

The respiratory disease burden of non-traumatic fractures for adults with cerebral palsy

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ABSTRACT

Background: Individuals with cerebral palsy (CP) are vulnerable to non-trauma fracture (NTFx) and premature mortality due to respiratory disease (RD); however, very little is known about the contribution of NTFx to RD risk among adults with CP. The purpose of this study was to determine if NTFx is a risk factor for incident RD and if NTFx exacerbates RD risk in the adult CP population.

Methods: Data from 2011 to 2016 Optum Clinformatics® Data Mart and a random 20% sample Medicare fee-for-service were used for this retrospective cohort study. Diagnosis codes were used to identify adults (18+ years) with and without CP, NTFx, incident RD at 3-, 6-, 12-, and 24-month time points (pneumonia, chronic obstructive pulmonary disease, interstitial/pleura disease), and comorbidities. Crude incidence rates per 100 person years of RD were estimated. Cox regression estimated hazard ratios (HR and 95% confidence interval [CI]) for RD measures, comparing: (1) CP and NTFx (CP + NTFx); (2) CP without NTFx (CP w/o NTFx); (3) without CP and with NTFx (w/o CP + NTFx); and (4) without CP and without NTFx (w/o CP w/o NTFx) after adjusting for demographics and comorbidities.

Results: The crude incidence rate was elevated for CP + NTFx vs. CP w/o NTFx and w/o CP + NTFx for each RD measure. After adjustments, the HR was elevated for CP + NTFx vs. CP w/o NTFx for pneumonia and interstitial/pleura disease at all time points (all $P < 0.05$), but not chronic obstructive pulmonary disease (e.g., 24-month HR = 1.07; 95%CI = 0.88–1.31). The adjusted HR was elevated for CP + NTFx vs. w/o CP + NTFx for pneumonia at all time points, interstitial/pleura disease at 12- and 24-month time points, and chronic obstructive pulmonary disease at 24-months (all $P < 0.05$). There is evidence of a time-dependent effect of NTFx on pneumonia and interstitial/pleura disease for CP + NTFx as compared to CP w/o NTFx.

Conclusions: Study findings suggest that NTFx is a risk factor for incident RD, including pneumonia and interstitial/pleura disease, among adults with CP and that NTFx exacerbates RD risk for adults with vs. without CP.

1. Introduction

Cerebral palsy (CP), a neurodevelopmental condition, is the most common pediatric motor disability, affecting approximately 3 per 1000 children in the United States (Christensen et al., 2014; Maenner et al., 2016). CP refers to a group of conditions marked by chronic disorders affecting movement and posture that result from disturbances in the developing fetal/infant brain (Rosenbaum et al., 2007). Children with

CP exhibit an underdeveloped trabecular bone microarchitecture (Modlesky et al., 2008; Modlesky et al., 2015), fatty infiltration of bone marrow and skeletal muscle (Johnson et al., 2009; Whitney et al., 2017), lower bone strength (Whitney et al., 2017), and an increased risk of non-trauma fracture (NTFx) (Stevenson et al., 2006). The early-onset skeletal fragility continues throughout the lifespan, and studies show that adults with CP have a higher prevalence of musculoskeletal issues compared to adults without CP, such as rheumatoid arthritis, osteoporosis,

Abbreviations: CP, cerebral palsy; NTFx, non-trauma fracture; RD, respiratory disease.

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osteoarthritis (Whitney et al., 2018a; Whitney et al., 2018b), and fractures (Whitney et al., 2019a).

In the general older adult population, sustaining an NTFx is associated with mortality (Bliuc et al., 2009). The NTFx and mortality association is stronger for adults 18 years and older with vs. without neurodevelopmental disabilities (Whitney et al., 2019b). While the mechanisms and pathways are not completely understood, sustaining an NTFx may exert its effect on premature mortality directly or indirectly (Schousboe, 2017) through post-fracture development of diseases (Katsoulis et al., 2017), including respiratory disease (RD) (von Friesendorff et al., 2016), such as pneumonia, chronic obstructive pulmonary disease, and interstitial/pleura disease. RDs are well-documented causes of morbidity and mortality in CP, even in the absence of fracture (Boel et al., 2019; Proesmans, 2016), and have been found to be a leading cause of death for children (Evans and Alberman, 1991; Reddihough et al., 2001) and adults (Durufle-Tapin et al., 2014; Strauss et al., 1999; Ryan et al., 2019) with CP. Specifically, RD-related mortality is 14-fold higher for adults with CP compared to the general population, which is considerably higher than the 3-fold and 1.4-fold higher risk of mortality due to cardiovascular disease and cancer, respectively (Ryan et al., 2019).

A better understanding of the relationship between skeletal fragility with acute and long-term risk of RD among adults with CP could lead to improved post-NTFx healthcare management of RD and reduce the attributable RD burden. Therefore, the primary objective of this study was to determine if NTFx among adults with CP is associated with a greater 2-year RD incidence rate compared to both adults with CP that did not sustain an NTFx and adults without CP that did sustain an NTFx. The hypothesis was that adults with CP that sustained an NTFx would have higher post-NTFx incidence of pneumonia, chronic obstructive pulmonary disease, and interstitial/pleura disease compared to both groups, suggesting that: (1) NTFx is a risk factor for RD risk among adults with CP; and (2) NTFx leads to a greater RD burden for adults with vs. without CP. To determine if there were time dependent effects, RD incidence was examined at 3-, 6-, 12-, and 24-month periods.

2. Methods

2.1. Data source

Data from 2011 to 2016 were merged from administrative claims databases for this retrospective cohort study. Data from privately insured beneficiaries that had commercial or Medicare Advantage plans was leveraged from Optum Clinformatics® Data Mart Database (OptumInsight™, Eden Prairie, MN, USA) and data from publicly insured beneficiaries was leveraged from a random 20% sample of the Medicare fee-for-service database from the Centers for Medicare and Medicaid Services. Data are de-identified and the University IRB approved this study as non-regulated.

2.2. Sample selection

All medical conditions (e.g., CP, fracture, RD) were identified using the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10), Clinical Modification codes to account for the shift in reporting codes on October 1st, 2015.

Adults ≥ 18 years of age with CP were identified from Optum and Medicare databases by finding at least one claim which covered all diagnostic subtypes (e.g., spasticity). Information regarding severity of CP using common clinical measures, such as the gross motor function classification system, are not available in insurance claims. Further, more than 70% had “other” or “unspecified” CP (Whitney et al., 2019c). For these reasons, clinical subtypes of CP were unable to be stratified or statistically adjusted for. The comparison group included individuals without claims for CP from the Optum database, as Optum enhances the representativeness of the comparison group since enrollment criteria for

Medicare among individuals < 65 years of age requires permanent disability, such as end-stage renal disease. Using a single claim has good accuracy for identifying pediatric-onset conditions with 99% sensitivity and a positive predictive value of 79% (Reeves et al., 2014).

