Polypharmacy is a risk factor for mortality, severe chronic kidney disease, and liver disease among privately insured adults with cerebral palsy

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What is already known about this subject

- Adults with cerebral palsy (CP) have an early development of chronic kidney disease (CKD), liver disease, and premature mortality as compared with the general population.
- Adults with CP have an increased risk for polypharmacy (≥ 5 medications) and hyperpolypharmacy (≥ 10 medications) compared with the general population.

What this study adds

- Polypharmacy and hyperpolypharmacy are robust risk factors for mortality and incidence of severe stages of CKD (stage IV+) and liver disease among privately insured adults with CP across the adult lifespan.
- The effect of polypharmacy and hyperpolypharmacy on risk for outcomes was present even after accounting for demographics, comorbid neurodevelopmental disabilities, and multimorbidity.
- Incidence of severe CKD and liver disease mediates a small, but clinically significant, portion of the association between polypharmacy with liver disease (severe CKD as mediator) and severe CKD (liver disease as mediator).

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ABSTRACT

BACKGROUND: Adults with cerebral palsy (CP) have an increased risk for polypharmacy, premature mortality, and early development of several morbidities, including conditions associated with excess medication exposure, such as chronic kidney disease (CKD) and liver disease. To date, very little is known about the consequence of polypharmacy for adults with CP.

OBJECTIVE: To determine if polypharmacy is associated with an increased risk for mortality, severe CKD, and liver disease among adults with CP, before and after adjusting for comorbid neurodevelopmental disabilities (NDDs) and multimorbidity.

METHODS: This is an exploratory treatment effectiveness study. Data from the Optum Clinformatics Data Mart were used for this retrospective cohort study. Adults aged 18 years or older with a diagnosis of CP and without severe CKD (stages IV+) and liver disease were identified from the calendar year 2013 and were subsequently followed from January 1, 2014, to death, severe CKD, liver disease, loss to follow-up, or end of study period (December 31, 2017). Diagnosis codes were used to identify NDDs (intellectual disabilities, epilepsy, autism spectrum disorders, spina bifida) and 24 relevant morbidities at baseline (i.e., calendar year 2013). Polypharmacy was defined as ≥ 5 medications and hyperpolypharmacy was defined

as ≥ 10 medications at baseline. Cox regression models were developed to examine the association (as HR and 95% CI) between polypharmacy and hyperpolypharmacy with mortality, severe CKD, and liver disease separately, before and after adjusting for covariates (demographics, NDDs, multimorbidity). Exploratory analyses examined the mediating effect of incident severe CKD or liver disease on the association between the exposure (polypharmacy or hyperpolypharmacy) on outcomes.

RESULTS: Of the 9,238 adults with CP, 58.5% had polypharmacy and 29.5% had hyperpolypharmacy. The fully adjusted HR for mortality was 2.14 (95% CI=1.59-2.89) for

polypharmacy and 1.65 (95% CI=1.31-2.09) for hyperpolypharmacy. The fully adjusted HR for severe CKD was 1.66 (95% CI=1.17-2.36) for polypharmacy and 1.67 (95% CI=1.27-2.19) for hyperpolypharmacy. The fully adjusted HR for liver disease was 1.57 (95% CI=1.27-1.94) for polypharmacy and 1.72 (95% CI=1.42-2.08) for hyperpolypharmacy. Incident liver disease mediated 5.37% (polypharmacy) and 7.54% (hyperpolypharmacy) of the association between the exposure with incident severe CKD for nonelderly (aged <65 years), while incident severe CKD mediated 7.05% (polypharmacy) and 6.64% (hyperpolypharmacy) of the association between the exposure with incident liver disease for elderly (aged ≥65 years).

CONCLUSIONS: Polypharmacy and hyperpolypharmacy are robust risk factors for risk of mortality, severe CKD, and liver disease among privately insured adults with CP. While incidence of severe CKD and liver disease had negligible effects on the association between polypharmacy with mortality, there is evidence that they mediate a considerable portion of one another and require further examination.

Cerebral palsy (CP) is a neurological syndrome that results from damage to or malformation of the developing brain, and is the most common physical disability of childhood.¹ Children with CP often experience several complications regarding health and function, including low physical activity levels, underdeveloped and weak muscles and bones,^{2,3} excess body fat in the abdominal and musculoskeletal depots,²⁻⁵ communication impairments, and mental health disorders.⁶ Having health and function complications in childhood increases risk for early development of chronic diseases, other medical health problems (e.g., depression, anxiety),⁷⁻¹⁰ and premature mortality as individuals with CP age into their adult years.^{11,12} For example, the prevalence of multimorbidity is more than 3-fold higher for young adults (aged 18-30 years) with versus without CP.⁷

