



## Full Length Article

# The effect of low-trauma fracture on one-year mortality rate among privately insured adults with and without neurodevelopmental disabilities



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## ABSTRACT

**Background:** Individuals with neurodevelopmental disabilities (NDDs) have poor development and preservation of skeletal health throughout the lifespan, and are especially vulnerable to low-trauma fracture and post-fracture health complications. However, no studies have examined if adults with NDDs have greater post-fracture mortality risk compared to adults without NDDs. The purpose of this study was to determine whether adults with NDDs have greater 12-month mortality rates following a low-trauma fracture compared to adults without NDDs. **Methods:** Data from 2011 to 2017 was leveraged from Optum Clinformatics® Data Mart; a nationwide claims database from a single private payer in the U.S. Data were extracted from adults (18+ years) with and without NDDs that sustained a low-trauma fracture between 01/01/2012–12/31/2016, as well as pre-fracture chronic diseases (i.e., cardiovascular diseases, cerebrovascular diseases, diabetes, chronic obstructive pulmonary diseases, cancer). Mortality rate was estimated for adults with and without NDDs, and the mortality rate ratio (RR) and 95% confidence interval (CI) was calculated. Cox regression was used to estimate hazard ratio (HR) and 95% CI for 1-, 3-, 6-, and 12-month post-fracture mortality rates between adults with and without NDDs after adjusting for age, sex, race, U.S. region, and pre-fracture chronic diseases.

**Results:** Mean age (SD) at baseline was 56.7 (20.6) for adults with NDDs (n = 3749; 45.2% men) and 63.9 (19.2) for adults without NDDs (n = 585,910; 34.4% men). During the 12-month follow-up period, 182 adults with NDDs (mean age [SD] = 69.8 [14.7]; 46.2% men) and 25,456 adults without NDDs (mean age [SD] = 78.9 [9.8]; 38.3% men) died. Crude mortality rate was not different between adults with and without NDDs for any time points (e.g., 12-months: 5.40 vs. 4.96 per 100 person years; RR = 1.09; 95% CI = 0.94–1.26); however, it was greater for adults with intellectual disabilities compared to adults without NDDs (RR = 1.46; 95% CI = 1.23–1.79). After adjustments, adults with NDDs had greater post-fracture mortality rates for 3-, 6-, and 12-month time points (e.g., 12-months: HR = 1.46; 95% CI = 1.27–1.69). When stratified by the type of NDD, adults with intellectual disabilities and adults with autism spectrum disorders, but not adults with cerebral palsy, had greater 12-month post-fracture mortality risk. When stratified by fracture location, lower extremities were associated with greater crude mortality rate (HR = 1.69; 95% CI = 1.22–2.35) and adjusted mortality risk (HR = 2.41; 95% CI = 1.73–3.35), while upper extremities were associated with greater adjusted mortality risk (HR = 1.76; 95% CI = 1.23–2.50) for adults with vs. without NDDs.

**Conclusions:** Among privately insured adults with NDDs, low-trauma fracture is associated with greater mortality risk within 1 year of the fracture event, even after adjusting for pre-fracture chronic diseases. Study findings suggest the need for earlier fracture prevention strategies and improved post-fracture healthcare management.

**Abbreviations:** NDD, neurodevelopmental disabilities

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## 1. Introduction

Fractures represent a major public health issue in terms of disease [1] and medical cost [2] burdens. Among older adults, fracture is a primary cause of functional disability [3], morbidity [4], poor quality of life [5], and premature mortality [3,6,7]. Pre-fracture health status is a strong predictor of post-fracture health, functional, and survival outcomes [3]. As such, fracture risk and its related sequela (e.g., chronic diseases, premature mortality) may disproportionately impact adults with neurodevelopmental disabilities (NDDs), due to barriers for these individuals in acquiring adequate skeletal and overall health throughout the lifespan. However, the burden of low-trauma fracture, an indicator of skeletal fragility, for adults with NDDs is largely unknown.

Three common NDDs include intellectual disabilities, cerebral palsy, and autism spectrum disorders, which can be comorbid with one another. While the etiology of these conditions vary, what links all individuals with NDDs is the potential for having complex and unmet healthcare needs due to factors that are inherent (e.g., genetic predisposition) and secondary (e.g., communication impairments) to the disability, as well as lack of clinical knowledge of their aging process [8–11]. Collectively, these factors increase risk for developing health complications throughout the lifespan. Throughout growth, children with NDDs exhibit low fitness levels [12,13], excess body fat [14–17], poor psychosocial development [18–21], and an underdeveloped musculoskeletal system [14,22–24]. As children with NDDs age into and throughout their adult years, there is potential for a further decline of function and mobility [25] with subsequent loss in regular weight-bearing activities. As such, the pediatric to adult transition is accompanied by a concerning prevalence of musculoskeletal diseases leading to a substantially increased risk for skeletal fragility and fracture [26–29].