Between 2012 and 2014, NTFx of the vertebral column, hip (including proximal femur), non-proximal femur, tibia/fibula, humerus, ulna/radius, or unspecified location was defined as fracture without trauma codes (e.g., vehicle accident) 7 days before to 7 days after the index fracture date, as previously described (Whitney et al., 2019b; Whitney et al., 2020). The time frame of 2012 to 2014 was selected to account for at least one full year of a “look back” period for those that sustained an NTFx in 2012 to ascertain baseline comorbidity data and up to 2 years of follow up for those that sustained an NTFx in 2014 for the outcome. Using a single claim has excellent accuracy for identifying fractures with up to 98% positive predictive value, which is similar or better than other claims-based algorithms (e.g., 2+ claims) (Narongroeknawin et al., 2012). Clinically, NTFx typically represents spontaneous fractures. However, in order to identify fractures without high-impact (e.g., vehicle accident) in claims data to provide a proxy of skeletal fragility, fractures without trauma codes are identified and defined as NTFx. Therefore, NTFx in this study reflects the lack of associated trauma codes and does not necessarily reflect clinical spontaneous fractures only.

The sample was then categorized based on the status of CP and NTFx: (1) with CP and NTFx (CP + NTFx); (2) with CP and without NTFx (CP w/o NTFx); (3) without CP and with NTFx (w/o CP + NTFx); and (4) without CP and without NTFx (w/o CP w/o NTFx). The start date of the follow up was defined as the index date of NTFx for CP + NTFx and w/o CP + NTFx or a randomly assigned date for those that did not sustain an NTFx, in which a uniform distribution was used to randomly assign a date during the individual's enrollment period between January 1, 2012 to December 31, 2014.

Individuals that had at least 12 full months of continuous enrollment in a health plan prior to their start date of follow up were included to sequester baseline data, which is consistent with claims-based research studies (Chang et al., 2012). Individuals were excluded if they were covered by Health Maintenance Organization plans or had dual eligibility with Medicaid (Medicare database only) due to incomplete Medicare claims. We excluded individuals if they had unknown/missing data for sex or U.S. region ($n = 71,018$, $< 1\%$ of sample).

2.3. Outcome measure

The outcome measures were selected based on their relevance to fracture, cause of morbidity and mortality for CP, and accuracy of identification in administrative claims data. Incidence of pneumonia, chronic obstructive pulmonary disease, and interstitial/pleura disease of the lungs was defined by at least one claim between 14 and 730 days after the start date of the follow up. The latent period of 14 days was selected to omit individuals that were diagnosed with RD around the time of NTFx, which may have been due to medical screening from the NTFx event. The 730 days was selected to harmonize adequate follow up time to capture RDs that may take time to develop (e.g., chronic obstructive pulmonary disease) and retention of participants continuously enrolled in a health plan, as breaks or cessation of health plans are not uncommon making longitudinal claims-based studies with long follow up periods challenging. Using a single claim has shown excellent accuracy for identifying pneumonia (Wiese et al., 2018), chronic obstructive pulmonary disease (Quint et al., 2014), and other RD complications (e.g., respiratory infections (Hwee et al., 2018)) with positive predictive values from 85 to 97%.

2.4. Covariates

Sociodemographic variables included age, sex, race, and U.S. region of residence. Baseline comorbidities were identified within 12 months

prior to the start date of follow up (i.e., “look back” period) and included: hypertension, diabetes (type 1 or 2), cardiovascular disease (i.e., ischemic heart disease, heart failure, cerebrovascular disease), chronic kidney disease (stages III-V), and any cancer, as previously described (Whitney et al., 2019b).

2.5. Statistical analysis

The three RD outcome measures were treated independently as to not truncate the sample for each analysis. Individuals were excluded from analysis for each RD outcome measure if they had the RD outcome measure prior to their start date of follow up. Incidence was examined at 3-, 6-, 12-, and 24-month periods to differentiate short- and relatively long-term effects by each RD, which can assist healthcare management by identifying the timing proximity of these RD measures to an NTFx event.

Baseline descriptive characteristics of all participants prior to exclusion for each RD outcome measure were summarized for each group. Incidence rates (IR) and 95% confidence intervals (CI) of each RD outcome measure were estimated for each group as the number of outcome events divided by the amount of person-years for each time point. IR ratios (IRR) and 95% CI (Rothman and S, 2008) were estimated comparing each group to one another.

Cox regression was used to adjust for covariates when comparing IR, by estimating hazard ratios (HR and 95% CI) of each RD outcome measure, comparing each group to one another. The primary group comparisons of interest were: (1) CP + NTFx vs. CP w/o NTFx to determine if NTFx is a risk factor for RD incidence among adults with CP; and (2) CP + NTFx vs. w/o CP + NTFx to determine if NTFx exacerbates RD incidence for adults with vs. without CP. Covariates were used to explain the difference in crude rates between groups and included: age (as continuous), sex, U.S. region, hypertension, diabetes, cardiovascular disease, chronic kidney disease stages III-V, and cancer. Possible interactions between exposure status and age or sex were assessed by conducting separate analyses for age or sex strata and including product terms in the Cox models for the 24-month time period as the number of outcome cases for the CP + NTFx group were too few for reliable estimates for earlier time points. Individuals were right censored if they died or had discontinued enrollment within the follow-up period or did not develop RD at the end of the follow-up period. Cox regression did not adjust for race to limit bias due to the extent of missing data from Optum and difference in coding race between Optum and Medicare. Proportionality of hazards assumption was visually inspected and was met.

2.6. Sensitivity analysis

Two sets of sensitivity analyses were performed. First, due to the observational design of this study and lack of statistical adjustment for race, results are subject to bias from unmeasured confounding. To estimate the extent of unmeasured confounding for the 24-month time period, e-values were computed, which measures the minimum strength of association needed to explain away a specific exposure-outcome association, conditional on the set of covariates (VanderWeele and Ding, 2017). Second, the latent 14-day period to identify incidence of RD measures may underestimate the incidence of pneumonia, which can develop rapidly following fracture, unlike chronic obstructive pulmonary disease and interstitial/pleura disease that may take more time. We therefore examined incidence of pneumonia ranging from 4 days after the start date of follow up to 730 days. The latent 4-day period was selected to capture earlier pneumonia events but rule out the scenario that pneumonia may have led to the NTFx event, but both pneumonia and NTFx were billed on the same date (e.g., the NTFx event led to the individual going to the hospital for treatment, in which pneumonia was discovered).

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Baseline characteristics of CP + NTFx (n = 1384), CP w/o NTFx (n = 9710), w/o CP + NTFx (n = 330,226), and w/o CP w/o NTFx (n = 5,154,511) are presented in Table 1. Of the 5,495,831 individuals, 77,627 had pneumonia prior to their start date of follow up (CP + NTFx,

Table 1

Baseline descriptive characteristics by status of cerebral palsy (CP) and non-trauma fracture (NTFx).

