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Psychiatric diagnoses in children and adolescents with chronic kidney disease

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Abstract

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Background: Children with chronic kidney disease (CKD) are subject to a myriad of complex physical and psychosocial challenges, which may confer increased risk of developing a psychiatric disorder when compared with the general population. Currently available studies are limited by small sample size, narrow geographic region, or inconsistent disease definitions. This study uses a large multi-institutional database of children with CKD in comparison to a national population database to assess differences in key psychiatric diagnoses.

Methods: We used parent-report surveys from the Chronic Kidney Disease in Children (CKiD) study baseline assessments and the National Survey of Children's Health (NSCH) to evaluate the prevalence of depression, anxiety, and attention deficit and hyperactivity disorder (ADHD) diagnoses in children with CKD in comparison to the general population. Children and adolescents ages 2 to 17 who saw a medical provider in the year prior to evaluation were included. Using logistic regression with Poisson distribution, we determined the prevalence ratio

(PR) comparing the above diagnoses in children at the time of their entry into the CKiD study to those participants in the NSCH, both overall and within categories based on sex, race, and maternal education status. Analysis was conducted separately for mild (stage 1-2), moderate (stage 3), severe (stage 4-5), and for all stages of CKD. Models were adjusted for age, sex, and race differences.

Results: A total of 875 subjects with CKD and 72,699 controls met inclusion criteria. Of the former, 109 subjects had mild CKD, 447 had moderate CKD, and 316 had severe CKD. Those with CKD had aPR of 1.32 (95%CI 1.01 to 1.74) for a diagnosis of depression, 0.72 (95%CI .52 to 0.99) for anxiety, and 0.62 (95%CI 0.48 to 0.80) for ADHD compared to the general population. The pattern of results differed little according to sex, race, or maternal education. There were no appreciable differences in the PRs in subsets of children with mild, moderate, and severe CKD.

Discussion: In this analysis, children with CKD demonstrated slightly higher prevalence of depression and lower prevalence of anxiety and ADHD as compared to a general population. There was no evidence that this association differed in those with more advanced CKD or within strata of sex, race/ethnicity, or maternal education status. This is not consistent with the results of other studies which have observed a higher prevalence of psychiatric diagnoses in children with CKD compared to other children, particularly in children with more severe kidney disease. These inconsistencies suggest that this subset of the CKiD data may have limited utility in evaluating history of mental health disorders and that further adjustment and evaluation of baseline data collection is needed.

TABLE OF CONTENTS

List of Figures	ii
List of Tables	iii
1. Introduction.....	6
2. Methods.....	8
2.1 Study Design.....	8
2.2 Study Setting.....	8
2.3 Study Subjects.....	8
2.4 Data Sources	9
2.4.1 CKiD.....	9
2.4.2 NSCH.....	10
2.5 Data Analysis	10
3. Results.....	11
3.1 Subject Demographics	12
3.2 Results.....	13
4. Discussion.....	18
4.1 Limitations	19
4.2 Conclusions.....	19
References.....	21

LIST OF FIGURES

Figure 1. Consort Diagram	12
Figure 2. Prevalence ratios of psychiatric diagnoses in those with mild, moderate, and severe CKD compared to the general population	16
Figure 3. Crude prevalence of selected psychiatric diagnosis by year in CKiD and NSCH17	

LIST OF TABLES

Table 1. Subject demographics for NSCH controls and CKiD cases by stage of CKD. .	13
Table 2. Prevalence of mental health diagnoses in those with and without CKD.	14
Table 3. Prevalence and 95% CI of mental health diagnoses in selected strata.	15

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DEDICATION

To everyone who supported this last first step.

1. INTRODUCTION

Children with chronic kidney disease (CKD) are subject to a myriad of complex physical and psychosocial challenges.¹ Common physical sequelae of CKD include nutritional deficits, anorexia, poor growth, bone disease, heart disease, endocrine disorders, high blood pressure, chronic inflammation, and anemia. Monitoring of the disease process exposes children to frequent medical visits and invasive procedures including blood draws. These in turn are associated with complex psychosocial effects, poor neurodevelopmental outcomes, and increased stressors in personal, peer, and familial domains.¹⁻⁴ The combination of physical and psychosocial stressors associated with CKD may confer increased risk of mental disorders when compared with the general population.

