Advanced CKD Among Adults With Cerebral Palsy: Incidence and Risk Factors

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Rationale & Objective: Recent evidence suggests that adults with cerebral palsy have an elevated risk for developing advanced chronic kidney disease (CKD). To develop effective interventions, the objective was to identify whether demographics and preexisting medical conditions are risk factors for advanced CKD among adults with cerebral palsy.

Study Design: Retrospective cohort study.

Setting & Participants: Data were from the Optum Clinformatics Data Mart. Adults 18 years or older with cerebral palsy and without advanced CKD (CKD stage 4 or later) were identified from 2013 and subsequently followed up from January 1, 2014, to the development of advanced CKD, death, loss to follow-up, or end of the study period (December 31, 2017), whichever came first. Diagnostic, procedure, and diagnosis-related group codes were used to identify cerebral palsy, incident cases of advanced CKD, comorbid intellectual disability, and 10 preexisting medical conditions.

Exposures: Demographic variables and 10 preexisting medical conditions: CKD stages 1-3, hypertension, diabetes, heart and cerebrovascular disease, non-CKD urologic conditions, bowel conditions, respiratory disease, skeletal fragility, arthritis, and dysphagia.

Outcome: Incidence of advanced CKD.

Analytic Approach: Crude incidence rate (IR) of advanced CKD and IR ratios with 95% CIs were estimated. Cox proportional hazards regression models that were adjusted for demographics, intellectual disability, and preexisting medical conditions were used to evaluate the adjusted independent effect of predictor variables.

Results: 237 of the 8,011 adults with cerebral palsy developed advanced CKD during follow-up (IR, 10.16/1,000 person years; 95% CI, 8.87-11.46). In the crude analysis, all preexisting medical conditions were associated with an elevated IR and IR ratio of advanced CKD. In the fully adjusted Cox proportional hazards regression model, the HR was elevated for older age, CKD stages 1-3 (HR, 3.32; 95% CI, 2.39-4.61), diabetes (HR, 2.69; 95% CI, 2.03-3.57), hypertension (HR, 1.54; 95% CI, .10-2.16), heart and cerebrovascular disease (HR, 1.53; 95% CI, 1.12-2.07), and non-CKD urologic conditions (HR, 1.39; 95% CI, 1.05-1.84).

Limitations: Private insurance database, short follow-up period, and lack of laboratory values, such as albuminuria/proteinuria.

Conclusions: Advanced CKD was common among adults with cerebral palsy and its development was associated with both traditional and nontraditional urologic risk factors.

Cerebral palsy results from damage to or malformation of the developing brain and is the most common physical disability of childhood.[1] Children with cerebral palsy encounter several problems relating to health and function, affecting neuromuscular,[2] musculoskeletal,[3,4] and other physiologic systems.[5] These problems can increase in severity as they transition into and throughout their adult years.[6-9] As a consequence, individuals with cerebral palsy have increased risk for the early development of chronic diseases (eg, cardiometabolic and musculoskeletal) compared with the general population.[7,8,10] This represents a public health issue because the adult population with cerebral palsy is expanding due to improved survival rates[11] and a stable or marginally increased prevalence of cerebral palsy[12] during recent decades. The growing life span and early development of chronic diseases in this population increases the risk for chronic kidney disease (CKD) and accelerated CKD progression to advanced stages (ie, stage ≥4).

A recent report suggests that the incidence of advanced CKD is 72% higher for adults with versus without cerebral palsy after adjusting for cardiometabolic diseases,[13] which are well-established risk factors for CKD.[14] The findings suggest that there may be other factors in addition to cardiometabolic diseases that increase the risk for advanced CKD specific to adults with cerebral palsy. Because advanced CKD is irreversible, costly, and fatal,[15] preventing the onset of CKD or slowing CKD progression to advanced stages is critical to improve healthful aging for adults with cerebral palsy and to mitigate the attributable medical and societal cost burden. Identifying risk factors for advanced CKD specific to adults with cerebral palsy may provide unique opportunities for intervention.