	CP + NTFx (n = 1384)	CP w/o NTFx (n = 9710)	w/o CP + NTFx (n = 330,226)	w/o CP w/o NTFx (n = 5,154,511)
	% (n)	% (n)	% (n)	% (n)
Demographic characteristics				
Age, mean (SD)	63.5 (16.8)	53.0 (18.9)	64.7 (18.5)	51.3 (18.3)
18–40 years	11.1 (154)	27.6 (2678)	12.9 (42,420)	30.8 (1,586,393)
41–64 years	36.1 (500)	40.5 (3931)	29.1 (96,031)	41.9 (2,158,089)
≥65 years	52.8 (730)	31.9 (3101)	58.1 (191,775)	27.4 (1,410,029)
Sex				
Women	57.0 (789)	46.8 (4546)	66.1 (218,357)	51.5 (2,652,634)
Men	43.0 (595)	53.2 (5164)	33.9 (111,869)	48.5 (2,501,877)
Race				
White	79.7 (1103)	72.6 (7045)	69.3 (228,888)	64.1 (3,304,795)
Black	5.9 (82)	9.9 (962)	6.7 (22,163)	8.6 (445,266)
Hispanic	4.9 (68)	6.4 (621)	7.8 (25,771)	9.5 (487,733)
Asian	1.7 (23)	1.9 (181)	2.4 (8013)	4.1 (213,116)
Unknown/missing	7.8 (108)	9.3 (901)	13.8 (45,391)	13.7 (703,601)
US region				
West	23.8 (330)	21.1 (2053)	28.3 (93,519)	23.9 (1,231,005)
Midwest	23.2 (321)	25.6 (2488)	24.2 (80,054)	24.9 (1,282,791)
South	36.6 (506)	39.4 (3822)	36.5 (120,595)	41.2 (2,121,361)
Northeast	16.4 (227)	13.9 (1347)	10.9 (36,058)	10.1 (519,354)
Comorbidities				
Hypertension	53.3 (738)	36.8 (3570)	51.6 (170,269)	27.2 (1,400,982)
Cardiovascular disease	26.9 (372)	14.1 (1365)	22.1 (72,871)	7.7 (396,387)
Diabetes	20.5 (284)	14.3 (1390)	19.8 (65,522)	11.2 (579,544)
Chronic kidney disease (stages III-V)	6.6 (91)	3.1 (296)	7.7 (25,488)	2.4 (121,610)
Cancer	16.0 (222)	11.9 (1154)	19.2 (63,316)	11.1 (573,472)
Fracture distribution^a				
Unspecified location	2.8 (39)	0	4.7 (15,514)	0
Vertebral column	28.2 (390)	0	25.8 (85,240)	0
Hip	22.7 (314)	0	16.7 (55,107)	0
Femur, non-proximal	6.3 (87)	0	3.1 (10,170)	0
Tibia/fibula	24.5 (339)	0	22.8 (75,302)	0
Humerus	11.8 (163)	0	9.7 (31,898)	0
Ulna/radius	6.5 (90)	0	18.8 (62,052)	0

^a Some individuals had an NTFx across multiple sites.

$n = 112$ [8.09%]; CP w/o NTFx, $n = 432$ [4.45%]; w/o CP + NTFx, $n = 16,458$ [4.98%]; w/o CP w/o NTFx, $n = 60,625$ [1.18%]), 375,072 had chronic obstructive pulmonary disease prior to their start date of follow up (CP + NTFx, $n = 241$ [17.41%]; CP w/o NTFx, $n = 1077$ [11.09%]; w/o CP + NTFx, $n = 53,646$ [16.25%]; w/o CP w/o NTFx, $n = 320,108$ [6.21%]), and 58,612 had interstitial/pleura disease prior to their start date of follow up (CP + NTFx, $n = 71$ [5.13%]; CP w/o NTFx, $n = 210$ [2.16%]; w/o CP + NTFx, $n = 14,027$ [4.25%]; w/o CP w/o NTFx, $n = 44,304$ [0.86%]).

3.1. Crude incidence of RD

The crude IR of each RD measure for each time point was highest for CP + NTFx, followed by w/o CP + NTFx, CP w/o NTFx, and w/o CP w/o NTFx (Fig. 1). The crude IRR was higher for CP + NTFx compared to CP w/o NTFx for all time points for each RD measure (Fig. 2). The IRR was higher for CP + NTFx compared to w/o CP + NTFx for pneumonia at 6-, 12-, and 24-months, chronic obstructive pulmonary disease at 24-months, and interstitial/pleura disease at 12- and 24-months.

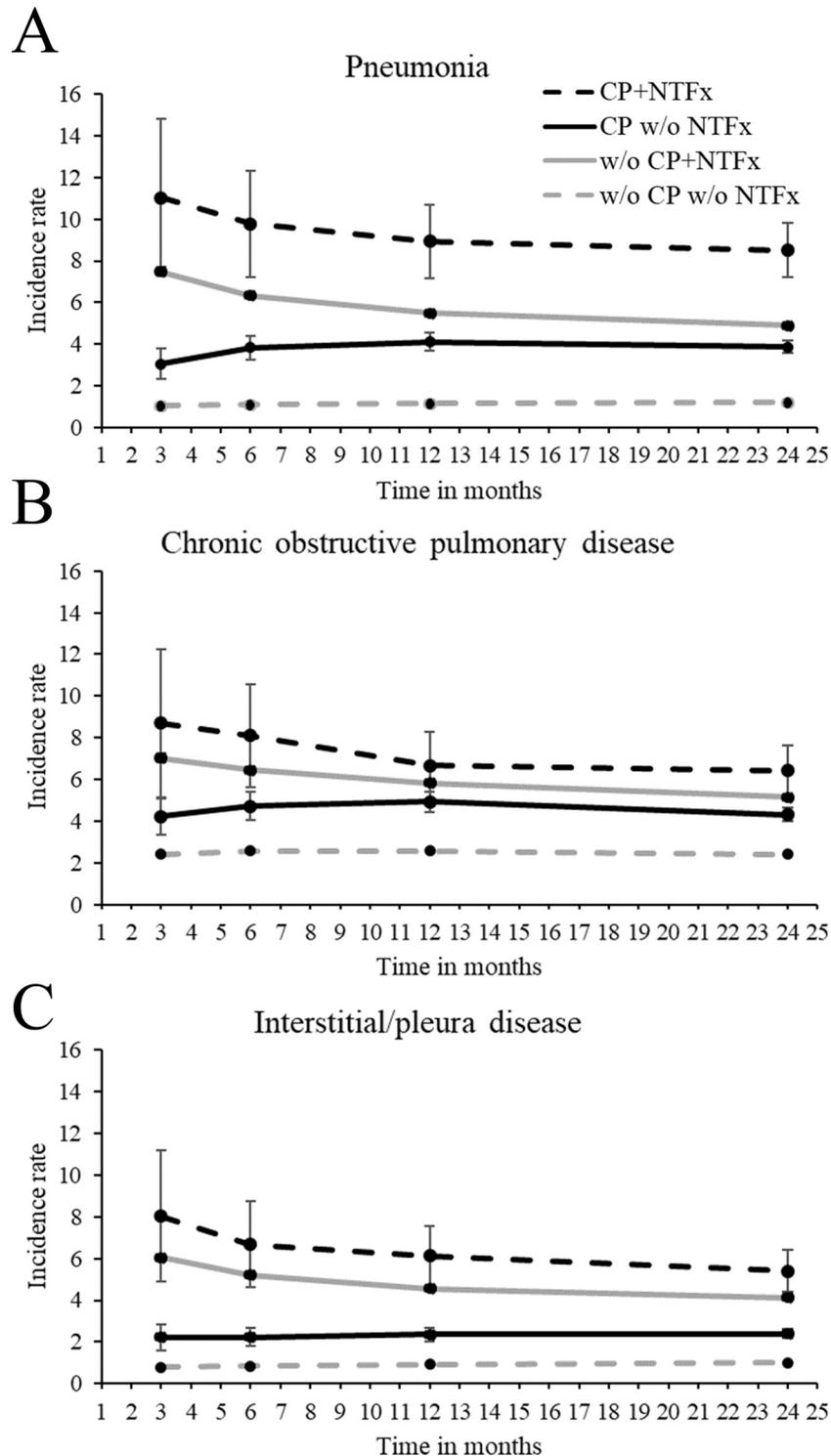


Fig. 1. Crude incidence rate (filled circle) and 95% confidence interval (lines above and below filled circle) of respiratory diseases for participants by status of cerebral palsy (CP) and non-trauma fracture (NTFx) at 3-, 6-, 12-, and 24-month time intervals.