Furthermore, adults with NDDs are at risk for early mortality compared to adults without NDDs. Population-based studies have shown that adults with intellectual disabilities [30], cerebral palsy [31], and autism spectrum disorders [32] die approximately 15–30 years premature (i.e., earlier compared to adults without NDDs). This premature mortality is likely governed, at least in part, by early development of chronic diseases across several biological systems for these NDD populations [30,31], including an elevated prevalence of cardiometabolic diseases [26,33], mental health disorders [33,34], and kidney and liver diseases [35] compared to adults without NDDs.

Despite the increased risk for skeletal fragility throughout the lifespan and the overall poor health status in adulthood, no studies have examined how skeletal fragility contributes to health and survival outcomes for adults with NDDs. A better understanding of the potential link between skeletal fragility with poor health and premature mortality among these vulnerable populations is needed. If skeletal fragility increases risk for premature mortality for adults with NDDs as compared to adults without NDDs, clinicians should be alerted to the heightened need for strategies to prevent skeletal fragility and intensively manage low-trauma fractures when they do occur in their patients with NDDs as compared to their patients without NDDs, with the ultimate aim of improving healthful aging throughout the lifespan. Accordingly, the primary objective of this study was to compare the 1-, 3-, 6-, and 12-month mortality rates following a low-trauma fracture, and by location of low-trauma fracture, between adults with vs. without NDDs. We hypothesized that adults with NDDs would have greater post-fracture mortality rates compared to adults without NDDs, even after adjusting for pre-fracture chronic diseases.

## 2. Methods

### 2.1. Data source

Data from 2011 to 2017 were extracted from the Clinformatics®

Data Mart Database (OptumInsight™, Eden Prairie, MN, USA), which is a U.S. nationwide de-identified single private payer administrative claims database. The claims data includes all health service utilization (e.g., inpatient, outpatient) for each beneficiary throughout enrollment. Date of death is also recorded. To preserve patient identity, researchers leveraging this database are allowed either the Date of Death or Socioeconomic Status table. This study leveraged the Date of Death table and therefore some information regarding socioeconomic status (i.e., income, education) were not available. Since data are de-identified, the university Institutional Review Board approved this study as non-regulated.

### 2.2. Sample selection

All medical conditions (e.g., NDDs, fracture) 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. We identified adults  $\geq 18$  years of age that had at least one claim for a low-trauma fracture between 2012 and 2016 of the vertebral column, hip (including proximal femur), non-proximal femur, tibia/fibula, humerus, ulna/radius, or unspecified location. We defined low-trauma fracture as the first fracture in at least 12 months from the participant's index date of health plan enrollment without trauma codes (e.g., motor vehicle accident) 7 days before to 7 days after the index date of fracture, as guided by previous studies [36,37]. We included individuals that had at least 12 full months of continuous enrollment in a health plan prior to their index date of low-trauma fracture to sequester baseline chronic disease data. The single claim-based definition has shown excellent accuracy (up to 98% positive predictive value) for fractures, which was similar or better than other algorithms (e.g., 2+ claims) [38].

Individuals with NDDs were identified by at least one claim for intellectual disabilities, cerebral palsy, or autism spectrum disorders. The comparison group included individuals with no claims for any of these NDDs. This single claim-based definition has shown good accuracy for identifying individuals with pediatric-onset conditions using administrative claims data with 99% sensitivity and a positive predictive value of 79% [39].

### 2.3. Outcome measure

Mortality rate for 1-, 3-, 6-, and 12-months post-fracture was determined as the number of days from the index date of low-trauma fracture to date of death. The Date of Death table from Optum is kept up-to-date and is sourced by the Death Master File which is maintained by the Social Security Office.

### 2.4. Covariates

Covariates were selected based on their relevance to adults with NDDs, fracture, mortality, and availability in the administrative claims database [26,40,41]. Sociodemographic variables included age, sex, race, and U.S. region of residence (West, Midwest, South, and Northeast). Data regarding severity of cerebral palsy or autism spectrum disorders using common clinical measures (e.g., gross motor function classification system for cerebral palsy) are not available in administrative claims, and  $> 70\%$  of the cerebral palsy cohort had “other” or “unspecified” cerebral palsy [35]. Since analyses were unable to stratify or statistically account for clinical subtypes of cerebral palsy (e.g., spasticity/athetoid, hemiplegic) or autism spectrum disorders, intellectual disabilities were not stratified by severity (e.g., mild, severe) for consistency.