Individuals with cerebral palsy experience an array of medical complications that may be involved in the pathogenesis of decreased kidney function through direct or indirect mechanisms. Cardiometabolic diseases are nearly 3-fold more prevalent among young adults with versus

PLAIN-LANGUAGE SUMMARY

Emerging evidence suggests that adults with cerebral palsy have an elevated risk for developing advanced stages of chronic kidney disease (CKD). To date, very little is known about risk factors for advanced CKD or other pathogenic mechanisms leading to decreased kidney function for the population with cerebral palsy. This claims-based study of 8,011 privately insured adults with cerebral palsy found that traditional CKD risk factors (eg, hypertension, diabetes, and cardiovascular disease) and urologic conditions were associated with elevated risk for advanced CKD. Clinicians treating adult patients with cerebral palsy should be aware of the greater and earlier risk for advanced CKD and consider monitoring and testing for kidney function when their patient has traditional CKD risk factors or urologic conditions.

without cerebral palsy.[8] Non-CKD urologic (eg, neurogenic bladder) and bowel conditions (eg, constipation) are common among individuals with cerebral palsy,[16,17] which can result in recurrent infections and kidney deterioration over time.[18] Respiratory disease is associated with a 14-fold increased risk for mortality among adults with cerebral palsy[19] and increased risk for CKD among adults without cerebral palsy.[20] Skeletal fragility, defined as low bone mass or nontraumatic fracture, is present in almost half the adults with cerebral palsy 18 years or older.[7] A recent study found that skeletal fragility increased the risk for cardiovascular disease among adults with versus without cerebral palsy,[21] which may accelerate the pathologic process driving CKD. Arthritis is more prevalent among adults with versus without cerebral palsy[8,22] and is associated with CKD among adults without cerebral palsy.[23] Moreover, intellectual disability is present in ~45% of individuals with cerebral palsy, which can increase the medical complexity for the individual,[24] and dysphagia is present in up to 85% of children with cerebral palsy,[25] which can lead to kidney damage through poor nutrition and chronic dehydration.

By determining whether medical conditions common to cerebral palsy are risk factors for advanced CKD, interventions can be developed to target these risk factors with the goal of preventing or mitigating CKD progression to advanced stages, such as exercise or improved medication prescription regimens. Accordingly, the objective of this study was to determine whether commonly known medical conditions for CKD (eg, cardiometabolic diseases) and other medical conditions common to cerebral palsy (eg, skeletal fragility and dysphagia) are associated with a higher incidence of advanced CKD among adults with cerebral palsy.

METHODS

Data Source

We obtained data from 2013 to 2017 from the Optum Clinformatics Data Mart Database (OptumInsight Inc), which is a national single private payer administrative claims database containing information from privately insured or Medicare Advantage members, as previously described.[26] To be enrolled in a private payer health plan, beneficiaries of any age, income, or disability status either pay for coverage or are covered through their employer. Administrative claims data are primarily used for billing reimbursement purposes, and health conditions (eg, CKD) are identified using specific codes attached to individual claims, which can be examined longitudinally as long as beneficiaries remain on their insurance plan.

Data are deidentified and the institutional review board deemed this study as nonregulated (IRB approval #: HUM00158800); therefore, the need for informed consent was waived.
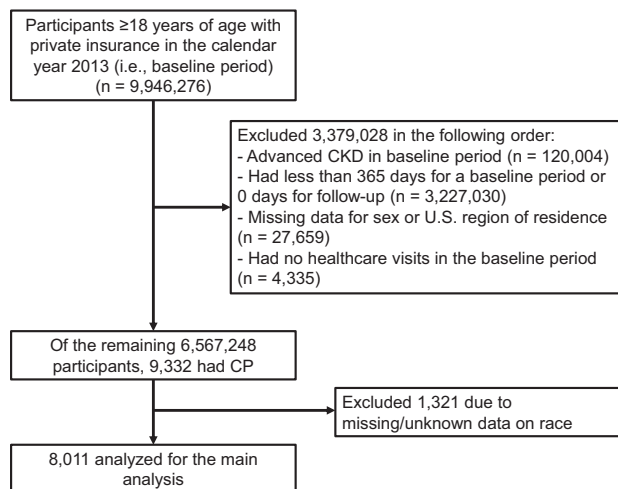
Sample Selection

The full calendar year 2013 was used to identify eligible participants: adults 18 years or older with cerebral palsy, complete data for race, without advanced CKD, continuous enrollment in a health plan, and had 1 or more service utilization, to limit detection bias due to failure of CKD detection among persons who were not seen by a clinician (Fig 1).[13] Participants were followed up from January 1, 2014, to advanced CKD, death, loss to follow-up, or end of the study period, December 31, 2017.