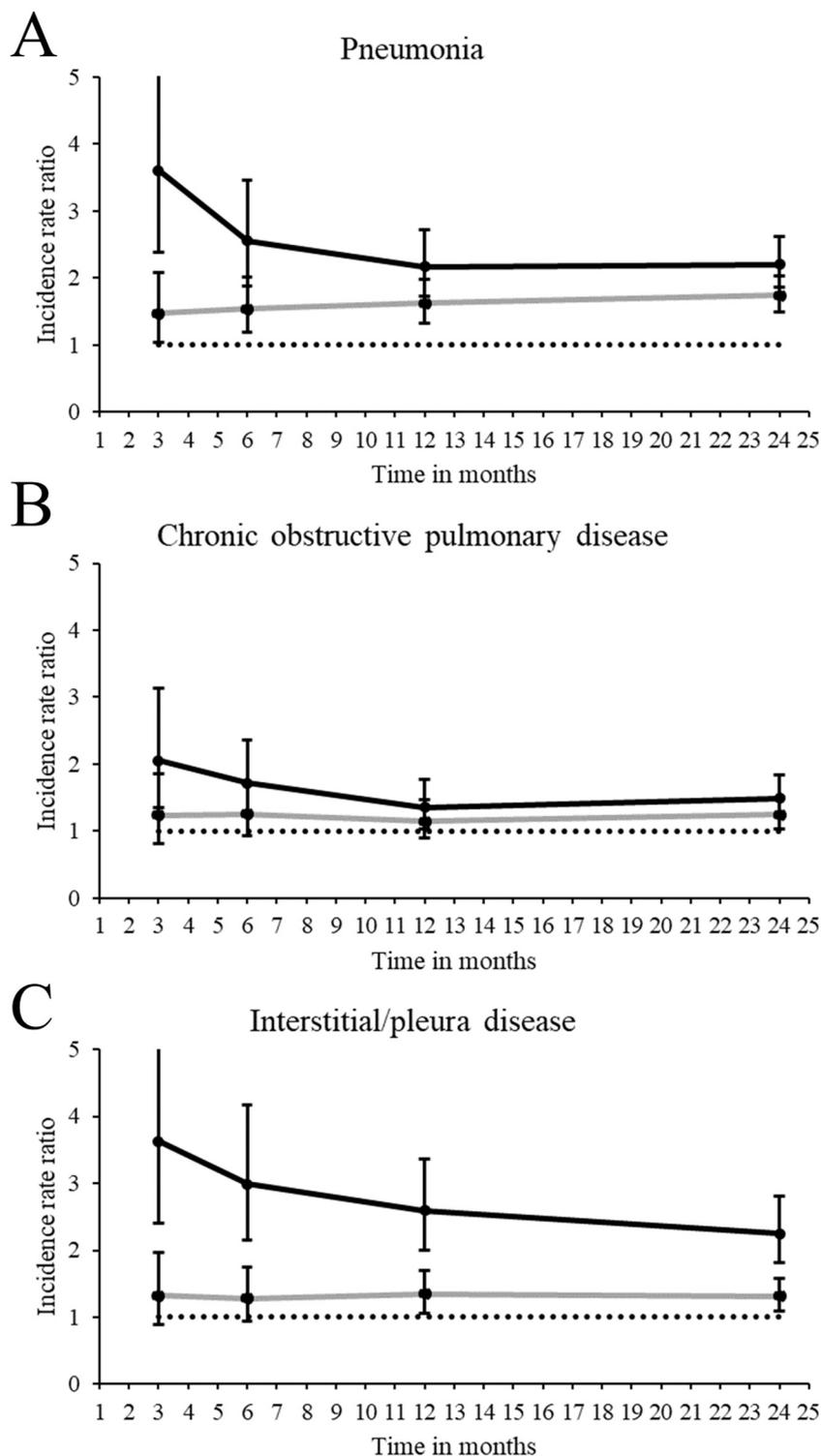


Fig. 2. Crude incidence rate ratio (filled circle) and 95% confidence interval (lines above and below filled circle) of respiratory diseases at 3-, 6-, 12-, and 24-month time intervals. The primary group of interest, adults with cerebral palsy (CP) that sustained a non-trauma fracture (NTFx), was compared to: (1) adults with CP that did not sustain an NTFx (black line) and (2) adults without CP that sustained an NTFx (gray line). The dotted horizontal line represents the reference value of 1.0. If the 95% confidence interval crosses 1.0 then the group comparison is not significantly different at $P < 0.05$.

Although, interpretation for 3-months should be made with caution as the number of RD cases were small for the CP + NTFx group for pneumonia ($n = 33$), chronic obstructive pulmonary disease ($n = 23$), and interstitial/pleura disease ($n = 25$).

3.2. Adjusted risk of RD

The number of RD cases was too few for statistical adjustment and were not included in the Cox regression analysis. The adjusted HR comparing CP + NTFx to CP w/o NTFx was elevated for pneumonia and

interstitial/pleura disease at 6-, 12-, and 24-months, but not for chronic obstructive pulmonary disease for any of the time points (Fig. 3). The adjusted HR comparing CP + NTFx to w/o CP + NTFx was elevated for pneumonia at 6-, 12-, and 24-months, chronic obstructive pulmonary disease at 24-months, and interstitial/pleura disease at 12- and 24-months.

As a summary, Table 2 presents the number of RD cases, crude IR, crude IRR, and adjusted HR for the 24-month time point for each RD measure. Compared to CP w/o NTFx, the adjusted rate over the 2-year period for CP + NTFx was 37% higher for pneumonia and 35% higher