Polypharmacy (use of ≥5 drugs at a given time) and hyperpolypharmacy (use of ≥10 drugs at a given time) is often studied in the geriatric population.^{13,14} However, polypharmacy and hyperpolypharmacy may be common for individuals with CP across the adult lifespan to manage their greater morbidity-related burden. Polypharmacy for adults with CP may be further complicated by the presence of other neurodevelopmental disabilities (NDDs), as intellectual disabilities, epilepsy, autism spectrum disorders, and spina bifida can be comorbid with CP and are themselves associated with high medication use.^{1,15} Indeed, we have recently reported that adults aged ≥18 years with CP only and with CP and other NDDs (CP+NDDs) were 38% and 142%, respectively, more likely to have polypharmacy,

and 38% and 112%, respectively, more likely to have hyperpolypharmacy as compared with adults without CP after adjusting for demographics and multimorbidity.¹⁶ We also reported that patients with CP aged 18-40 years had a similar (CP only) or higher (CP+NDDs) adjusted odds of polypharmacy compared with the geriatric (aged ≥65 years) population without CP, while the odds of polypharmacy were even higher for the middle-aged (aged 41-64 years) CP groups.¹⁶ These new findings suggest that adults with CP may be exposed to a polypharmacy-induced toxic environment (e.g., medication interactions) early in their adult lifespan.^{17,18} To date, there is little understanding of how polypharmacy or hyperpolypharmacy contributes to unhealthful aging specific to adults with CP.

Studies in non-CP populations (mostly of geriatric age) and adults aged ≥50 years with intellectual disabilities have shown that polypharmacy is a risk factor for premature mortality.¹⁹⁻²¹ The link between polypharmacy and mortality may be due to the negative effect of polypharmacy on kidney and liver health. The kidneys and liver are primarily responsible for clearance of several medications and are subject to pathophysiological decline in the presence of polypharmacy.^{22,23} Recent work has shown that adults with CP have an increased risk for severe chronic kidney disease (CKD) (stages IV+) and liver disease at younger ages compared with adults without CP.^{8,24} Importantly, severe CKD is irreversible, costly, and fatal,²⁵ and many patients with CKD will die of cardiovascular disease prior to reaching end-stage renal disease.²⁶ Both kidney and liver health for individuals with CP is a relatively unexplored field of study. It is possible that polypharmacy may be exacerbating kidney and liver function decline early in life for adults with CP, which may be contributing, in part, to the greater risk of premature mortality for this population.²⁷

A better understanding of the association between polypharmacy, severe CKD, liver disease, and mortality among adults with CP could lead to improvements in medication-prescribing strategies that balance treatment or management of health conditions while preserving kidney and liver health and prolong life. Accordingly, the objective of this study was to determine if polypharmacy is associated with an increased risk for mortality, severe CKD, and liver disease among adults with CP, beyond the effect of comorbid NDDs and multimorbidity. We also explored if incidence of severe CKD or liver disease mediated the association between polypharmacy and adverse health outcomes among adults with CP.

Methods

DATA SOURCE

Optum Clinformatics Data Mart Database (OptumInsight, Eden Prairie, MN) is a national, single, private-payer administrative claims database. The years 2013–2017 were leveraged for this retrospective cohort study. This database contains information on individuals who have either commercial or Medicare Advantage health plans and has been described previously.²⁸ Since data are deidentified, the University Institutional Review Board approved this study as nonregulated.

SAMPLE SELECTION

The methodology to acquire the sample has been described previously.²⁴ Briefly, the full calendar year 2013 was used as the baseline period to identify individuals who were aged 18 years or older with CP, did not have severe CKD or liver disease, had unbroken enrollment (i.e., continuous) in any private health plan, and had 1 or more visit to a health care provider. The requirement for one or more service utilization was to limit detection bias among individuals who were not seen by a health care provider. Participants were followed from January 1, 2014, to development of the outcome (i.e., mortality, severe CKD, or liver disease separately), death when severe CKD or liver disease was the outcome, loss to follow-up, or end of study period (December 31, 2017), whichever came first.

All baseline medical conditions (e.g., CP, NDDs, morbidities) in the year 2013 were identified using the *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* codes (ICD-9/10-CM). The outcome measures of severe CKD and liver disease from 2014–2017 used both ICD-9 and ICD-10 codes to account for the shift in reporting codes on October 1, 2015 ([Supplementary Table 1](#), available in online article).²⁴

Individuals with CP and NDDs (i.e., intellectual disabilities, epilepsy, autism spectrum disorders, spina bifida) were identified on the basis of a single claim that included 1 of the relevant ICD codes, covering all diagnostic subtypes, as previously described.²⁹ We created a binary variable to indicate the presence or absence of NDDs. Unfortunately, information regarding severity of CP using clinical measures are not available in administrative claims data. Further, more than 70% of the cohort with CP and 60% of the cohort with NDDs had an “other” or “unspecified” condition.³⁰ For these reasons, we were not able to stratify or statistically adjust for the clinical subtypes of CP or other NDDs.