Cerebral palsy was identified using the *International Classification of Diseases, Ninth Revision* (ICD-9), Clinical Modification codes 343.x and 333.71. Information regarding the severity of cerebral palsy using clinical measures (eg, gross motor function classification system) are not available in claims data and >70% had "other" or "unspecified" cerebral palsy.[10] Thus, this disallows stratification or statistical adjustment for the clinical subtypes of cerebral palsy.

Outcome Measure

The outcome measure was the occurrence of new advanced CKD from January 1, 2014, to December 31, 2017. We defined advanced CKD in part using the procedures by the US Renal Data System for identifying end-stage kidney disease within the Optum Clinformatics Data Mart Database[27] and adding ICD-9 and *ICD, Tenth Revision* (ICD-10) codes (due to a shift in reporting ICD codes on October 1, 2015) to identify new CKD at stage 4 or later when first identified.[13] Specifically, advanced CKD was identified as ICD codes for CKD stage 4 (ICD-9: 585.4; ICD-10: N18.4), stage 5 (ICD-9: 585.5; ICD-10: N18.5), or end-stage kidney disease (ICD-9: 585.6; ICD-10: N18.6); procedure codes for dialysis in the outpatient setting; and diagnosis-related group codes for kidney transplantation surgery (see Table 10.1 for procedure and diagnosis-related group codes in "CKD Analytical Methods" in

Figure 1. Flow chart describes the sample selection process. Abbreviations: CKD, chronic kidney disease; CP, cerebral palsy.

reference 29). Using administrative claims data to identify advanced CKD has shown up to 67% sensitivity, 95% specificity, and 76% to 97% positive predictive value.[28,29]

Predictor Variables

Variables were selected based on their relevance to cerebral palsy, CKD, and availability and reliability of coding in the claims database. Demographic variables included age, sex, race, US region of residence, and comorbid intellectual disability (ICD-9: 317-319). Because lifestyle factors are not available (eg, physical activity) or reliably coded (eg, wheelchair, smoking, and weight) in claims databases to use for research, this study examined preexisting medical conditions as risk factors, which are proxy variables for lifestyle factors. Given the paucity of work on this topic resulting in very little knowledge for this population, we grouped medical conditions to represent biological systems to provide direction for future study. Preexisting medical conditions (yes/no) were identified using 2 or more medical claims in the calendar year 2013,[30,31] including CKD stages 1-3 (ICD-9: 585.1-3). hypertension (ICD-9: 401-405.x), diabetes (ICD-9: 249.x, 250.x), heart and cerebrovascular disease (ICD-9: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 410-414.x, 428.x, and 430-437.x), non-CKD urologic conditions (ICD-9: 580-584.x, and 587-599.x), bowel conditions (ICD-9: 564.0, 564.1, and 564.81), respiratory disease (ICD-9: 461-466.x, 480-486.x, 490-496.x, and 510-519.x), skeletal fragility (ICD-9: 733.0, 733.1, and 800-829.x without trauma codes E800-849.x), arthritis (ICD-9: 714.x and 715.x), and dysphagia (ICD-9: 787.2x).

Statistical Analysis

Baseline descriptive characteristics were summarized for the entire sample. The crude incidence rate (IR) of advanced CKD was estimated as the number of outcome events divided by the number of person-years and expressed per 1,000 person-years. Crude IR ratio (IRR and 95% confidence interval [CI]) was estimated for each variable (the crude IRR is a numerical approximation of the unadjusted hazard ratio [HR]).

Cox proportional hazards regression adjusted for all predictor variables in a single model to evaluate the adjusted independent effect (as HRs) for each of the predictor variables with advanced CKD as the outcome. We assessed clinically relevant interaction effects for age, sex, and race, as well as between age, sex, and race with each of the preexisting medical conditions by including the product terms in separate Cox proportional hazards regression models. If the interaction was statistically significant, subsequent analyses were considered with stratification on one of the variables included in the interaction. The proportional hazards assumption was met for all analyses. Participants were right censored if they died or were lost to follow-up before acquiring advanced CKD or if they did not have advanced CKD by the end of the study period.