It is also important to consider that the physical and psychosocial stressors associated with CKD occur on a spectrum, with more pronounced effects in children with more severe CKD. As such, the impact on mental health may be the most striking in more severe stages of disease. We do know that there are differences in quality of life and mental disorders between groups of children with mild to moderate CKD, end stage kidney disease (ESRD), and those who are post-transplant.⁵⁻⁸ Even mild CKD, however, may be associated with subtle physiological changes that could lead to mental health disorders. Hypertension and early cardiovascular disease, for example, are known to occur in earlier stages of CKD⁹ and may play a role in neurocognitive dysfunction seen in children with CKD^{2,10} as well as increasing risk for psychiatric disorders. Other subtle physiological changes that affect the brain and general nervous system and increase susceptibility of children to mental disorders may occur in early stages of CKD. Understanding the mental health

of children with CKD across the range of illness severity is an important piece of working within the complex system of care to promote optimal outcomes for this vulnerable group of patients.

Despite the exposure of children with CKD to physiological stressors and intensive and invasive treatments that could contribute to the potentiation of mental disorders, there is a dearth of evidence quantifying and characterizing these conditions in pediatric CKD. Studies suggest a prevalence of any mental health disorder among children with CKD of 60-70%^{5,6}, with multiple mental disorders present in up to 50% of those with a mental disorder^{6,11} and depression prevalence estimates ranging from 7% to 35%.¹¹⁻¹⁵ This compares to a prevalence of 50% for any mental health disorder and 11% for depression in population-based studies of children in the U.S.¹⁶

Susceptibility markers for psychiatric disorders in children with CKD are poorly understood. However, correlations between duration of CKD and impaired attention symptoms^{2,10} and maternal education beyond high school and depressive symptoms¹¹ have been reported. Studies of mental disorder prevalence in pediatric CKD are limited, however, by small sample size^{5,6,12-15}, samples with a narrow representation of ethnic groups and geographic areas^{5,6,12,15}, or inconsistent definitions of psychiatric disorders, as reflected in the use of a variety of symptom-based screening tools¹¹⁻¹⁵, all of which limit the clinical applicability and generalizability of the findings.

The risk of chronic kidney disease varies with age, as does risk of psychiatric diagnosis. The occurrence of chronic kidney disease and mental disorders differs between boys and girls. Similarly, race/ethnicity is associated with both chronic kidney disease and with the likelihood of mental disorder, with particular differences seen in black and Hispanic as compared to white children. As such, age, sex, and race will be evaluated as potential confounders in this analysis. As above, maternal education level has been correlated with depression diagnosis in children with

CKD. Maternal education is also a surrogate indicator of socioeconomic status, a known determinant of mental health diagnosis risk such that it may modify the relationship between CKD and mental health status. The risk associated with sex and race/ethnicity may also differ in magnitude between children with and without CKD. Maternal education level, sex, and race/ethnicity, therefore, will also be evaluated as potential effect modifiers of the association between CKD and mental disorders.

This study was designed to extend our current understanding of mental disorders in pediatric CKD. The study uses data from the Chronic Kidney Disease in Children cohort study (CKiD) and from the National Survey of Children's Health (NSCH).

2. METHODS

2.1 STUDY DESIGN

Data from the CKiD and NSCH databases were used to compare a history of a psychiatric diagnoses in children with chronic kidney disease and children in the general population. Specific outcomes were diagnoses of depression, anxiety, and ADHD as reported by the parent informant.

2.2 STUDY SETTING

This study includes data from children and adolescents across North America enrolled in the CKiD and NSCH databases, which are described in further detail below. Analysis was conducted at the University of Washington and Seattle Children's Hospital.