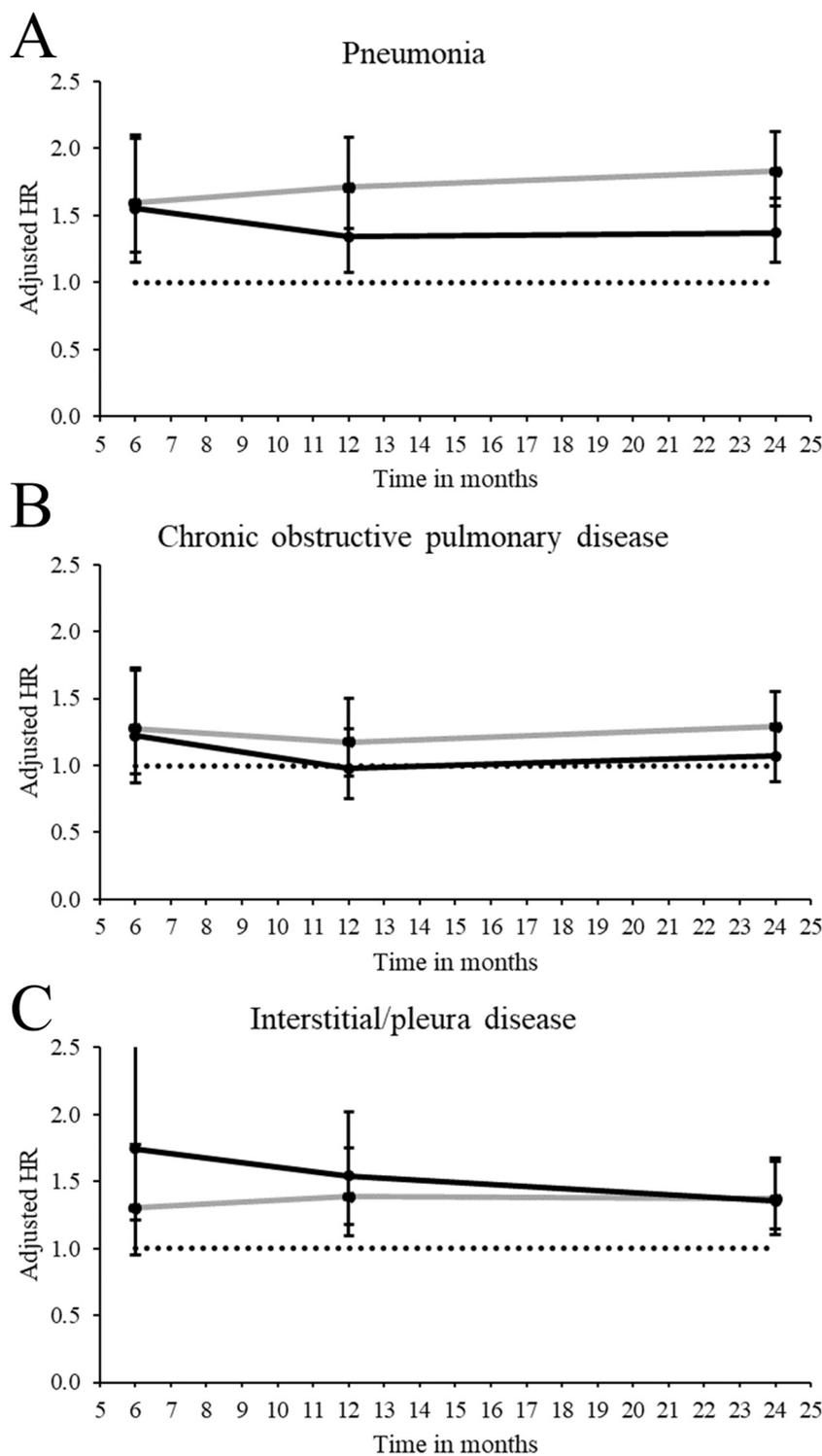


Fig. 3. Adjusted hazard ratio (HR, filled circle) and 95% confidence interval (lines above and below filled circle) of respiratory diseases at 6-, 12-, and 24-month time intervals. The primary group of interest, adults with cerebral palsy (CP) that sustained a non-trauma fracture (NTFx), was compared to: (1) adults with CP that did not sustain an NTFx (black line) and (2) adults without CP that sustained an NTFx (gray line). The dotted horizontal line represents the reference value of 1.0. If the 95% confidence interval crosses 1.0 then the group comparison is not significantly different at $P < 0.05$. Models were adjusted for age, sex, US region, hypertension, cardiovascular disease, diabetes, chronic kidney disease stages III-V, and cancer.

for interstitial/pleura disease. Compared to w/o CP + NTFx, the adjusted rate over the 2-year period for CP + NTFx was 83% higher for pneumonia, 29% higher for chronic obstructive pulmonary disease, and 37% higher for interstitial/pleura disease.

There was strong evidence of an age and sex interaction for each RD outcome measure when examined up to 2 years of follow up (all P for interaction < 0.001). Tables 3–5 shows the number of RD cases and adjusted HR of each RD measure by age category (< 65 years vs. ≥ 65 years to enhance model parsimony) and sex (women vs. men). The adjusted HR for pneumonia was elevated for CP + NTFx vs. CP w/o

NTFx and w/o CP + NTFx for both age and sex strata, with a larger HR for < 65 years and men for the comparison to w/o CP + NTFx (Table 3). The adjusted HR for chronic obstructive pulmonary disease was elevated for CP + NTFx vs. w/o CP + NTFx for < 65 years and men (Table 4). The adjusted HR for interstitial/pleura disease was elevated for CP + NTFx vs. CP w/o NTFx for both age strata and for men, while the adjusted HR was elevated for CP + NTFx vs. w/o CP + NTFx for < 65 years (Table 5).

Table 2

2-year crude incidence rate (IR), IR ratio (IRR), and adjusted^a hazard ratio (HR) of respiratory disease (RD) by status of cerebral palsy (CP) and non-trauma fracture (NTFx).

Cases	Pneumonia (n = 5,418,204)	Chronic obstructive pulmonary disease (n = 5,120,759)	Interstitial/pleura disease (n = 5,437,219)
	N	N	N
w/o CP w/o NTFx	95,197	177,852	79,630
w/o CP + NTFx	22,023	20,042	18,766
CP w/o NTFx	612	630	395
CP + NTFx	167	112	113

Crude IR	Pneumonia (n = 5,418,204)	Chronic obstructive pulmonary disease (n = 5,120,759)	Interstitial/pleura disease (n = 5,437,219)
	N per 100 person years (95% CI)	N per 100 person years (95% CI)	N per 100 person years (95% CI)
w/o CP w/o NTFx	1.20 (1.19, 1.21)	2.41 (2.39, 2.42)	1.00 (0.99, 1.01)
w/o CP + NTFx	4.89 (4.83, 4.96)	5.16 (5.09, 5.23)	4.12 (4.06, 4.18)
CP w/o NTFx	3.86 (3.55, 4.17)	4.31 (3.97, 4.64)	2.40 (2.16, 2.64)
CP + NTFx	8.51 (7.22, 9.80)	6.43 (5.24, 7.62)	5.41 (4.41, 6.41)

Crude IRR	Pneumonia (n = 5,418,204)	Chronic obstructive pulmonary disease (n = 5,120,759)	Interstitial/pleura disease (n = 5,437,219)
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Reference: w/o CP w/o NTFx			
w/o CP + NTFx	4.07 (4.01, 4.13)	2.14 (2.11, 2.18)	4.12 (4.05, 4.18)
CP w/o NTFx	3.21 (2.96, 3.47)	1.79 (1.66, 1.94)	2.40 (2.17, 2.65)
CP + NTFx	7.08 (6.08, 8.24)	2.67 (2.22, 3.22)	5.41 (4.49, 6.50)
Reference: w/o CP + NTFx			
CP w/o NTFx	0.79 (0.73, 0.86)	0.84 (0.77, 0.90)	0.58 (0.53, 0.64)
CP + NTFx	1.74 (1.49, 2.03)	1.25 (1.03, 1.50)	1.31 (1.09, 1.58)
Reference: CP w/o NTFx			
CP + NTFx	2.21 (1.86, 2.62)	1.49 (1.21, 1.84)	2.25 (1.81, 2.80)