OUTCOME MEASURES

One of the 3 outcome measures was incidence of severe CKD defined by at least 1 claim, as previously described.²⁴ Briefly, severe CKD included CKD at stage IV or later (i.e., end-stage renal disease), dialysis, or kidney transplant. The second outcome measure was liver disease defined by at least 1 claim, which included liver necrosis/failure, nonalcoholic chronic liver disease, nonalcoholic fibrosis/cirrhosis, biliary cirrhosis, chronic hepatitis, or “other” or “unspecified” liver disease. The final outcome measure was all-cause mortality. Studies using administrative claims data have shown up to 67% sensitivity, 95% specificity, and 76%–97% positive predictive value to identify severe CKD,^{31,32} and 98%–99% sensitivity, 91%–96% specificity, and 80% positive predictive value to identify liver disease.^{33,34}

MEDICATIONS

Prescribed medications were identified on the basis of at least 1 outpatient pharmacy claim in the baseline period and excluded vaccinations, dietary supplements, and vitamins, as previously described.¹⁶ The total number of medications were determined as the number of unique medications, based on the generic names in the database, prescribed to each individual over the 12-month period in 2013. There were 2 separate and nonmutually exclusive exposure groups performed using separate models: polypharmacy (≥ 5 medications compared with < 5 medications) and hyperpolypharmacy (≥ 10 medications compared with < 10 medications).^{13,14} This method was selected given the lack of related research attention for adults with CP to date, thus providing new information regarding the effect of various polypharmacy definitions on outcomes to inform future research and clinical practice.

MORBIDITIES

Morbidities were selected with guidance from the literature on CP, CKD, liver disease, and mortality among adults.^{7–9,11,24,35–45} We included 24 morbidities, listed in [Supplementary Table 1](#) (available in online article), which were identified on the basis of at least 1 claim on at least 2 different days in the baseline period, as this claims-based definition generally improves detection of chronic diseases.^{46,47} We then created a multimorbidity score as the sum of individual morbidities ranging from 0 to 24.

STATISTICAL ANALYSIS

Baseline descriptive characteristics were summarized. Cox regression was used to identify the association between the exposure variable (i.e., polypharmacy, hyperpolypharmacy) with the 3 outcome measures separately (i.e., mortality, severe CKD, liver disease). Three groups of covariates were

TABLE 1 Baseline Descriptive Characteristics of Study Participants with Cerebral Palsy (N = 9,238)

	n (%)	
Age, mean (SD)	49.5	(19.8)
18-50 years	48.8	(4,505)
51-60 years	18.2	(1,684)
61-70 years	16.3	(1,504)
71-80 years	10.9	(1,011)
> 80 years	5.8	(534)
Sex		
Women	49.8	(4,603)
Men	50.2	(4,635)
Race		
White	65.5	(6,052)
Black	9.8	(909)
Hispanic	7.9	(733)
Asian	2.6	(238)
Unknown/missing	14.1	(1,306)
U.S. region of residence		
West	25.9	(2,390)
Midwest	25.4	(2,343)
South	36.4	(3,363)
Northeast	12.4	(1,142)
Neurodevelopmental disabilities		
Any	25.1	(2,319)
Intellectual disabilities	10.7	(987)
Epilepsy	17.6	(1,629)
Autism spectrum disorders	2.0	(183)
Spina bifida	1.1	(98)
Polypharmacy	58.5	(5,458)
Hyperpolypharmacy	29.5	(2,750)
Multimorbidity		
0 morbidities	33.9	(3,132)
1 morbidity	25.2	(2,329)
2 morbidities	16.4	(1,518)
3 morbidities	10.0	(927)
4 morbidities	6.1	(563)
5 morbidities	3.7	(340)
6 morbidities	1.9	(172)
7 morbidities	1.2	(106)
≥ 8 morbidities	1.6	(151)

SD = standard deviation.

used: model 1—age, sex, and U.S. region of residence; model 2—model 1 covariates plus comorbid NDDs; and model 3—model 2 covariates plus multimorbidity. Clinically relevant interactions between the exposure variable with age and sex were assessed by conducting separate analyses for age or sex and including the product term in the Cox model.

SENSITIVITY ANALYSIS

Cox regression models did not adjust for race due to the extent of missing/unknown data for the race variable. We therefore conducted 2 related sensitivity analyses to assess possible confounding and selection bias, as previously described.^{24,48} Briefly, sensitivity analysis #1 involved the restricted study population with complete data on race but not adjusting for race; sensitivity analysis #2 involved the same study population in #1 but adjusted for race. The Cox regression results were compared from sensitivity analyses #1 and #2 and the main analysis to assess possible confounding by race and selection bias from exclusion of adults without race data.

Since this study was observational, results are subject to bias due to unmeasured confounding. To estimate the extent of unmeasured confounding for the main analysis, e-values were computed, which measure the minimum strength of association needed to explain away a specific exposure-outcome association, conditional on the set of covariates.⁴⁹

Competing risk analysis was performed to determine if mortality was a competing event for the association between the exposure with severe CKD and liver disease separately. For the fully adjusted Cox model, the subdistribution hazard model proposed by Fine and Gray (1999) was used.⁵⁰ The Fine and Gray approach examines the outcome of interest (i.e., severe CKD, liver disease) while accounting for the competing event (i.e., mortality) and adjusting for covariates. This approach models the hazards on the premise of the cumulative incidence function.⁵¹

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A 2-tailed P value of <0.05 was considered statistically significant.