2.3 STUDY SUBJECTS

Children and adolescents age 2 to 17 years (called "children") with chronic kidney disease who participated in the CKiD study between 2005 and 2015, or in the 2007 or 2011/12 NSCH.

The CKiD sample included 891 participants, and the NSCH included 91,642 participants. For this study, NSCH participants who had not seen a healthcare provider within the last 12 months were excluded to ensure equivalence in opportunity for outcome assessment between the NSCH and CKiD comparator groups, as all CKiD enrollees must have seen a medical provider within 12 months to enroll in the study. Additional details are listed under the database descriptions below.

2.4 DATA SOURCES

2.4.1 CKiD

Data were obtained from the Chronic Kidney Disease in Children cohort study database. The CKiD study is a multi-center longitudinal cohort study of children with CKD across North America. Study recruitment began in 2005, and data obtained at the time of entry into the study are available through 2015 for cohorts 1 and 2, which are included in this analysis. Subjects were recruited from 54 pediatric nephrology centers to include children from age 1-16 with CKD. Study participants complete a two-part baseline assessment within 24 months of study enrollment and subsequently are followed annually using clinician, laboratory, and survey evaluation until transplantation, dialysis initiation, or transfer of care to an adult center. Children with prior malignancy, transplant, or dialysis within the past 3 months were excluded. Additional detail of the study design and objectives has been previously described.¹⁷

In CKiD, the outcome of interest is ascertained from the following question asked of a parent informant in the baseline interview: “Has a doctor or any other healthcare professional ever told you that (*name of child*) has any of the following diseases?”

- Attention Deficit Disorder
- Attention Deficit Hyperactivity Disorder

- Depression
- Anxiety Disorder

2.4.2 *NSCH*

The National Survey of Children’s Health (NSCH) is a health survey conducted in the U. S., that employs random digit dialing techniques and evaluates childhood well-being, including demographic, medical, social, and mental health aspects of child health across a nationally representative sample of children age 0 – 17 years. In 2007, data were collected over household landline telephone with 91,642 completed interviews. In 2011/2012, the sample was stratified by cell phone or landline group and by state and included 95,677 households with clustering of children within homes.

In the NSCH, the outcome of interest is ascertained from the following question asked of a parent informant in the baseline interview: “Has a doctor or other health care provider ever told you that [name] had...”

- Attention Deficit Disorder or Attention Deficit Hyperactive Disorder (that is, ADD or ADHD)
- Depression
- Anxiety

2.5 DATA ANALYSIS

History of psychiatric diagnoses in the two samples was compared using logistic regression with Poisson distribution adjusted for age (continuous), sex (male, female), and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic other). Stratified analysis was conducted to assess for differences in prevalence ratio by sex, race/ethnicity, and maternal

education status, as well as for differences by stage of CKD (mild, moderate, or severe). Sensitivity analysis was conducted comparing prevalence of mental disorders between CKiD data and NSCH data collected in 2007 and in 2011/12. Using 891 subjects from the CKiD study and 91,642 subjects from the NCHS sample, at a significance level of $\alpha = 0.05$, this study is able to detect a 2% difference in the prevalence of depression or anxiety diagnoses and a 3% difference in the proportion of ADHD diagnosis between the two groups, presuming diagnosis prevalence of 4%, 5%, and 9%, respectively, in the NCHS sample.

3. RESULTS

A total of 72,699 subjects from the NSCH and 875 subjects from CKiD met inclusion criteria and were included in the analysis for the first research question. For the within-CKiD research question, three CKiD subjects were missing baseline eGFR data and were therefore excluded from analysis. The remaining CKiD population included 109 subjects with mild kidney disease, 447 with moderate kidney disease, and 316 with severe kidney disease, as shown in figure 1.