Adjusted HR	Pneumonia (n = 5,418,204)	Chronic obstructive pulmonary disease (n = 5,120,759)	Interstitial/pleura disease (n = 5,437,219)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Reference: w/o CP w/o NTFx			
w/o CP + NTFx	2.07 (2.04, 2.10)	1.37 (1.35, 1.39)	1.97 (1.94, 2.00)
CP w/o NTFx	2.77 (2.56, 3.00)	1.64 (1.52, 1.78)	1.98 (1.79, 2.19)
CP + NTFx	3.79 (3.26, 4.41)	1.76 (1.46, 2.12)	2.68 (2.23, 3.22)
Reference: w/o CP + NTFx			
CP w/o NTFx	1.34 (1.23, 1.45)	1.20 (1.11, 1.30)	1.01 (0.91, 1.11)
CP + NTFx	1.83 (1.57, 2.13)	1.29 (1.07, 1.55)	1.37 (1.14, 1.65)
Reference: CP w/o NTFx			
CP + NTFx	1.37 (1.15, 1.63)	1.07 (0.88, 1.31)	1.35 (1.10, 1.67)

^a Adjusted for age, sex, US region, hypertension, cardiovascular disease, diabetes, chronic kidney disease stages III-V, and cancer. Individuals that had multiple RDs on the same day are only counted once for each of the RD subtypes.

3.3. Sensitivity analysis

The e-value (lower 95% CI) needed to fully explain away the effect at 24-months for CP + NTFx vs. CP w/o NTFx was 2.08 (1.57) for pneumonia and 2.04 (1.43) for interstitial/pleura disease. The e-value (lower 95% CI) needed to fully explain away the effect at 24-months for CP + NTFx vs. w/o CP + NTFx was 3.06 (2.52) for pneumonia, 1.90 (1.34) for chronic obstructive pulmonary disease, and 2.08 (1.54) for interstitial/pleura disease. Given the large e-values, it appears unlikely that unmeasured confounding largely biased effect estimates.

In total, 122,415 developed incident pneumonia over the 2-year period when examined from 4 to 730 days from the start date of follow up (CP + NTFx, n = 179 [14.1%]; CP w/o NTFx, n = 625 [6.7%]; w/o CP + NTFx, n = 24,532 [7.8%]; w/o CP w/o NTFx, n = 97,079 [1.9%]). While conclusions were the same as the primary analysis, the fully adjusted HRs were slightly larger compared to the primary analysis when comparing CP + NTFx to CP w/o NTFx and w/o CP + NTFx for the 6-, 12-, and 24-month periods (Table 6). Further, there were enough pneumonia cases at 3-months in the CP + NTFx group to perform the fully adjusted analyses, which showed significantly elevated HRs when

comparing CP + NTFx to CP w/o NTFx and w/o CP + NTFx.

4. Discussion

Findings from this study suggest that adults with CP have a greater risk of RD compared to adults without CP, and that NTFx is a robust additive burden. Among adults with CP, NTFx was associated with a higher incidence of pneumonia and interstitial/pleura disease within 2 years, and especially at earlier time periods, suggesting that NTFx is a risk factor for RD in this population with evidence of time-dependent effects. Another main finding was that among those that sustained an NTFx, adults with CP had a higher incidence of pneumonia, chronic obstructive pulmonary disease, and interstitial/pleura disease within 2 years, suggesting a greater NTFx-attributable RD burden for adults with vs. without CP. Collectively, study findings suggest that NTFx, an indicator of skeletal fragility, may be implicated in the pathogenesis of respiratory disease for adults with CP with effects that last up to at least 2 years. Clinically, more aggressive healthcare monitoring for post-NTFx RD and its risk factors is needed for patients with CP that sustain an NTFx.

Table 3

2-year adjusted hazard ratio (HR) of pneumonia by status of cerebral palsy (CP) and NTFx location and by age and sex.

Cases	<65 years (n = 3,865,279)	≥65 years (n = 1,552,925)	Women (n = 2,833,921)	Men (n = 2,584,283)
	N	N	N	N
w/o CP w/o NTFx	30,104	65,093	48,160	47,037
w/o CP + NTFx	3396	18,627	14,554	7469
CP w/o NTFx	283	329	259	353
CP + NTFx	52	115	91	76
Adjusted HR	<65 years (n = 3,865,279)	≥65 years (n = 1,552,925)	Women (n = 2,833,921)	Men (n = 2,584,283)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Reference: w/o CP w/o NTFx				
w/o CP + NTFx	2.34 (2.26, 2.42)	1.99 (1.95, 2.02)	1.98 (1.95, 2.02)	2.29 (2.23, 2.35)
CP w/o NTFx	4.26 (3.79, 4.79)	2.09 (1.88, 2.33)	2.43 (2.15, 2.75)	3.09 (2.78, 3.43)
CP + NTFx	5.86 (4.47, 7.69)	3.17 (2.64, 3.80)	3.26 (2.66, 4.01)	4.70 (3.75, 5.89)
Reference: w/o CP + NTFx				
CP w/o NTFx	1.82 (1.61, 2.06)	1.05 (0.95, 1.18)	1.23 (1.08, 1.39)	1.35 (1.21, 1.50)
CP + NTFx	2.50 (1.90, 3.29)	1.59 (1.33, 1.91)	1.65 (1.34, 2.02)	2.06 (1.64, 2.58)
Reference: CP w/o NTFx				
CP + NTFx	1.37 (1.02, 1.84)	1.51 (1.22, 1.87)	1.34 (1.06, 1.71)	1.52 (1.19, 1.95)

Adjusted for age, sex (except when sex stratified), US region, hypertension, diabetes, cardiovascular disease, chronic kidney disease stages III-V, and cancer.

By leveraging both private and public insurance databases and having a 2-year follow up period, meaningful and time-dependent estimates were able to be provided while adjusting for pre-NTFx chronic diseases in order to better appreciate the contribution of NTFx to RD risk for adults with CP. In the fully adjusted model, adults with CP that sustained an NTFx were found to have a significantly higher 2-year rate of pneumonia by 37% and interstitial/pleura disease by 35% when compared to adults with CP that did not sustain an NTFx. The adjusted risk was even higher at earlier time points- 55% for pneumonia and 74% for interstitial/pleura disease at 6-months. When compared to adults without CP that sustained an NTFx, adults with CP that sustained an NTFx were found to have a higher 2-year rate of pneumonia by 83%, chronic obstructive pulmonary disease by 29%, and interstitial/pleura disease by 37%. The reason for the statistically and clinically non-significant elevated rate of chronic obstructive pulmonary disease between the two CP groups (HR = 1.07; 95% CI = 0.88-1.31) may be due to the short follow up period of 2 years, as it often takes years to decades for symptoms of chronic obstructive pulmonary disease to develop (Løkke et al., 2006).