Baseline chronic disease comorbidities were identified by at least two claims on separate days, and the date of the first claim had to be within 12 months prior to the index date of low-trauma fracture. Using the algorithm of at least 2 claims on separate days was selected to omit

“rule out” scenarios for these chronic diseases, which has been shown to improve accuracy in identifying non-event chronic diseases, such as diabetes and cardiovascular diseases [42,43]. Chronic disease comorbidities were grouped as cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, and cancer. Cardiovascular disease comorbidities included: (1) ischemic heart diseases (i.e., angina pectoris, acute or old myocardial infarction, other acute ischemic heart diseases [e.g., coronary thrombosis], and chronic ischemic heart diseases [e.g., atherosclerosis of coronary arteries, aneurysm]); (2) heart failure; (3) cerebrovascular diseases (i.e., intracranial hemorrhage, cerebral infarction, occlusion and stenosis of precerebral and cerebral arteries, and other cerebrovascular diseases); and (4) hypertension. Diabetes included type 1 or type 2. Chronic obstructive pulmonary diseases included: (1) chronic bronchitis; (2) emphysema; and (3) other chronic obstructive pulmonary diseases. Cancer anywhere in the body included malignant, secondary, in situ, and benign neoplasms, as well as neoplasms of unspecified behavior.

### 2.5. Statistical analysis

Baseline descriptive characteristics for the entire sample and for the sample that died during the 12-month follow up were summarized. Group differences between adults with vs. without NDDs were examined using independent *t*-tests for continuous variables or Chi-square tests for categorical variables.

Crude mortality rates (and 95% confidence intervals [CI]) for 1-, 3-, 6-, and 12-month time points were estimated for adults with and without NDDs, and by NDD subgroups, as the number of mortality cases divided by the amount of person-years, and expressed per 100 person-years. Mortality rate ratios (RR and 95% CI) were calculated as the mortality rate for the groups with NDDs divided by the mortality rate for the group without NDDs. The NDD subgroups included adults with intellectual disabilities (ID only), cerebral palsy (CP only), autism spectrum disorders (ASD only), and comorbid NDDs, including ID + CP, ID + ASD, CP + ASD, and all three NDDs.

Cox proportional hazards regression models were developed to estimate hazard ratios (HR and 95% CI) for 1-, 3-, 6-, and 12-month post-fracture mortality rates, comparing each exposure groups (e.g., entire sample with NDDs; NDD subgroups) with the reference group without NDDs, adjusting for covariates. Model 1 adjusted for age, sex, race, and US region; and Model 2 adjusted for the variables in Model 1 and chronic disease comorbidities. Analyses were performed when the number of mortality cases in the NDD group and subgroups were 5–9 per number of covariates, as this range provides coverage and bias within acceptable levels, which is similar to the more established rule of thumb of 10 or more events per number of covariates for Cox models [44]. Individuals were right censored if they discontinued enrollment within the follow-up periods following the index date of low-trauma fracture or if they were alive at the end of the follow-up periods. Possible interactions between exposure status (NDD vs. no NDD) and sex were assessed by conducting separate analyses for sex strata (to estimate NDD effects) and by including product terms in the Cox models (to test for interactions).

Subsequent Cox proportional hazards regression models compared the 12-month post-fracture mortality rate between adults with and without NDDs stratified by location of low-trauma fracture (vertebral column, hip, lower extremities, upper extremities), adjusting for the variables in model 1 and 2 where appropriate.

$P \leq 0.05$  (two-tailed) was used to determine statistical significance. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## 3. Results

Baseline descriptive characteristics of adults with ( $n = 3749$ ) and without ( $n = 585,910$ ) NDDs that sustained a low-trauma fracture are

**Table 1**  
Baseline descriptive characteristics of participants with and without neurodevelopmental disabilities (NDDs) that sustained a low-trauma fracture.