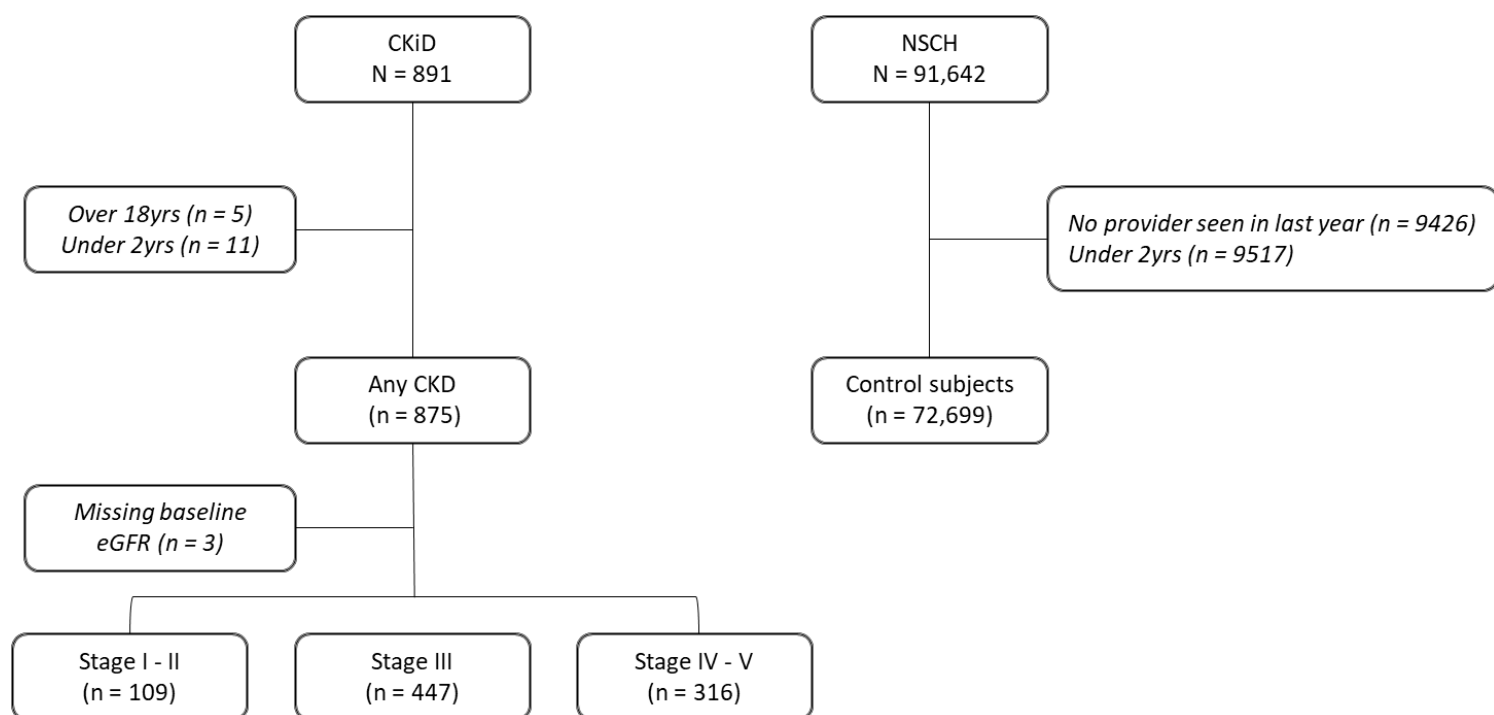


Figure 1. Consort Diagram

3.1 SUBJECT DEMOGRAPHICS

Demographic characteristics of the NSCH and CKiD samples are shown in table 1. The general population sample had approximately equal sex representation versus the CKiD population, which was predominantly male. Higher proportions of black and Hispanic/Latino groups were represented in the CKiD sample than in the NSCH. Maternal education beyond high school was seen in a larger portion of the NSCH sample than the overall, mild CKD, or moderate CKD samples, but was similar to the proportion of those with a maternal education beyond high school in the subset of those with severe CKD. Mean age was similar across all groups at 10-11 years old.

Table 1. Subject demographics for NSCH controls and CKiD cases by stage of CKD.