Sensitivity Analysis

We excluded individuals who had missing data for race for the primary analysis (n = 1,321; 14.2% of cerebral palsy sample). We therefore conducted 2 related sensitivity analyses using the fully adjusted Cox proportional hazards regression models to assess possible confounding and selection bias for the association of predictor variables with advanced CKD incidence. Sensitivity analysis 1 involved the same sample as the primary analysis but did not adjust for race. Sensitivity analysis 2 involved the full study sample without restriction based on race (n = 9,332) and without adjusting for race. Results were compared from sensitivity analysis 1 and the primary analysis to assess possible confounding by race. Results were also compared from sensitivity analyses 1 and 2 to assess possible selection bias from exclusion of adults without race data.

Competing-risk analysis was performed on the unadjusted and fully adjusted models to determine whether mortality was a competing event for the associations in the primary analysis. For the unadjusted model, the SAS macro %CIF[32] was used with advanced CKD as the primary event, death as the competing event, and all others censored. Gray test for equality of cumulative incidence functions[33] was examined for each predictor variable separately, and χ^2 and P value were compared with the Cox proportional hazards regression values. For the fully adjusted model, we used the subdistribution hazard model proposed by Fine and Gray.[34] The Fine and Gray approach examines the outcome of interest (ie, advanced CKD) while accounting for the competing event (ie, mortality) and adjusting for covariates and models the hazards on the premise of the cumulative incidence function.[35]

Analyses were performed using SAS, version 9.4 (SAS Institute). P≤0.05 (2 tailed) was considered statistically significant.

RESULTS

Baseline descriptive characteristics of adults with cerebral palsy (n = 8,011) are presented in Table 1. During follow-up for a mean of 1,062 ± 497 days and median of 1,460 (interquartile range, 607-1,460) days, 237 adults with cerebral palsy developed advanced CKD (IR, 10.16 per 1,000 person years; 95% CI, 8.87-11.46), which is considerably higher than the IR of 6.24 (95% CI, 6.20-6.28) of advanced CKD among adults without cerebral palsy or other neurodevelopmental disabilities using the same methodology.[13] During follow-up, 3,566 were right censored due to death (n = 296) or health plan disen-rollment (n = 3,270) before acquiring advanced CKD and the end of the study period.

Crude IR of Advanced CKD

The crude IR of advanced CKD increased with older age, from 3.40 per 1,000 person-years (95% CI, 2.32-4.48) among 18 to 50 year olds to 29.04 per 1,000 person-years (95% CI, 19.68-38.39) among those 80 years and older (Table 2). The crude IR of advanced CKD was not different between women or men and was highest among Hispanic individuals (IR, 13.96; 95% CI, 9.12-18.80). The crude IR of advanced CKD was higher for adults without versus with comorbid intellectual disability. Of the preexisting medical conditions, CKD stages 1-3 (IR, 53.77; 95% CI, 39.93-67.60), diabetes (IR, 34.88; 95% CI, 28.47-41.28), and heart and cerebrovascular disease (IR, 32.20; 95% CI, 25.58-38.81) had the highest crude IRs of advanced CKD.

Crude IRR of Advanced CKD

The crude IRR was elevated for each age group compared with 18 to 50 year olds, Hispanics compared with whites, and Northeast compared with all other regions, and lower for those with versus without comorbid intellectual disability (Table 2). The crude IRR was elevated for those with versus without each of the preexisting medical conditions, with CKD stages 1-3, diabetes, hypertension, heart and cerebrovascular disease, and non-CKD urologic conditions having the highest relative crude rate of advanced CKD.

Adjusted HR of Advanced CKD

After adjusting for all predictor variables, the HR was elevated for older age, CKD stages 1-3 (HR, 3.32; 95% CI, 2.39-4.61), diabetes (HR, 2.69; 95% CI, 2.03-3.57), hypertension (HR, 1.54; 95% CI, 1.10-2.16), heart and cerebrovascular disease (HR, 1.53; 95% CI, 1.12-2.07), and non-CKD urologic conditions (HR, 1.39; 95% CI, 1.05-1.84; Table 2).