	With NDDs ( $n = 3749$ )	Without NDDs ( $n = 585,910$ )	<i>P</i> value
	No. (%)	No. (%)	
<b>NDD characteristics</b>			
Intellectual disabilities only	1670 (44.5)	0	
Cerebral palsy only	1094 (29.2)	0	
Autism spectrum disorders only	619 (16.5)	0	
NDD comorbidity	366 (9.8)	0	
<b>1st fracture characteristics</b>			
Fracture distribution			
Unspecified location	105 (2.8)	22,546 (3.9)	< 0.001
Vertebral column	857 (22.9)	147,453 (25.2)	
Hip	698 (18.6)	96,180 (16.4)	
Femur, non-proximal	147 (3.9)	15,219 (2.6)	
Tibia/fibula	966 (25.8)	135,942 (23.2)	
Humerus	412 (11.0)	57,908 (9.9)	
Ulna/radius	564 (15.0)	110,662 (18.9)	
<b>Demographic characteristics</b>			
Age, mean (SD)			
18–39 years	56.7 (20.6)	63.9 (19.2)	< 0.001
40–59 years	827 (22.1)	79,332 (13.5)	
60–79 years	1025 (27.3)	127,745 (21.8)	
80+ years	1372 (36.6)	225,529 (38.5)	
	525 (14.0)	153,304 (26.2)	
Sex			
Women	2056 (54.8)	384,237 (65.6)	< 0.001
Men	1693 (45.2)	201,673 (34.4)	
Race			
White	2406 (64.2)	394,034 (67.3)	< 0.001
Black	383 (10.2)	42,185 (7.2)	
Hispanic	278 (7.4)	47,968 (8.2)	
Asian	93 (2.5)	14,439 (2.5)	
Unknown/missing	589 (15.7)	87,284 (14.9)	
US region			
West	1018 (27.2)	164,639 (28.1)	< 0.001
Midwest	873 (23.3)	141,098 (24.1)	
South	1366 (36.4)	220,110 (37.6)	
Northeast	492 (13.1)	60,063 (10.3)	
<b>Chronic disease comorbidities</b>			
Ischemic heart diseases	525 (14.0)	82,674 (14.1)	0.852
Heart failure	369 (9.8)	48,084 (8.2)	< 0.001
Cerebrovascular diseases	357 (9.5)	44,548 (7.6)	< 0.001
Hypertension	1885 (50.3)	301,701 (51.5)	0.139
Diabetes	844 (22.5)	115,892 (19.8)	< 0.001
Chronic obstructive pulmonary disease	500 (13.3)	71,646 (12.2)	0.039
Cancer	598 (16.0)	124,577 (21.3)	< 0.001

presented in Table 1. Compared to adults without NDDs, adults with NDDs were on average 7.2 years younger at baseline and had a higher proportion of men, Black race, and residency in the Northeast region of the U.S. Adults with NDDs had higher unadjusted prevalence of heart failure, cerebrovascular diseases, diabetes, and chronic obstructive pulmonary disease, but lower prevalence of cancer, compared to adults without NDDs. Over the 12-month study period, 182 adults with NDDs died (4.9% of sample) and 25,456 adults without NDDs died (4.3%). Among those that died (Table 2), adults with NDDs were on average 9.1 years younger than adults without NDDs.

### 3.1. Post-fracture mortality rate

Post-fracture crude mortality rate and RR between adults with and without NDDs, and by NDD subgroups, is presented in Table 3. For adults without NDDs, the crude mortality rate for 1-, 3-, 6-, and 12-months was 13.60, 9.02, 6.61, and 4.96, respectively. For adults with NDDs, it was 12.46 (RR = 0.92; 95% CI = 0.67), 8.48 (RR = 0.94; 95% CI = 0.75–1.18), 7.16 (RR = 1.08; 95% CI = 0.91–1.29), and 5.40 (RR = 1.09; 95% CI = 0.94–1.26), respectively. When examined by the NDD subgroups, adults with ID only had greater crude mortality rate for

**Table 2**  
Baseline descriptive characteristics of participants with and without neurodevelopmental disabilities (NDDs) that died during the 12-month follow up.