	NSCH (n=72605)	CKiD			
		All (n=875)	Stage 1-2 (n=109)	Stage 3 (n=447)	Stage 4-5 (n=316)
Sex					
Female	34939 (48%)	335 (38%)	31 (28%)	179 (40%)	124 (39%)
Race					
White	48842 (67%)	487 (56%)	57 (52%)	261 (58%)	168 (53%)
Black	7510 (10%)	152 (17%)	22 (20%)	70 (16%)	58 (18%)
Hispanic/Latino	8612 (12%)	185 (21%)	26 (24%)	94 (21%)	65 (21%)
Other	6539 (9%)	51 (6%)	4 (4%)	22 (5%)	25 (8%)
Missing	1102 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Highest level of maternal education					
High school or less	18226 (25%)	342 (39%)	58 (53%)	175 (39%)	108 (34%)
More than high school	48794 (67%)	514 (59%)	48 (44%)	262 (59%)	202 (64%)
Missing	5585 (8%)	19 (2%)	3 (3%)	10 (2%)	6 (2%)
Age in years					
Mean (SD)	10.1 (4.75)	10.9 (4.28)	11.5 (3.90)	10.9 (4.24)	10.8 (4.41)
Duration of CKD in years					
Mean (SD)	NA	8.06 (4.90)	9.97 (4.84)	8.38 (4.80)	7.00 (4.80)

3.2 RESULTS

The crude prevalence and adjusted PR comparing those with CKD to the general population for diagnoses of depression, anxiety, ADHD, and for those with multiple diagnoses are displayed in table 2. The prevalence of depression was 32% greater in children with CKD than the general population. Anxiety was 28% less prevalent in those with CKD. ADHD was 38% less prevalent in those with CKD. The prevalence of multiple diagnoses was 42% lower in those with CKD than in the general adolescent population. These differences were statistically significant with p-values for each of the above comparisons < 0.05.

Table 2. Prevalence of mental health diagnoses in those with and without CKD.

Diagnosis	Crude prevalence		Adjusted PR*	95% confidence interval			<i>p-value</i>
	CKiD	NSCH					
Depression	5.7%	3.9%	1.32	1.01	to	1.73	0.04
Anxiety	4.0%	5.4%	0.72	0.52	to	0.99	0.04
ADHD	6.4%	9.2%	0.62	0.48	to	0.80	0.00
<i>Multiple</i>	2.6%	4.2%	<i>0.58</i>	<i>0.39</i>	<i>to</i>	<i>0.87</i>	<i>0.01</i>

*Adjusted for age, sex, and race/ethnicity

Adjusted prevalence ratios associated with individual strata of sex, race/ethnicity, and maternal education comparing those with and without CKD are presented in table 3. Black participants had lower prevalence of anxiety than white or Hispanic groups. There were no appreciable differences in prevalence trends between strata for depression, anxiety, or ADHD diagnoses.

Table 3. Adjusted prevalence* and 95% CI of mental health diagnoses in selected strata.

			95% CI			
			aPR	2.5%	97.5%	p-value
Depression	Sex	Female	1.52	1.03	2.26	0.04
		Male	1.19	0.82	1.72	0.36
	Race/Ethnicity	White	1.43	1.00	2.04	0.05
		Black	1.68	0.91	3.11	0.10
		Hispanic	1.13	0.61	2.10	0.69
		Other	0.60	0.15	2.39	0.46
	Maternal Education	Less than HS	1.30	0.86	1.94	0.21
		HS or more	1.53	1.06	2.20	0.02
Anxiety	Sex	Female	0.60	0.34	1.08	0.09
		Male	0.78	0.53	1.15	0.21
	Race/Ethnicity	White	0.92	0.64	1.32	0.66
		Black	0.17	0.02	1.25	0.08
		Hispanic	0.66	0.32	1.38	0.27
		Other	0.00	0.00	0.00	0.00
	Maternal Education	Less than HS	0.63	0.36	1.09	0.10
		HS or more	0.85	0.57	1.26	0.42
ADHD	Sex	Female	0.50	0.27	0.92	0.02
		Male	0.66	0.50	0.87	0.00
	Race/Ethnicity	White	0.56	0.39	0.80	0.00
		Black	0.74	0.44	1.24	0.25
		Hispanic	0.70	0.38	1.26	0.24
		Other	0.66	0.25	1.70	0.39
	Maternal Education	Less than HS	0.53	0.34	0.81	0.00
		HS or more	0.71	0.52	0.98	0.04