Sensitivity Analyses

A comparison of HR estimates from sensitivity analysis 1 and the primary analysis show similar results (Table 3), suggesting that race is not a confounder in the primary analysis. A comparison of HR estimates from sensitivity analyses 1 and 2 show similar results for all predictor

Table 1. Baseline Descriptive Characteristics Among Adults With Cerebral Palsy by Status of Incident Advanced CKD

	Entire Sample
Sample size	8,011
Age, y	49.4 ± 19.9
18-50 y	3,910 (48.8%)
51-60 y	1,462 (18.3%)
61-70 y	1,312 (16.4%)
71-80 y	869 (10.9%)
>80 y	458 (5.7%)
Sex	
Women	3,999 (49.9%)
Men	4,012 (50.1%)
Race	
White	6,103 (76.2%)
Black	920 (11.5%)
Hispanic	748 (9.3%)
Asian	240 (3.0%)
US region	
West	2,023 (25.3%)
Midwest	2,052 (25.6%)
South	2,957 (36.9%)
Northeast	979 (12.2%)
Intellectual disability	1,628 (20.3%)
Preexisting medical conditions	
CKD 1-3	336 (4.2%)
Hypertension	2,793 (34.9%)
Diabetes	1,152 (14.4%)
Heart and cerebrovascular disease	1,032 (12.9%)
Urologic conditions, non-CKD	1,499 (18.7%)
Bowel conditions	579 (7.2%)
Respiratory disease	1,938 (24.2%)
Skeletal fragility	816 (10.2%)
Arthritis	830 (10.4%)
Dysphagia	496 (6.2%)

Note: Data for categorical variables expressed as number (percent).
Abbreviation: CKD, chronic kidney disease.

variables, except that sensitivity analysis 2 had a higher HR for sex and lower HR for US region of residence. However, these differences were modest and did not change any of the conclusions drawn from the primary analysis of the main exposure variable results, suggesting little evidence of selection bias.

Treating mortality as a competing event resulted in the same conclusions as the primary analysis regarding associations between predictor variables with incidence of advanced CKD for the unadjusted and fully adjusted models (Table 4).

DISCUSSION

Advanced CKD was relatively common among adults with cerebral palsy and associated with both traditional CKD risk factors and the presence of urologic disease. Specifically, after adjusting for all predictor variables, the HR for all preexisting medical conditions remained elevated for most

Table 2. Crude IR and IRR and Adjusted HR for Incidence of Advanced CKD Among Adults With Cerebral Palsy

	Advanced CKD Cases	Crude IR (95% CI)	Crude IRR (95% CI)	Adjusted[a] HR (95% CI)
Age				
18-50 y	38	3.40 (2.32, 4.48)	Reference	Reference
51-60 y	41	9.25 (6.42-12.08)	2.72 (1.75-4.23)	1.68 (1.06-2.68)
61-70 y	64	16.59 (12.53-20.66)	4.88 (3.27-7.29)	2.24 (1.43-3.51)
71-80 y	57	22.14 (16.40-27.89)	6.51 (4.32-9.82)	2.26 (1.40-3.64)
>80 y	37	29.04 (19.68-38.39)	8.54 (5.43-13.43)	2.49 (1.45-4.27)
Sex				
Women	114	9.71 (7.92-11.49)	Reference	Reference
Men	123	10.63 (8.75-12.51)	1.09 (0.85-1.41)	1.16 (0.89-1.50)
Race				
White	165	9.32 (7.90-10.75)	Reference	Reference
Black	33	12.49 (8.23-16.75)	1.34 (0.92-1.95)	1.09 (0.74-1.60)
Hispanic	32	13.96 (9.12-18.80)	1.50 (1.03-2.19)	1.18 (0.80-1.74)
Asian	<10	10.16 (2.63-17.68)	1.09 (0.51-2.32)	0.99 (0.46-2.13)
US region				
West	67	10.81 (8.22-13.40)	Reference	Reference
Midwest	42	7.39 (5.16-9.63)	0.67 (0.46-0.99)	0.96 (0.64-1.43)
South	83	9.55 (7.50-11.61)	0.88 (0.64-1.21)	1.04 (0.74-1.45)
Northeast	45	16.34 (11.57-21.12)	1.50 (1.03-2.19)	1.34 (0.91-1.98)
Intellectual disability				
Without	202	10.92 (9.41-12.42)	Reference	Reference
With	35	7.26 (4.86-9.67)	0.67 (0.46-0.95)	1.21 (0.83-1.77)
Preexisting medical conditions				
CKD 1-3				
Without	179	6.85 (5.85-7.86)	Reference	Reference
With	58	53.77 (39.93-67.60)	7.85 (5.83-10.55)	3.32 (2.39-4.61)
Hypertension				
Without	69	4.54 (3.47-5.61)	Reference	Reference
With	168	20.70 (17.57-23.83)	4.56 (3.45-6.04)	1.54 (1.10-2.16)
Diabetes				
Without	123	6.13 (5.05-7.22)	Reference	Reference
With	114	34.88 (28.47-41.28)	5.69 (4.41-7.34)	2.69 (2.03-3.57)
Heart and cerebrovascular disease				
Without	146	7.12 (5.97-8.28)	Reference	Reference
With	91	32.20 (25.58-38.81)	4.52 (3.48-5.87)	1.53 (1.12-2.07)
Urologic conditions, non-CKD				
Without	149	7.77 (6.53-9.02)	Reference	Reference
With	88	21.18 (16.75-25.61)	2.72 (2.09-3.55)	1.39 (1.05-1.84)
Bowel conditions				
Without	211	9.74 (8.43-11.05)	Reference	Reference
With	26	15.71 (9.67-21.75)	1.61 (1.07-2.42)	1.24 (0.82-1.89)
Respiratory disease				
Without	162	9.08 (7.69-10.48)	Reference	Reference
With	75	13.67 (10.57 16.76)	1.50 (1.14-1.98)	1.04 (0.78-1.39)
Skeletal fragility				
Without	202	9.62 (8.30-10.95)	Reference	Reference
With	35	15.03 (10.05-20.02)	1.56 (1.09-2.24)	1.09 (0.76-1.58)
Arthritis				
Without	184	8.79 (7.52-10.06)	Reference	Reference
With	53	22.24 (16.25-28.23)	2.53 (1.86-3.43)	1.35 (0.98-1.86)
Dysphagia				
Without	212	9.62 (8.32-10.91)	Reference	Reference
With	25	19.66 (11.96-27.37)	2.05 (1.35-3.10)	1.13 (0.73-1.73)