Importantly, we found strong evidence of age and sex interactions with each RD outcome measure. When analyses were stratified by age (<65 years vs. ≥65 years) or sex, findings were largely consistent across both age and sex strata for pneumonia. However, differences from the primary analysis included: the adjusted rate of chronic obstructive pulmonary disease was only elevated for (1) <65 year olds or (2) men (18+ years) with CP that sustained an NTFx as compared to adults without CP that sustained an NTFx; (3) the adjusted rate of interstitial/pleura disease was not elevated for ≥65 year olds with CP that sustained an NTFx as compared to adults without CP that sustained an NTFx; and

Table 4

2-year adjusted hazard ratio (HR) of chronic obstructive pulmonary disease by status of cerebral palsy (CP) and NTFx location and by age and sex.

Cases	<65 years (n = 3,726,852)	≥65 years (n = 1,393,907)	Women (n = 2,651,285)	Men (n = 2,469,474)
	N	N	N	N
w/o CP w/o NTFx	88,203	89,649	99,550	78,302
w/o CP + NTFx	5189	14,853	13,832	6210
CP w/o NTFx	335	295	278	352
CP + NTFx	44	68	58	54
Adjusted HR	<65 years (n = 3,726,852)	≥65 years (n = 1,393,907)	Women (n = 2,651,285)	Men (n = 2,469,474)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Reference: w/o CP w/o NTFx				
w/o CP + NTFx	1.47 (1.43, 1.51)	1.39 (1.37, 1.42)	1.36 (1.34, 1.39)	1.51 (1.47, 1.55)
CP w/o NTFx	1.89 (1.70, 2.10)	1.40 (1.25, 1.57)	1.42 (1.26, 1.60)	1.88 (1.69, 2.09)
CP + NTFx	2.22 (1.65, 2.99)	1.57 (1.24, 2.00)	1.48 (1.14, 1.92)	2.31 (1.77, 3.01)
Reference: w/o CP + NTFx				
CP w/o NTFx	1.28 (1.15, 1.43)	1.01 (0.90, 1.13)	1.04 (0.92, 1.17)	1.25 (1.12, 1.39)
CP + NTFx	1.51 (1.12, 2.03)	1.13 (0.89, 1.43)	1.09 (0.84, 1.41)	1.53 (1.17, 2.00)
Reference: CP w/o NTFx				
CP + NTFx	1.18 (0.86, 1.61)	1.12 (0.86, 1.46)	1.04 (0.79, 1.38)	1.23 (0.92, 1.63)

Adjusted for age, sex (except when sex stratified), US region, hypertension, diabetes, cardiovascular disease, chronic kidney disease stages III-V, and cancer.

(4) the adjusted rate of interstitial/pleura disease was only elevated for men (18+ years) with CP that sustained an NTFx as compared to adults with CP that did not sustain an NTFx. These age- and sex-stratified findings provide further detail regarding post-NTFx risk of RD for adults with CP that can be used for clinical monitoring and preventive medicine.

The effect of skeletal fragility on RD risk in the general population may largely stem from the functional decline following a fracture, especially of the hip, inducing physiological stress, resulting in enhanced vulnerability to health complications (Schousboe, 2017). Individuals with CP have compromised mobility and function early in life, which only gets worse as they age into and throughout their adult years (Day et al., 2007). It is unknown if the association between NTFx and RD is initiated or exacerbated by an even further loss of mobility and function due to the NTFx (especially of the hip or lower extremities), or if the NTFx is setting off a cascade of events leading to the earlier onset of RD. Although, it is important to note that this study was designed to investigate the pathway of NTFx to incident RD, and we found robust associations; however, this study does not rule out the possibility that RD or other factors may be involved in the early pathogenic pathway leading to NTFx. In the current study, adults with CP that sustained an NTFx had a higher prevalence of each RD outcome measure in the baseline period compared to the other three groups; these individuals were excluded from analyses examining post-NTFx RD incidence. Taken together, this may suggest that RD is associated with NTFx risk among adults with CP, and NTFx is associated with greater RD incidence for adults with CP that did not have RD prior to NTFx.

Factors linking NTFx and RD specific to adults with CP remains unknown, but may include shared mechanisms (e.g., NTFx and RD are

Table 5

2-year adjusted hazard ratio (HR) of interstitial/pleura disease by status of cerebral palsy (CP) and NTFx location and by age and sex.

Cases	<65 years	≥65 years	Women	Men
	(n = 3,873,662)	(n = 1,563,557)	(n = 2,845,650)	(n = 2,591,569)
	N	N	N	N
w/o CP w/o NTFx	20,644	58,986	38,570	41,060
w/o CP + NTFx	2683	16,083	12,458	6308
CP w/o NTFx	171	224	156	239
CP + NTFx	40	73	52	61

Adjusted HR	<65 years	≥65 years	Women	Men
	(n = 3,873,662)	(n = 1,563,557)	(n = 2,845,650)	(n = 2,591,569)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Reference: w/o CP w/o NTFx				
w/o CP + NTFx	2.50 (2.40, 2.60)	1.88 (1.85, 1.92)	1.92 (1.88, 1.96)	2.06 (2.01, 2.12)
CP w/o NTFx	3.38 (2.60, 3.92)	1.47 (1.29, 1.68)	1.70 (1.45, 1.99)	2.22 (1.95, 2.52)
CP + NTFx	5.43 (3.98, 7.41)	2.03 (1.61, 2.55)	2.04 (1.56, 2.68)	3.60 (2.80, 4.63)
Reference: w/o CP + NTFx				
CP w/o NTFx	1.35 (1.16, 1.58)	0.78 (0.69, 0.89)	0.88 (0.76, 1.04)	1.76 (1.37, 2.26)
CP + NTFx	2.17 (1.59, 2.97)	1.08 (0.86, 1.36)	1.06 (0.81, 1.40)	1.08 (0.95, 1.22)
Reference: CP w/o NTFx				
CP + NTFx	1.61 (1.14, 2.27)	1.38 (1.06, 1.79)	1.20 (0.88, 1.65)	1.63 (1.23, 2.15)

Adjusted for age, sex (except when sex stratified), US region, hypertension, diabetes, cardiovascular disease, chronic kidney disease stages III-V, and cancer.

associated), biological interactions (e.g., causal pathways), or both. For example, factors involved in the pathogenesis of RD in the CP population include spine and/or chest wall deformity, impaired airway clearance, abnormal muscle tone and muscle dysfunction, malnutrition, and swallowing dysfunction (Boel et al., 2019; Proesmans, 2016), which are factors that can also influence the status of skeletal fragility. Regarding potential causal pathways, one hypothesis is that fracture induces an inflammatory cascade that leads to RD. Studies have found elevated levels of interleukin (IL)-6 and IL-1β after fracture (Kobbe et al., 2008; Miller et al., 2006); these pro-inflammatory cytokines have been implicated in lung tissue edema, acute respiratory distress syndrome (Bhatia and Moochhala, 2004), pleural effusion (Martinez et al., 2011), and community-acquired pneumonia (Antunes et al., 2002). IL-6 and IL-1β could cause inflammation of the alveoli, a common feature seen among individuals with pneumonia. Elevated serum levels of pro-inflammatory cytokines after fracture are combated by a similar increase in anti-inflammatory cytokines, such as IL-10 (Glynn et al., 1999). Concentrations of IL-10 (Glynn et al., 1999; Gallagher et al., 2003) and IL-6 (Antunes et al., 2002) are correlated with the severity of pneumonia, and patients with lower serum IL-6 concentrations are more likely to recover from the disease.