*Adjusted for age, sex, and race/ethnicity

The prevalence ratios for depression, anxiety, and ADHD diagnoses in those with mild, moderate, and severe CKD are presented in figure 2. There is a trend toward decreased prevalence of depression with advancing CKD stage, though these differences are not statistically significant. There were no differences in prevalence by stage of CKD for anxiety or ADHD diagnoses as compared to the general population sample.

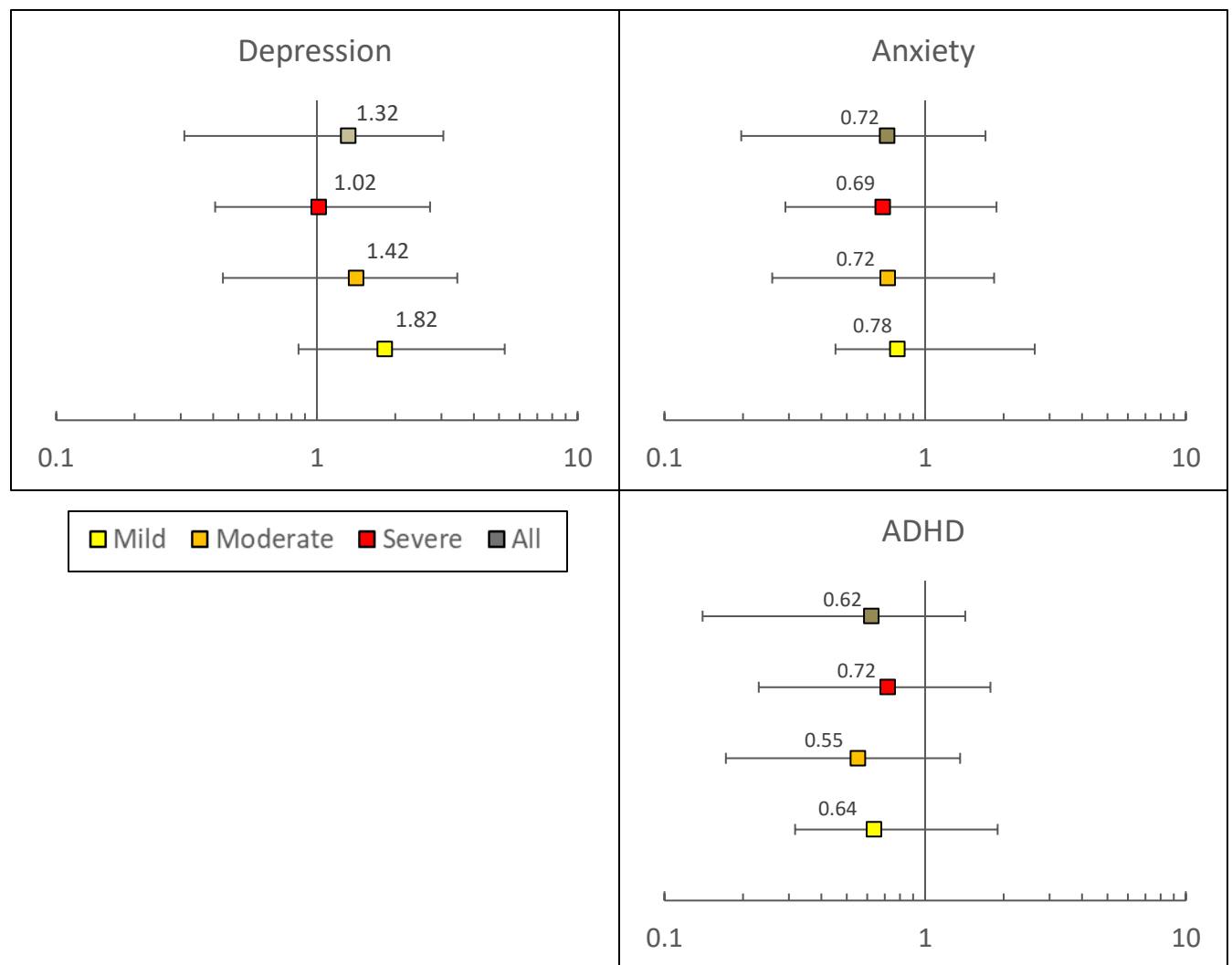


Figure 2. Prevalence ratios of psychiatric diagnoses in those with mild, moderate, and severe CKD compared to the general population

Crude prevalence of depression, anxiety, and ADHD diagnoses in the CKiD and NSCH populations in 2007 and 2012 are shown in figure 3. There were increases in prevalence of all diagnoses between 2007 and 2012 in the NSCH general population sample. Trends in annual prevalence in the CKiD study varied by diagnosis. Depression prevalence increased overall where both anxiety and ADHD diagnosis prevalence decreased over time in the CKiD group.

