute: A Multidisciplinary Consortium to Improve Care for Nephrotic Syndrome. *Kidney Int Rep*, 2018. **3**(2): p. 439-446.
34. Schwartz, G.J., et al., New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*, 2009. **20**(3): p. 629-37.
35. Levey, A.S., et al., A new equation to estimate glomerular filtration rate. *Ann Intern Med*, 2009. **150**(9): p. 604-12.
36. Kessler, R.C., et al., Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, 2005. **62**(6): p. 617-27.
37. Palmer, S., et al., Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney Int*, 2013. **84**(1): p. 179-91.
38. Bautovich, A., et al., Depression and chronic kidney disease: A review for clinicians. *Aust N Z J Psychiatry*, 2014. **48**(6): p. 530-41.
39. Ortega, A.N., et al., Childhood asthma, chronic illness, and psychiatric disorders. *J Nerv Ment Dis*, 2002. **190**(5): p. 275-81.
40. Unal, S., et al., Evaluation of the psychological problems in children with sickle cell anemia and their families. *Pediatr Hematol Oncol*, 2011. **28**(4): p. 321-8.
41. Merikangas, K.R., et al., Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*, 2010. **49**(10): p. 980-9.
42. Goodwin, R.D., D.M. Fergusson, and L.J. Horwood, Asthma and depressive and anxiety disorders among young persons in the community. *Psychol Med*, 2004. **34**(8): p. 1465-74.
43. Kewalramani, A., M.E. Bollinger, and T.T. Postolache, Asthma and Mood Disorders. *Int J Child Health Hum Dev*, 2008. **1**(2): p. 115-123.
44. Warrington, T.P. and J.M. Bostwick, Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc*, 2006. **81**(10): p. 1361-7.

Figures

Figure 1

Flow diagram of included participants

Figure 2

Time to diagnosis of any psychiatric disorder (n=943 participants; n=109 events; risk=14.7 cases per 1,000 person-years)

Figure 3

Time to diagnosis of anxiety disorder (n=943 participants; n=74 events; risk=9.8 cases per 1,000 person-years)

Figure 4

Time to diagnosis of mood disorder (n=943 participants; n=56 events; risk=7.4 cases per 1,000 person-years)

Supplementary Files

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