EXPLORATORY ANALYSIS

The mediation effect of severe CKD or liver disease incidence on the association between the exposure with mortality, severe CKD (mediator, liver disease), or liver disease (mediator, severe CKD) was estimated using an SAS macro developed by Valeri and VanderWeele (2013, 2015) that allows for mediation analysis using Cox regression.^{52,53} Mediation analysis attempts to delineate the underlying mechanism between an independent (e.g., polypharmacy) and dependent (e.g., mortality) variable by a third variable,

the mediator (e.g., CKD incidence), that occurs on the timeline between the independent and dependent variable. All mediation models were adjusted for model 3 covariates described above. The assumption of a rare outcome for the mediation analyses was met.⁵³ Results from the mediation analyses are presented as hazard ratios (HRs with 95% CI) for the natural direct effect, natural indirect effect, and total effect. The natural direct effect represents the effect of the exposure variable on the outcome not through the mediator variable, and the natural indirect effect represents this effect through the mediator variable. The total effect is the total association between the exposure and outcome. From these values, the mediation proportion was estimated,⁵²⁻⁵⁴ which is the percentage of the total association mediated by the mediator.

Results

Baseline descriptive characteristics and prevalence of polypharmacy, hyperpolypharmacy, and multimorbidity for adults with CP (n=9,238) are presented in Table 1. Polypharmacy was present in 58.5% and hyperpolypharmacy was present in 29.5% of the CP sample. The prevalence of individual morbidities that make up the multimorbidity score are presented in [Supplementary Table 2](#) (available in online article). In total, 387 (4.2%) died for a mean (SD) of 1,082 (487) days of follow-up, 272 (2.9%) developed severe CKD for a mean (SD) of 1,063 (496) days of follow-up, and 586 (6.3%) developed liver disease for a mean (SD) of 1,047 (495) days of follow-up.

ASSOCIATION BETWEEN POLYPHARMACY AND HYPERPOLYPHARMACY WITH MORTALITY

The unadjusted HR for mortality was elevated for polypharmacy and hyperpolypharmacy (Table 2). While still elevated, the HR for polypharmacy and hyperpolypharmacy decreased when model 1 covariates (i.e., age, sex, U.S. region of residence) were introduced, with little change after further adjustment for comorbid NDDs (i.e., model 2). The HRs decreased after further adjustment for multimorbidity (i.e., model 3) but still remained elevated for polypharmacy and hyperpolypharmacy.

We observed a statistically significant interaction between hyperpolypharmacy with age and sex (both *P* for interaction <0.05). To enhance model parsimony, we categorized age as nonelderly (18-64 years) and elderly (≥65 years). In the fully adjusted model (age as continuous, without sex adjustment for sex-stratified analyses), the HR for mortality was elevated for hyperpolypharmacy for nonelderly (HR=1.90; 95% CI=1.29-2.79) and elderly (HR=1.55; 95% CI=1.16-2.09) groups, and for women (HR=2.10; 95% CI=1.47-2.98) and men

(1.34; 95% CI=0.97-1.85; *P*=0.076) but was more pronounced in the nonelderly group and for women.

ASSOCIATION BETWEEN POLYPHARMACY AND HYPERPOLYPHARMACY WITH SEVERE CKD INCIDENCE

The unadjusted HR for severe CKD was elevated for polypharmacy and hyperpolypharmacy (Table 3). While still elevated, the HR for polypharmacy and hyperpolypharmacy decreased when model 1 covariates were introduced, with little change after further adjustment for comorbid NDDs. The HRs decreased after further adjustment for multimorbidity but still remained elevated for polypharmacy and hyperpolypharmacy.

We observed a statistically significant interaction between polypharmacy and hyperpolypharmacy with age (both *P* for interaction <0.01). In the fully adjusted model (age as continuous), the HR for severe CKD was elevated for polypharmacy for both nonelderly (HR=2.15; 95% CI=1.20-3.86) and elderly (HR=1.39; 95% CI=0.90-2.15) groups, but the association in the elderly group was not statistically significant (*P*=0.139). The adjusted HR for severe CKD was elevated for hyperpolypharmacy for both nonelderly (HR=1.91; 95% CI=1.22-2.98) and elderly (HR=1.58; 95% CI=1.11-2.25) but was more pronounced in the nonelderly group.

ASSOCIATION BETWEEN POLYPHARMACY AND HYPERPOLYPHARMACY WITH LIVER DISEASE INCIDENCE

The unadjusted HR for liver disease was elevated for polypharmacy and hyperpolypharmacy (Table 4). While still elevated, the HR for polypharmacy and hyperpolypharmacy decreased when model 1 covariates were introduced, with little change after further adjustment for comorbid NDDs. The HRs decreased after further adjustment for multimorbidity but still remained elevated for polypharmacy and hyperpolypharmacy.