Note: n = 8,011.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio.
[a]Adjusted for all variables in this table.

Table 3. Sensitivity Analysis: Adjusted HR of Advanced CKD for Individuals With And Without Complete Data for Race

	Sensitivity Analysis 1 (n = 8,011)	Sensitivity Analysis 2 (n = 9,332)
	HR (95% CI)	HR (95% CI)
Age		
18-50 y	Reference	Reference
51-60 y	1.67 (1.05-2.65)	1.63 (1.05-2.529)
61-70 y	2.22 (1.42-3.46)	2.42 (1.60-3.65)
71-80 y	2.24 (1.39-3.61)	2.38 (1.53-3.71)
>80 y	2.44 (1.43-4.19)	2.63 (1.60-4.31)
Sex		
Women	Reference	Reference
Men	1.16 (0.89-1.50)	1.25 (0.99-1.59)
US region		
West	Reference	Reference
Midwest	0.94 (0.64-1.40)	0.82 (0.58-1.18)
South	1.04 (0.75-1.45)	0.91 (0.67-1.22)
Northeast	1.33 (0.90-1.97)	1.11 (0.78-1.59)
Intellectual disability		
Without	Reference	Reference
With	1.21 (0.83-1.77)	1.17 (0.82-1.66)
CKD 1-3		
Without	Reference	Reference
With	3.34 (2.41-4.64)	3.30 (2.45-4.44)
Hypertension		
Without	Reference	Reference
With	1.55 (1.11-2.17)	1.63 (1.19-2.22)
Diabetes		
Without	Reference	Reference
With	2.73 (2.06-3.61)	2.54 (1.97-3.28)
Heart and cerebrovascular disease		
Without	Reference	Reference
With	1.52 (1.12-2.07)	1.48 (1.12-1.95)
Urologic conditions, non-CKD		
Without	Reference	Reference
With	1.39 (1.05-1.84)	1.36 (1.05-1.76)
Bowel conditions		
Without	Reference	Reference
With	1.25 (0.82-1.89)	1.31 (0.90-1.92)
Respiratory disease		
Without	Reference	Reference
With	1.04 (0.78-1.39)	1.16 (0.90-1.51)
Skeletal fragility		
Without	Reference	Reference
With	1.09 (0.76-1.58)	0.99 (0.70-1.40)
Arthritis		
Without	Reference	Reference
With	1.35 (0.98-1.87)	1.30 (0.97-1.75)
Dysphagia		
Without	Reference	Reference
With	1.12 (0.73-1.73)	1.14 (0.78-1.69)

Note: HRs adjusted for all variables in this table. Sensitivity analysis 1, adults with cerebral palsy who had complete data for race. Sensitivity analysis 2, adults with cerebral palsy unrestricted to complete race data.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

conditions, but only CKD stages 1-3, cardiometabolic diseases, and non-CKD urologic conditions had statistically and largely elevated HRs, suggesting that these medical conditions are robust risk factors for advanced CKD. Importantly, these medical conditions can be prevented, treated, and properly managed in the clinical setting.