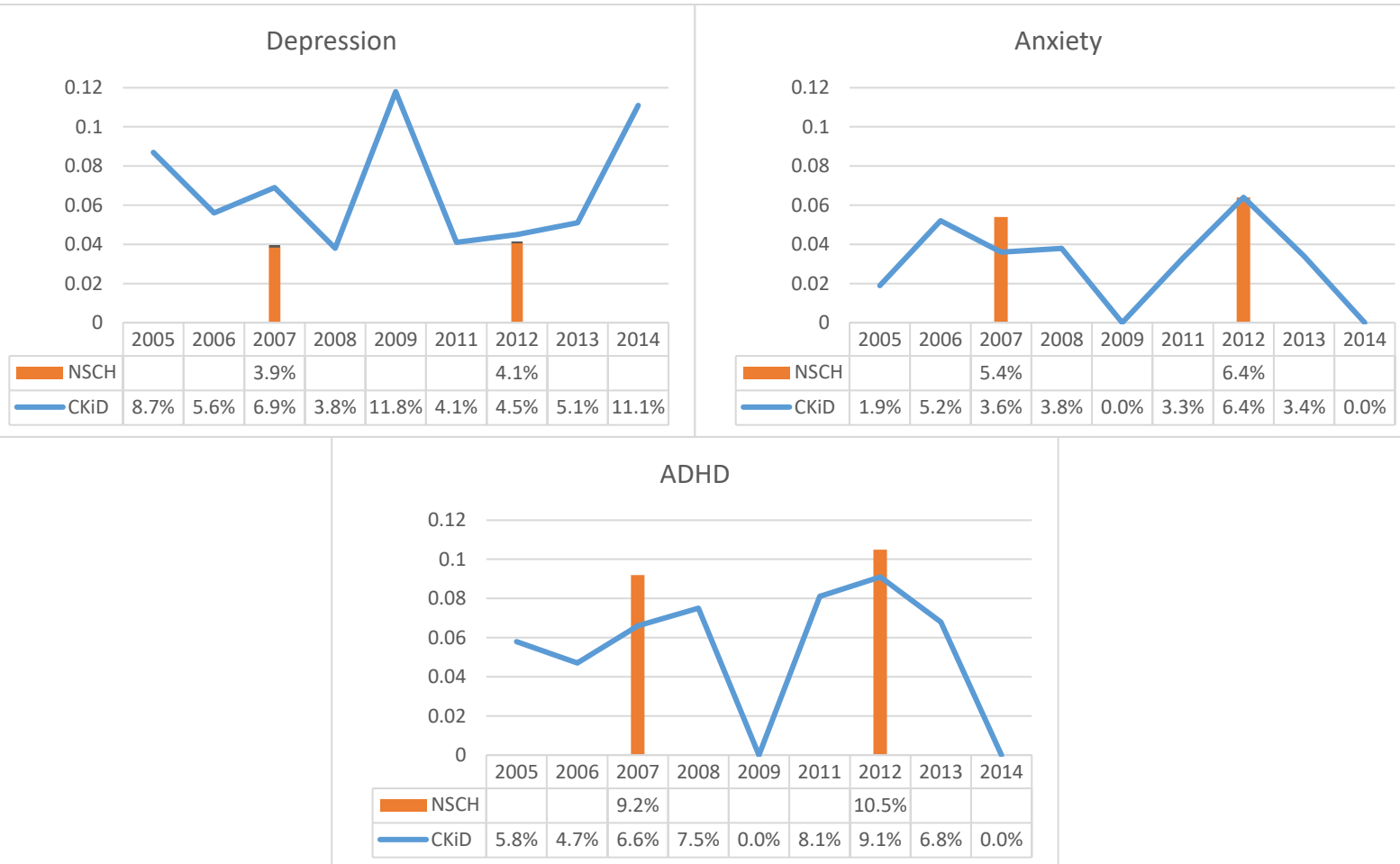


Figure 3. Crude prevalence of selected psychiatric diagnosis by year in CKiD and NSCH

4. DISCUSSION

In this analysis, children with CKD demonstrated higher prevalence of depression and lower prevalence of anxiety and ADHD as compared to a general population sample when adjusted for age, sex, and race.

While the crude prevalence of depression in children with CKD in this study at 5.7% was similar to the previously reported 5% proportion of CKiD participants reporting increased depressive symptoms at baseline,¹¹ the other findings in this study are not consistent with other studies which have demonstrated higher prevalence of depression and anxiety in children with CKD compared to healthy controls and higher prevalence with advanced stages of kidney disease.^{6,14} Lower prevalence of ADHD in CKD is also inconsistent with known impacts of even mild CKD on attention and executive functioning seen in neurocognitive tests of children with CKD.^{2,10} It should be noted that direct comparison with other studies of psychiatric diagnoses in CKD is limited by a lack of information regarding the timing of psychiatric diagnosis ascertainment relative to the duration of CKD diagnosis.

Using the annual psychiatric diagnosis trends as a rough assessment of data fidelity, we did not expect differential prevalence changes among those with and without CKD over time. While the overall trend in the CKD subjects is likely influenced by limited entrants to the CKiD study especially in 2009 and 2014, there is substantial annual variability that remains evident across other study years. Taken together, these findings suggest that the baseline data on mental health history may be of limited utility in evaluating the prevalence of mental health disorders in the child and adolescent CKD population.

4.1 LIMITATIONS