We observed a statistically significant interaction between polypharmacy and hyperpolypharmacy with age (both *P* for interaction <0.01). In the fully adjusted model (age as continuous), the HR for liver disease was elevated for polypharmacy for both nonelderly (HR=1.68; 95% CI=1.30-2.17) and elderly (HR=1.28; 95% CI=0.89-1.85) groups, but the association in the elderly group was not statistically significant (*P*=0.189). The adjusted HR for liver disease was elevated for hyperpolypharmacy for both nonelderly (HR=1.82; 95% CI=1.44-2.30) and elderly (HR=1.42; 95% CI=1.02-1.98) but was more pronounced in the nonelderly group.

TABLE 2 Cox Regression for the Association Between Polypharmacy and Hyperpolypharmacy with Mortality Among Adults with Cerebral Palsy (N=9,238)

	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Polypharmacy model				
Polypharmacy (ref: no)	3.92 (2.98-5.15)	2.85 (2.16-3.76)	2.73 (2.06-3.60)	2.14 (1.59-2.89)
Age (continuous)		1.05 (1.04-1.05)	1.05 (1.04-1.06)	1.04 (1.03-1.05)
Sex (ref: women)		1.36 (1.11-1.66)	1.35 (1.11-1.65)	1.37 (1.12-1.68)
Region of residence (ref: West)				
Midwest		1.09 (0.79-1.49)	1.08 (0.79-1.49)	1.02 (0.74-1.41)
South		1.26 (0.96-1.64)	1.27 (0.97-1.65)	1.18 (0.90-1.54)
Northeast		2.05 (1.55-2.71)	2.05 (1.55-2.71)	1.85 (1.39-2.46)
NDDs (ref: without NDDs)			1.52 (1.19-1.93)	1.41 (1.11-1.79)
Multimorbidity (ref: 0 morbidities)				
1 morbidity				0.97 (0.65-1.46)
2 morbidities				1.17 (0.78-1.75)
3 morbidities				1.57 (1.03-2.38)
4 morbidities				2.18 (1.42-3.37)
5 morbidities				2.66 (1.68-4.21)
6 morbidities				3.00 (1.77-5.07)
7 morbidities				2.55 (1.36-4.80)
≥8 morbidities				2.74 (1.58-4.75)
Hyperpolypharmacy model				
Hyperpolypharmacy (ref: no)	3.20 (2.62-3.91)	2.40 (1.95-2.94)	2.32 (1.89-2.85)	1.65 (1.31-2.09)
Age (continuous)		1.05 (1.04-1.05)	1.05 (1.04-1.06)	1.04 (1.03-1.05)
Sex (ref: women)		1.40 (1.14-1.71)	1.39 (1.13-1.70)	1.38 (1.13-1.69)
Region of residence (ref: West)				
Midwest		1.02 (0.74-1.41)	1.02 (0.74-1.40)	0.97 (0.71-1.34)
South		1.23 (0.94-1.60)	1.24 (0.95-1.62)	1.17 (0.89-1.52)
Northeast		2.00 (1.51-2.65)	1.99 (1.51-2.64)	1.83 (1.38-2.43)
NDDs (ref: without NDDs)			1.56 (1.22-1.98)	1.47 (1.15-1.87)
Multimorbidity (ref: 0 morbidities)				
1 morbidity				1.10 (0.74-1.64)
2 morbidities				1.36 (0.91-2.03)
3 morbidities				1.77 (1.17-2.69)
4 morbidities				2.34 (1.50-3.63)
5 morbidities				2.79 (1.75-4.47)
6 morbidities				3.00 (1.75-5.15)
7 morbidities				2.58 (1.35-4.91)
≥8 morbidities				2.74 (1.56-4.81)

CI=confidence interval; HR=hazard ratio; NDDs=neurodevelopmental disabilities.

TABLE 3 Cox Regression for the Association Between Polypharmacy and Hyperpolypharmacy with Incidence of Severe Chronic Kidney Disease Among Adults with Cerebral Palsy (N = 9,238)