Table 4. Sensitivity Analysis: Mortality as a Competing Event for the Association Between Predictor Variables and Advanced CKD

	Adjusted Model[a] From Main Analysis	Adjusted Model[a]
	Mortality as a Censored Event	Mortality as a Competing Event
	HR (95% CI)	HR (95% CI)
CKD 1-3	3.32 (2.39-4.61)	3.30 (2.35-4.64)
Hypertension	1.54 (1.10-2.16)	1.56 (1.09-2.24)
Diabetes	2.69 (2.03-3.57)	2.59 (1.93-3.48)
Heart and cerebrovascular disease	1.53 (1.12-2.07)	1.52 (1.08-2.14)
Urologic conditions, non-CKD	1.39 (1.05-1.84)	1.40 (1.07-1.84)
Bowel conditions	1.24 (0.82-1.89)	1.22 (0.79-1.88)
Respiratory disease	1.04 (0.78-1.39)	1.01 (0.75-1.36)
Skeletal fragility	1.09 (0.76-1.58)	1.05 (0.72-1.53)
Arthritis	1.35 (0.98-1.86)	1.33 (0.95-1.86)
Dysphagia	1.13 (0.73-1.73)	1.06 (0.68-1.65)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.
[a]Adjusted for age, sex, race, US region of residence, and all variables in this table.

Future studies are needed to determine whether better clinical management of these medical conditions can reduce or delay the risk for CKD development or progression to advanced stages for adults with cerebral palsy.

The lack of association for respiratory disease in the primary analysis may be due to the more global approach of how this disease category was examined, thus not allowing for identifying the association of specific respiratory diseases (eg, neuromuscular respiratory failure) that may be more relevant to cerebral palsy. The lack of association for skeletal fragility may be due to underdetection and underdiagnosis of osteoporosis. Consistent with the general population,[14] CKD stages 1-3 and cardiometabolic diseases had the highest adjusted HRs (HRs, 1.62-3.32). We also found that non-CKD urologic conditions possessed a considerably high HR of 1.39. However, this variable consisted of several and different types of urologic conditions.

Because very little research has been done to date regarding risk factors for advanced CKD among adults with cerebral palsy, this study was focused on identifying general biological systems that may be associated with advanced CKD risk. Future studies are needed to identify the association between specific non-CKD urologic conditions with CKD risk for adults with cerebral palsy. For example, a recent study found that congenital anomalies of the kidney and urinary tract, glomerular disease, and pyelonephritis in childhood were associated with a substantially increased risk for end-stage kidney disease in adulthood.[36] Taken together, these findings suggest that CKD stages 1-3, these cardiometabolic diseases, and non-CKD urologic conditions are robust risk factors for advanced CKD for adults with cerebral palsy.

In contradiction to the general population,[14] sex and race were not associated with incident advanced CKD among our sample of adults with cerebral palsy. In the general population, women have greater risk for CKD at earlier stages than men,[14] but men with CKD are more likely than women with CKD to progress to advanced stages of CKD and death.[37] The reason(s) for the lack of robust associations between advanced CKD with sex and race is not clear. A possible explanation is that the physiologic, socioeconomic, and health differences between sex strata and the socioeconomic and health differences between race strata that are associated with CKD risk may be less disparate under the context of cerebral palsy, possibly due to the burden of unhealthful aging associated with cerebral palsy.[10]

Moreover, comorbid intellectual disability was not associated with incident advanced CKD. In our previous study,[13] we found that adults with intellectual disabilities had an 88% higher adjusted rate of advanced CKD compared with adults without neurodevelopmental disabilities. Although our previous study suggests that advanced CKD risk is similarly elevated for adults with intellectual disabilities compared with adults with cerebral palsy, the current investigation suggests that the comorbid condition of intellectual disabilities may not be an additive burden for advanced CKD risk among adults with cerebral palsy. However, findings were derived from privately insured adults with cerebral palsy, which reflects a healthier segment of the cerebral palsy population.[38,39] This is evidenced by the lower than expected prevalence of intellectual disabilities found in this study (20.3%) compared with a population-based study of cerebral palsy (45%).[24] Therefore, generalizability may be limited to the healthier segment of the cerebral palsy population.