	With NDDs (n = 182)	Without NDDs (n = 25,456)	P value
	No. (%)	No. (%)	
<b>Mortality characteristics</b>			
<b>Mortality</b>			
1-month	38 (20.9)	6461 (25.4)	
3-months	76 (41.8)	12,521 (49.2)	
6-months	127 (69.8)	18,023 (70.8)	
12-months	182 (100)	25,456 (100)	
<b>NDD characteristics</b>			
Intellectual disabilities	110 (60.4)	0	
Cerebral palsy	37 (20.4)	0	
Autism spectrum disorders	27 (14.8)	0	
NDD comorbidity	8 (4.4)	0	
<b>1st fracture characteristics</b>			
<b>Fracture distribution</b>			
Unspecified location	7 (3.9)	730 (2.9)	0.006
Vertebral column	52 (28.6)	9397 (36.9)	
Hip	56 (30.8)	8779 (34.5)	
Femur, non-proximal	10 (5.5)	744 (2.9)	
Tibia/fibula	26 (14.3)	2046 (8.0)	
Humerus	18 (9.9)	2151 (8.5)	
Ulna/radius	13 (7.1)	1609 (6.3)	
<b>Demographic characteristics</b>			
<b>Age, mean (SD)</b>			
18–39 years	69.8 (14.7)	78.9 (9.8)	< 0.001
40–59 years	9 (5.0)	117 (0.5)	
60–79 years	31 (17.0)	1269 (5.0)	
80+ years	85 (46.7)	8397 (33.0)	
<b>Sex</b>			
Women	57 (31.3)	15,673 (61.6)	0.029
Men	98 (53.9)	15,717 (61.7)	
<b>Race</b>			
White	84 (46.2)	9739 (38.3)	0.476
Black	129 (70.9)	17,834 (70.1)	
Hispanic	19 (10.4)	2395 (9.4)	
Asian	12 (6.6)	1654 (6.5)	
Unknown/missing	6 (3.3)	497 (2.0)	
<b>US region</b>			
West	16 (8.8)	3076 (12.1)	< 0.001
Midwest	31 (17.0)	7007 (27.5)	
South	28 (15.4)	4882 (19.2)	
Northeast	80 (44.0)	9423 (37.0)	
<b>Chronic disease comorbidities</b>			
Ischemic heart diseases	43 (23.6)	4144 (16.3)	0.996
Heart failure	59 (32.4)	8248 (32.4)	0.316
Cerebrovascular diseases	47 (25.8)	7438 (29.2)	0.021
Hypertension	44 (24.2)	4486 (17.6)	0.427
Diabetes	137 (75.3)	19,788 (77.7)	0.107
Chronic obstructive pulmonary disease	69 (37.9)	8223 (32.3)	0.408
Cancer	50 (27.5)	7714 (30.3)	0.095
	49 (26.9)	8338 (32.8)	

6-months (RR = 1.46; 95% CI = 1.17–1.83) and 12-months (RR = 1.49; 95% CI = 1.23–1.79). The crude mortality rate was similar for adults with CP and ASD only compared to adults without NDDs where analyses were able to be performed.

### 3.2. Adjusted post-fracture mortality risk for any fracture

Adjusted post-fracture mortality risk between adults with and without NDDs, and by NDD subgroups, is presented in Table 4. For the entire sample of adults with NDDs, post-fracture mortality risk was significantly greater for 3-, 6-, and 12-months after adjusting for the variables in model 1 and model 2. For adults with ID only, post-fracture mortality risk was significantly greater for 1-month after adjusting for the variables in model 1 (insufficient mortality cases for model 2 adjustment), and 3-, 6-, and 12-months after adjusting for the variables in model 1 and model 2. For adults with ASD only, there were insufficient

**Table 3**  
Crude post-fracture mortality rate and rate ratio (RR) between adults with and without neurodevelopmental disabilities (NDDs).

	1-month mortality	3-month mortality	6-month mortality	12-month mortality
Mortality cases	N	N	N	N
Without NDDs	6461	12,521	18,023	25,456
With NDDs	38	76	127	182
ID only	24	45	76	110
CP only	7	16	27	37
ASD only	6	10	18	27
Comorbid NDDs <sup>a</sup>	1	5	6	8
Crude mortality rate	N per 100 person years			
Without NDDs	13.60	9.02	6.61	4.96
With NDDs	12.46	8.48	7.16	5.40
ID only	17.70	11.31	9.66	7.38
CP only	<sup>b</sup>	6.10	5.19	3.74
ASD only	<sup>b</sup>	<sup>b</sup>	6.12	4.84
Comorbid NDDs <sup>a</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>
Mortality RR	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Without NDDs	Reference	Reference	Reference	Reference
With NDDs	0.92 (0.67, 1.26)	0.94 (0.75, 1.18)	1.08 (0.91, 1.29)	1.09 (0.94, 1.26)
ID only	1.30 (0.87, 1.94)	1.25 (0.94, 1.68)	1.46 (1.17, 1.83)	1.49 (1.23, 1.79)
CP only	<sup>b</sup>	0.68 (0.41, 1.10)	0.79 (0.54, 1.15)	0.75 (0.55, 1.04)
ASD only	<sup>b</sup>	<sup>b</sup>	0.93 (0.58, 1.47)	0.98 (0.67, 1.42)
Comorbid NDDs <sup>a</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>

ID, intellectual disabilities; CP, cerebral palsy; ASD, autism spectrum disorders; CI, confidence interval.