	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Polypharmacy model				
Polypharmacy (ref: no)	3.95 (2.85-5.47)	2.95 (2.12-4.11)	2.94 (2.11-4.09)	1.66 (1.17-2.36)
Age (continuous)		1.04 (1.03-1.05)	1.04 (1.03-1.05)	1.03 (1.02-1.03)
Sex (ref: women)		1.44 (1.13-1.82)	1.43 (1.13-1.82)	1.43 (1.12-1.82)
Region of residence (ref: West)				
Midwest		0.86 (0.60-1.23)	0.86 (0.60-1.23)	0.76 (0.53-1.09)
South		1.00 (0.74-1.35)	1.00 (0.75-1.35)	0.87 (0.65-1.18)
Northeast		1.17 (0.82-1.66)	1.17 (0.82-1.66)	0.94 (0.66-1.34)
NDDs (ref: without NDDs)			1.06 (0.78-1.44)	0.94 (0.69-1.28)
Multimorbidity (ref: 0 morbidities)				
1 morbidity				2.46 (1.31-4.60)
2 morbidities				4.23 (2.28-7.82)
3 morbidities				5.62 (2.98-10.61)
4 morbidities				8.96 (4.70-17.09)
5 morbidities				8.06 (4.01-16.18)
6 morbidities				9.50 (4.44-20.33)
7 morbidities				12.76 (5.75-28.32)
≥8 morbidities				15.18 (7.35-31.36)
Hyperpolypharmacy model				
Hyperpolypharmacy (ref: no)	3.84 (3.01-4.89)	2.98 (2.33-3.82)	2.97 (2.32-3.81)	1.67 (1.27-2.19)
Age (continuous)		1.04 (1.03-1.05)	1.04 (1.03-1.05)	1.03 (1.02-1.04)
Sex (ref: women)		1.49 (1.17-1.90)	1.49 (1.17-1.89)	1.45 (1.14-1.85)
Region of residence (ref: West)				
Midwest		0.81 (0.56-1.16)	0.81 (0.56-1.16)	0.74 (0.51-1.06)
South		0.98 (0.73-1.32)	0.98 (0.73-1.32)	0.87 (0.65-1.17)
Northeast		1.13 (0.80-1.61)	1.13 (0.80-1.61)	0.94 (0.66-1.35)
NDDs (ref: without NDDs)			1.07 (0.79-1.45)	0.96 (0.71-1.31)
Multimorbidity (ref: 0 morbidities)				
1 morbidity				2.60 (1.39-4.84)
2 morbidities				4.46 (2.43-8.19)
3 morbidities				5.67 (3.02-10.63)
4 morbidities				8.50 (4.45-16.25)
5 morbidities				7.48 (3.71-15.09)
6 morbidities				8.48 (3.92-18.32)
7 morbidities				11.36 (5.07-25.46)
≥8 morbidities				13.49 (6.46-28.17)

CI=confidence interval; HR=hazard ratio; NDDs=neurodevelopmental disabilities.

TABLE 4 Cox Regression for the Association Between Polypharmacy and Hyperpolypharmacy with Incidence of Liver Disease Among Adults with Cerebral Palsy (N = 9,238)

	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Polypharmacy model				
Polypharmacy (ref: no)	2.29 (1.90-2.77)	2.06 (1.70-2.50)	2.10 (1.73-2.54)	1.57 (1.27-1.94)
Age (continuous)		1.01 (1.01-1.02)	1.01 (1.01-1.02)	1.00 (1.00-1.01)
Sex (ref: women)		0.89 (0.76-1.05)	0.89 (0.76-1.05)	0.89 (0.75-1.05)
Region of residence (ref: West)				
Midwest		1.07 (0.84-1.35)	1.07 (0.84-1.36)	1.02 (0.81-1.30)
South		1.17 (0.95-1.44)	1.17 (0.95-1.44)	1.11 (0.90-1.36)
Northeast		1.06 (0.81-1.39)	1.06 (0.81-1.39)	0.97 (0.74-1.28)
NDDs (ref: without NDDs)			0.88 (0.71-1.07)	0.85 (0.69-1.04)
Multimorbidity (ref: 0 morbidities)				
1 morbidity				1.41 (1.07-1.85)
2 morbidities				2.06 (1.55-2.74)
3 morbidities				2.19 (1.59-3.01)
4 morbidities				2.47 (1.73-3.54)
5 morbidities				2.23 (1.45-3.43)
6 morbidities				2.99 (1.80-4.97)
7 morbidities				4.49 (2.65-7.63)
≥8 morbidities				3.26 (1.92-5.53)
Hyperpolypharmacy model				
Hyperpolypharmacy (ref: no)	2.48 (2.11-2.91)	2.24 (1.89-2.64)	2.26 (1.91-2.67)	1.72 (1.42-2.08)
Age (continuous)		1.01 (1.01-1.02)	1.01 (1.01-1.02)	1.01 (1.00-1.01)
Sex (ref: women)		0.92 (0.78-1.08)	0.92 (0.78-1.08)	0.91 (0.77-1.07)
Region of residence (ref: West)				
Midwest		1.03 (0.82-1.31)	1.04 (0.82-1.32)	1.01 (0.79-1.28)
South		1.15 (0.94-1.41)	1.15 (0.94-1.41)	1.10 (0.90-1.36)
Northeast		1.05 (0.80-1.38)	1.05 (0.80-1.38)	0.98 (0.75-1.29)
NDDs (ref: without NDDs)			0.90 (0.73-1.10)	0.87 (0.71-1.06)
Multimorbidity (ref: 0 morbidities)				
1 morbidity				1.45 (1.11-1.91)
2 morbidities				2.10 (1.59-2.78)
3 morbidities				2.09 (1.52-2.88)
4 morbidities				2.22 (1.54-3.20)
5 morbidities				1.96 (1.26-3.04)
6 morbidities				2.54 (1.51-4.26)
7 morbidities				3.78 (2.21-6.48)
≥8 morbidities				2.75 (1.60-4.71)

CI=confidence interval; HR=hazard ratio; NDDs=neurodevelopmental disabilities.