It is important to note that this study is limited by restrictions of administrative claims data. Although administrative codes to identify CKD are highly specific, sensitivity may be reduced in the cerebral palsy population given the reliance of estimated glomerular filtration rate calculation and CKD staging on serum creatinine level, which may be reduced in individuals with cerebral palsy due to the low muscle mass. We therefore selected more advanced stages of CKD for the outcome to limit this bias, which is also consistent with our previous study.[13] Thus, our estimates of the incidence of advanced CKD in the cerebral palsy population may be conservative. Administrative claims data also limit the ability to examine the full set of risk factors for advanced CKD, in part due to statistical considerations given the low number of outcome events and lack of representative codes for some risk factors. There are neurologic conditions other than intellectual disabilities that are often comorbid with cerebral palsy and may be associated with advanced CKD risk (eg, epilepsy).

It is not uncommon for adults with cerebral palsy to be prescribed several medications, which may affect kidney function. For example, chronic pain is highly prevalent for individuals with cerebral palsy and is more common among adults with versus without cerebral palsy.[10] Commonly used pain medications are recognized as nephrotoxic agents, including nonsteroidal anti-inflammatory drugs. Because the kidneys are involved in filtering blood, a complicated physiologic environment due to various medications, concomitant with unique drug-drug interactions, could lead to unintended kidney toxicity and organ damage.

In addition to examining a small set of potential risk factors for advanced CKD, we were unable to determine the association of advanced CKD incidence with lifestyle (eg, diet and activity), substance abuse, socioeconomic status (eg, income and education), or cerebral palsy characteristic (eg, severity and type) factors, which may be involved in CKD progression for adults with cerebral palsy. The examined variables were binary, which limits casual inference and loses information regarding how the severity of these conditions affects the outcome.

The sample likely reflects a healthier sector of the cerebral palsy population, which may dilute the strength of the associations examined in this study. Study conclusions should be considered within the scope of this particular population of privately insured adults with cerebral palsy. Further, the validity of using the cerebral palsy codes to detect individuals with cerebral palsy in administrative claims is unknown. Finally, laboratory values are not available in claims data, such as creatinine, cystatin C, or albuminuria/proteinuria, which could provide more insight into kidney function.

In conclusion, CKD stages 1-3, cardiometabolic diseases, and non-CKD urologic conditions are robust risk factors for advanced CKD among adults with cerebral palsy, whereas the presence of other preexisting medical conditions showed evidence of eliciting greater risk for advanced CKD, such as arthritis, bowel conditions, and dysphagia. Future research is needed to determine whether preventing, treating, or better managing these risk factors in adults with cerebral palsy offsets the CKD trajectory.

ARTICLE INFORMATION

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Adults with cerebral palsy: What predisposes to worsening kidney function?

Kidney Medicine

Methods and Cohort

Retrospective observational study
Data from Optum Clinformatics® Data Mart Database

Adults (aged ≥18 years)
N = 8011

With
Cerebral palsy

Without
Severe CKD
(eGFR > 30 at start)

Median follow-up
4 years

Outcome studied: Worsening of kidney function, defined as

eGFR decreasing to ≤30   **OR**   Dialysis   **OR**   Transplantation

Findings

Worsening kidney function was frequent
n = 237
(10.16 per 1000 person years)

⚠ Worsening kidney function was associated with:

Previous CKD 1-3
HR 3.32
(2.39–4.61)

Diabetes
HR 2.69
(2.03-3.57)

Increasing age
HR 1.68-2.49
(varies with age decile)

Hypertension
HR 1.54
(1.10-2.16)

Heart / Vascular disease
HR 1.53
(1.12-2.07)

Urological Conditions
HR 1.39
(1.05-1.84)

Conclusion: Advanced CKD is common among adults with cerebral palsy, and its development is associated with both traditional kidney disease risk factors and with urological risk factors.

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