This study is limited by the use of retrospective survey data, which may result in underreporting of mental disorders in both the CKD and general population sample. Additionally, legislation differs between states regarding mental health privacy rights of children and adolescents, such that there may be underreporting of psychiatric diagnoses by the parent/caregiver respondent in cases where the child has been diagnosed, but has not disclosed this to the caregiver. There may also be differences in psychiatric diagnostic practices and patterns at different centers that may induce misclassification, and it is unclear how such misclassification will affect the assessment of the association between mental health and CKD. Social desirability bias may also result in underreporting of mental disorders in both survey-based samples. It is unclear what differential effect social desirability bias might have between those with CKD and the general population.

The systematic measurement of mental disorders is not carried out via symptom scales or diagnostic interviews, which may increase the risk of low ascertainment of mental disorders and misclassification. The similar wording of and reporter for the mental disorder questions between CKiD and NCHS samples should minimize bias in comparing outcomes between groups.

4.2 CONCLUSIONS

This is the largest assessment to date of psychiatric diagnoses in the pediatric CKD population. In age, sex, and race/ethnicity-adjusted comparison to the general adolescent population, we found a higher prevalence of depression, and lower prevalence of anxiety and ADHD diagnoses in children with CKD. The inconsistencies in these data in regards to stage of CKD and annual diagnosis trends, however, suggest that this subset of the CKiD database may

have limited utility in evaluating history of mental health disorders and that further adjustment and evaluation of baseline data collection in the CKiD study may be needed.

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