TABLE 5 Mediating Effect of Incident Liver Disease on the Association Between Polypharmacy or Hyperpolypharmacy with Incident Severe Chronic Kidney Disease Among Adults with Cerebral Palsy^a

	Natural Direct Effect HR (95% CI)	Natural Indirect Effect HR (95% CI)	Total Effect HR (95% CI)	Percentage Mediated %
Polypharmacy model				
Entire sample, aged ≥18 years	1.99 (1.41-2.79)	1.03 (1.01-1.04)	2.04 (1.45-2.86)	4.86 ^b
Nonelderly, aged <65 years	2.41 (1.38-4.23)	1.03 (1.01-1.05)	2.49 (1.43-4.37)	5.37 ^b
Elderly, aged ≥65 years	1.64 (1.07-2.51)	1.01 (1.00-1.03)	1.66 (1.08-2.54)	2.93
Hyperpolypharmacy model				
Entire sample, aged ≥18 years	1.79 (1.36-2.36)	1.03 (1.01-1.05)	1.84 (1.40-2.43)	6.32 ^b
Nonelderly, aged <65 years	1.95 (1.25-3.04)	1.04 (1.01-1.07)	2.03 (1.30-3.15)	7.54 ^b
Elderly, aged ≥65 years	1.68 (1.18-2.40)	1.01 (1.00-1.03)	1.71 (1.20-2.43)	3.31

Note: The natural direct effect represents the effect of the exposure (i.e., polypharmacy or hyperpolypharmacy) on incidence of severe CKD not through the mediator (i.e., incident liver disease). The natural indirect effect represents the effect of the exposure on incidence of severe CKD through the mediator. The total effect is the total association between the exposure and incidence of severe CKD. All models adjusted for age (continuous), sex, U.S. region of residence, comorbid neurodevelopmental disabilities, and multimorbidity.

^aEntire sample, N=9,238; nonelderly, n=6,819; elderly, n=2,419.

^bP<0.05.

CI=confidence interval; CKD=chronic kidney disease; HR=hazard ratio.

SENSITIVITY ANALYSES

There were 7,932 adults with CP with complete data on race. The adjusted HR estimates for mortality from sensitivity analysis #1 (SA1), sensitivity analysis #2 (SA2), and the main analysis were similar for polypharmacy (SA1 HR=2.21; 95% CI=1.59-3.07; SA2 HR=2.20; 95% CI=1.58-3.06) and hyperpolypharmacy (SA1 HR=1.70; 95% CI=1.32-2.19; SA2 HR=1.71; 95% CI=1.33-2.21), suggesting that race is not a confounder and no evidence of selection bias in the main analysis when mortality is the outcome. The adjusted HR estimates for severe CKD were similar for SA1 and SA2 but slightly lower than the main analysis for polypharmacy (SA1 HR=1.52; 95% CI=1.04-2.22; SA2 HR=1.51; 95% CI=1.03-2.22) and hyperpolypharmacy (SA1 and SA2 HR=1.52; 95% CI=1.12-2.05). The adjusted HR estimates for liver disease were similar for SA1 and SA2 but slightly lower than the main analysis for polypharmacy (SA1 HR=1.52; 95% CI=1.21-1.92; SA2 HR=1.53; 95% CI=1.22-1.93) and hyperpolypharmacy (SA1 and SA2 HR=1.62; 95% CI=1.32-2.00). Although, for severe CKD and liver disease, the difference in SA1 and SA2 with the main analysis was modest and does not alter the conclusion drawn from these analyses, suggesting that race is not a confounder and little evidence of selection bias in the main analysis when severe CKD or liver disease is the outcome.

The e-value (lower 95% CI) needed to fully explain away the effect for polypharmacy was 3.70 (2.56) for mortality, 2.71 (1.62) for severe CKD, and 2.52 (1.86) for liver disease. The e-value (lower 95% CI) needed to fully explain away the effect for hyperpolypharmacy was 2.69 (1.95) for mortality, 2.73 (1.86) for severe CKD, and 2.83 (2.19) for liver disease. Given the large e-values and relative to other covariates in the models, it appears unlikely that unmeasured confounding largely biased effect estimates.

Treating mortality as a competing event led to similar HRs for polypharmacy when the outcome was severe CKD (HR=1.62; 95% CI=1.12-2.32) and liver disease (HR=1.55; 95% CI=1.24-1.92) and for hyperpolypharmacy when the outcome was severe CKD (HR=1.63; 95% CI=1.24-2.13) and liver disease (HR=1.69; 95% CI=1.40-2.05).

EXPLORATORY ANALYSIS

Incidence of severe CKD and liver disease were nonsignificant or negligible mediators (all proportion mediated <2.0%) of the association between the exposure with mortality (data not shown). However, for the entire sample of participants aged ≥18 years of age, incidence of liver disease mediated a statistically significant portion of the association between the exposure with severe CKD incidence (Table 5). The proportion mediated was larger for nonelderly than elderly. Incidence of severe CKD mediated a statistically significant portion of the association between the

exposure with liver disease incidence only for the elderly age group (proportion mediated, 7.05% for polypharmacy and 6.64% for hyperpolypharmacy; [Supplementary Table 3](#), available in online article).