In the current study, pneumonia was the most prominent RD outcome post-NTFx for adults with CP. The incidence of and complications from pneumonia are higher in immunocompromised individuals (Vila-Corcoles et al., 2009) as well as in the elderly (Marrie, 1996), perhaps due to the increasing levels of inflammatory cytokines with older age (Miller et al., 2006; Cohen et al., 1997). Higher systemic levels of pro-inflammatory cytokines may predispose the elderly to RDs and a post-NTFx inflammatory cascade would heighten this risk. Individuals

Table 6

Sensitivity analysis- crude incidence rate (IR), IR ratio (IRR), and adjusted^a hazard ratio (HR) of pneumonia (examined from 4 to 730 days after start of follow up) by status of cerebral palsy (CP) and non-trauma fracture (NTFx) (n = 5,418,204).

Cases	3-months	6-months	12-months	24-months
	N	N	N	N
w/o CP w/o NTFx	14,683	28,307	53,865	97,079
w/o CP + NTFx	8024	11,346	16,742	24,532
CP w/o NTFx	83	183	365	625
CP + NTFx	45	68	109	179

Crude IR	3-months	6-months	12-months	24-months
	N per 100 person years (95% CI)			
w/o CP w/o NTFx	1.18 (1.16, 1.20)	1.19 (1.18, 1.20)	1.21 (1.20, 1.22)	1.23 (1.22, 1.24)
w/o CP + NTFx	10.89 (10.65, 11.12)	8.13 (7.98, 8.28)	6.47 (6.38, 6.57)	5.45 (5.38, 5.52)
CP w/o NTFx	3.63 (2.85, 4.41)	4.12 (3.52, 4.72)	4.26 (3.82, 4.70)	3.94 (3.63, 4.25)
CP + NTFx	15.04 (10.64, 19.43)	11.87 (9.05, 14.69)	10.04 (8.15, 11.92)	9.12 (7.79, 10.46)

Crude IRR	3-months	6-months	12-months	24-months
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Reference: w/o CP w/o NTFx				
w/o CP + NTFx	9.20 (8.96, 9.46)	6.83 (6.70, 6.96)	5.37 (5.28, 5.46)	4.44 (4.40, 4.48)
CP w/o NTFx	3.06 (2.47, 3.80)	3.46 (2.99, 4.00)	3.53 (3.19, 3.92)	3.21 (3.17, 3.26)
CP + NTFx	12.71 (9.49, 17.03)	9.97 (7.86, 12.64)	8.33 (6.90, 10.05)	7.44 (6.87, 8.05)
Reference: w/o CP + NTFx				
CP w/o NTFx	0.33 (0.27, 0.41)	0.51 (0.44, 0.59)	0.66 (0.59, 0.73)	0.72 (0.67, 0.78)
CP + NTFx	1.38 (1.03, 1.85)	1.46 (1.15, 1.85)	1.55 (1.28, 1.87)	1.67 (1.45, 1.94)
Reference: CP w/o NTFx				
CP + NTFx	4.15 (2.89, 5.96)	2.88 (2.23, 3.73)	2.36 (1.89, 2.94)	2.31 (1.94, 2.76)

Adjusted HR	3-months	6-months	12-months	24-months
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Reference: w/o CP w/o NTFx				
w/o CP + NTFx	4.42 (4.29, 4.55)	3.31 (3.24, 3.39)	2.66 (2.61, 2.71)	2.26 (2.22, 2.29)
CP w/o NTFx	2.53 (2.04, 3.14)	2.87 (2.48, 3.32)	2.98 (2.68, 3.30)	2.78 (2.57, 3.00)
CP + NTFx	6.31 (4.71, 8.45)	5.00 (3.94, 6.35)	4.31 (3.57, 5.20)	3.98 (3.44, 4.61)
Reference: w/o CP + NTFx				
CP w/o NTFx	0.57 (0.46, 0.71)	0.87 (0.75, 1.00)	1.20 (1.01, 1.24)	1.23 (1.14, 1.33)
CP + NTFx	1.43 (1.07, 1.92)	1.51 (1.19, 1.92)	1.62 (1.34, 1.96)	1.77 (1.52, 2.04)
Reference: CP w/o NTFx				
CP + NTFx	2.50 (1.74, 3.59)	1.75 (1.32, 2.31)	1.45 (1.17, 1.80)	1.44 (1.22, 1.70)

^a Adjusted for age, sex, US region, hypertension, cardiovascular disease, diabetes, chronic kidney disease stages III-V, and cancer.

with CP have suppressed immune function (Lisovska et al., 2016) and show signs of “accelerated aging” (Verschuren et al., 2018; Peterson et al., 2012). It is plausible that a compromised immune system and/or elevated inflammation may exacerbate the risk of RD following an NTFx when compared to the general population.

The limitations of this study must be discussed. First, the clinical presentations of CP, including severity or type, were unable to be accounted for, as this data is not available in claims. Second, we were unable to sequester information on socioeconomic status (e.g., income, education) or statistically adjust for race due missing data from Optum and differences in coding between Optum and Medicare. Future studies are needed to examine disparities by race and other socioeconomic markers regarding the contribution of skeletal fragility to unhealthy aging for individuals with CP. Third, the comorbidities examined in this study have shown good accuracy for identification; however, it is unknown if there are differences in the diagnostic accuracy between groups that could result in biased estimates. Fourth, while data from a large, nationwide sample of adults with CP was able to be ascertained by leveraging Optum (private insurance) and Medicare (public insurance) administrative claims databases, we did not have access to Medicaid. There are considerable differences in enrollment criteria and the medical needs of adults with CP by insurance type. Therefore, not having Medicaid claims may have resulted in conservative estimates, and the associations found in this study may be diluted. Lastly, this study was not powered to examine site-specific effects. Recent studies have shown that the vertebral column and hip elicit the highest incidence of adverse outcomes following an NTFx for individuals with neurodevelopmental disabilities, but the relative risk is greater when NTFx occurs in the lower extremities (Whitney et al., 2019b; Whitney et al., 2020). How site-specific effects impact RD incidence requires future investigation.

5. Conclusion

Study findings suggest that: NTFx is a risk factor for RD among adults with CP with time-dependent effects; and adults with vs. without CP have a greater risk of post-NTFx RD incidence for up to 2 years. Future clinical research is needed to identify strategies to prevent and better manage post-NTFx RD risk for adults with CP.

CRedit authorship contribution statement

Jonathan P. Etter: Writing- Original Draft, Writing- Review & Editing, Data and Clinical Interpretation. **Sanjana Kannikeswaran:** Writing- Original Draft, Writing- Review & Editing, Data and Interpretation. **Edward A. Hurvitz:** Writing- Review & Editing, Data and Clinical Interpretation. **Mark D. Peterson:** Writing- Review & Editing, Data and Clinical Interpretation. **Michelle S. Caird:** Writing- Review & Editing, Data and Clinical Interpretation. **Karl J. Jepsen:** Writing- Review & Editing, Data and Clinical Interpretation. **Daniel G. Whitney:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing- Original Draft, Writing- Review & Editing, Data and Clinical Interpretation, Visualization, Supervision, Project Administration, Funding acquisition.

Declaration of competing interest

None.

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