Discussion

In this large cohort study of privately insured adults aged ≥ 18 years with CP, polypharmacy and hyperpolypharmacy were risk factors for mortality and incidence of severe CKD and liver disease. While it may be necessary to prescribe several medications to manage the greater morbidity-related burden associated with aging with CP,^{7,8,38} efforts are needed to optimize balancing risk and benefit to medication prescription for this vulnerable population. However, this study examined polypharmacy from a quantitative manner, and not from a qualitative manner. Future studies are needed to determine which medication combinations are being prescribed (e.g., qualitative assessment of polypharmacy) and if certain medication combinations have more potent effects on negative health outcomes for adults with CP.

The clinical implications of the current study findings should be interpreted with caution. As eloquently described elsewhere,¹⁹ the main conclusions drawn from this study require further investigation, including that (a) the association between polypharmacy and adverse outcomes are causal, and if this association is causal, that (b) polypharmacy is itself harmful. Adults with CP have an early development of chronic diseases,^{8,38} and the multimorbidity prevalence is 3-fold higher for adults aged 18–30 years with CP versus without CP.⁷ It is reasonable to assume that the number of medications would be greater to clinically manage the greater number of morbidities for this population. Therefore, there is a possibility that polypharmacy is an indicator of poor health status rather than a causal factor in the pathogenic pathway leading to severe CKD, liver disease, and mortality. In the current study, we examined the association between polypharmacy and hyperpolypharmacy with outcomes before and after accounting for demographics, comorbid NDDs, and multimorbidity. Our analyses suggest that multimorbidity was strongly associated with each outcome and does account for a considerable portion of the association between polypharmacy and hyperpolypharmacy with outcomes, as evidenced by the change in the exposure variable's HR from model 2 to model 3. However, after full adjustments including multimorbidity, risk of all outcomes was still considerably elevated for polypharmacy and hyperpolypharmacy.

The mechanisms linking polypharmacy to adverse outcomes among adults with CP are likely multifactorial and complicated by the altered physiological environment

caused by chronic unhealthful aging, early exposure to potentially harmful medications, altered body composition, and other relevant factors. While exploratory, the mediation analyses in the current study points toward potential avenues for further thought and investigation. The lack of a mediating effect by severe CKD or liver disease when mortality was the outcome may be due to the short follow-up period of 4 years. Polypharmacy-induced kidney and liver pathology may take more time to develop than what this study could capture, with additional time to affect mortality. Also, the study did not distinguish length of time for polypharmacy (e.g., recent vs. chronic), which may lead to differential mediating effects. Interestingly, the mediating effect of liver disease on the association between polypharmacy with severe CKD was more apparent for nonelderly than elderly participants, while the mediating effect of severe CKD when liver disease was the outcome was only present for the elderly group. The latter finding may be due to the later life development of severe CKD, resulting in less severe CKD cases in the nonelderly group. Nevertheless, the mediation analyses suggest differential age associations that could be used to improve polypharmacy-related risk prediction of clinical outcomes.

In the clinical setting, a more thorough examination of medication prescription practices may be needed, including fine-tuning medication doses that encompass current medical needs, medical history, and future risk for organ damage for adults with CP. These adopted medication prescription practices may need to be implemented on a case-by-case basis for this medically heterogeneous and complex population.

LIMITATIONS

This study has some limitations to consider. First, specific medications, along with their dosage and chronicity, were not examined in this study, which may have also led to the inclusion of nonsystematic medications. Further, this study was unable to access inpatient medications, which may have included relevant medications such as toxic intravenous antibiotics and chemotherapy.

Second, this study leveraged private insurance claims, which represent a healthier sector of the CP population,⁵⁵ since individuals with CP that have more severe medical needs are more likely to be covered through federal health plans, including Medicaid. Therefore, the prevalence of polypharmacy and associations examined may be diluted relative to the greater CP population.

Third, due to the issues of low muscle mass attainment and preservation for individuals with CP, CKD assessment, which is commonly performed via serum creatinine levels, in this study is likely a conservative estimate, as discussed previously.⁵⁶

Fourth, the total number of medications were defined over the 12-month period and were not necessarily concurrent medication prescriptions. As administrative claims data provide information on prescription fills, but not whether the individual takes the medication or adheres to the medication dosing and timing regimen, analysis of concurrent medication can be challenging. Therefore, in this study, the terminology of “polypharmacy” should be considered a proxy rather than an exact measure for polypharmacy.

When considering the ends of the definition spectrum, the total number of medications could capture adults that were prescribed 5 nonoverlapping medications in 2013 or 5 overlapping medications. Each scenario could represent unique clinical presentations, manifestations, and outcomes, and requires future study. Nevertheless, the current study provides, for the first time, clinically meaningful findings about the negative health and survival consequences associated with the number of medications that adults with CP are exposed to in a relatively short 12-month time span.

Conclusions

Polypharmacy and hyperpolypharmacy are robust risk factors for mortality and development of severe CKD and liver disease among privately insured adults with CP, even after accounting for comorbid NDDs and multimorbidity. While prescription of several medications may be needed to clinically manage the greater morbidity-related burden, efforts are certainly needed to optimize the balance between risk and benefit to prescribing medications for adults with CP.

DISCLOSURES

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