<sup>a</sup> Comorbid NDDs were grouped together due to insufficient sample size and include: ID + CP; ID + ASD; CP + ASD; or ID + CP + ASD.

<sup>b</sup> Number of mortality cases insufficient for analysis (N ≤ 10).

mortality cases to compare model 1 adjusted mortality rates at 1-, 3-, and 6-months, and model 2 adjusted 12-month mortality rate. Post-fracture mortality risk was significantly greater for 12-months after adjusting for the variables in model 1. Post-fracture mortality risk was similar for adults with CP only compared to adults without NDDs where analyses were able to be performed.

### 3.3. Post-fracture mortality rate and risk by fracture location

Twelve-month post-fracture mortality rate, RR, and risk between adults with and without NDDs, stratified by fracture location, is presented in Table 5. Low-trauma fracture of the lower extremities, but not vertebral column or hip, was associated with greater mortality RR and risk among adults with NDDs compared to adults without NDDs. Low-trauma fracture of the upper extremities was associated with greater mortality risk among adults with NDDs compared to adults without NDDs. Further, there was a significant group by sex interaction for upper extremities (P = 0.027). When stratified by sex and adjusted for age (due to small sample size), men with NDDs (HR = 2.71; 95% CI = 1.72–4.27), but not women with NDDs (HR = 1.22; 95% CI = 0.69–2.14), with an upper extremity fracture had greater 12-month mortality risk compared to adults without NDDs.

## 4. Discussion

Despite the younger age of death by nearly a decade, adults with NDDs had greater mortality risk within 12-months following a low-trauma fracture compared to adults without NDDs. Of the fracture locations, the lower extremities were associated with greater unadjusted and adjusted mortality risk, while the upper extremities were associated

**Table 4**  
Risk of post-fracture mortality rate between adults with neurodevelopmental disabilities (NDDs) and adults without NDDs (reference).<sup>a</sup>

	With NDDs	ID only	CP only	ASD only
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
1-month mortality				
Model 1	1.27 (0.92, 1.75)	1.62 (1.09, 2.42)	<sup>b</sup>	<sup>b</sup>
Model 2	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>
3-month mortality				
Model 1	1.31 (1.04, 1.64)	1.57 (1.17, 2.10)	<sup>b</sup>	<sup>b</sup>
Model 2	1.27 (1.02, 1.59)	1.53 (1.14, 2.05)	<sup>b</sup>	<sup>b</sup>
6-month mortality				
Model 1	1.50 (1.26, 1.79)	1.82 (1.45, 2.28)	0.98 (0.67, 1.43)	<sup>b</sup>
Model 2	1.45 (1.22, 1.73)	1.76 (1.41, 2.21)	<sup>b</sup>	<sup>b</sup>
12-month mortality				
Model 1	1.51 (1.31, 1.75)	1.86 (1.55, 2.25)	0.94 (0.68, 1.29)	1.63 (1.12, 2.38)
Model 2	1.46 (1.27, 1.69)	1.80 (1.49, 2.17)	<sup>b</sup>	<sup>b</sup>

ID, intellectual disabilities; CP, cerebral palsy; ASD, autism spectrum disorders; HR, hazard ratio; CI, confidence interval. N = 589,659 for all models. Model 1 adjusted for age, sex, race, and US region. Model 2 adjusted for age, sex, race, US region, cardiovascular diseases (i.e., ischemic heart diseases, heart failure, cerebrovascular diseases, and/or hypertension), diabetes (i.e., type 1 or 2, primary or secondary), chronic obstructive pulmonary diseases, and cancer.

<sup>a</sup> Number of mortality cases insufficient for analysis for comorbid NDD group.

<sup>b</sup> Number of mortality cases insufficient for analysis (model 1, N < 20; model 2, N < 40).

with greater adjusted mortality risk among adults with vs. without NDDs. In line with previous work [27–29], study findings corroborate the need for earlier strategies to detect and delay skeletal fragility for adults with NDDs. Previous studies in non-NDD populations have shown that screening for fracture risk [45], modest improvements in detecting skeletal fragility [46], and exercise and pharmaceutical intervention [1,45,47] have the potential to prevent fractures and reduce post-fracture burdens. Whether such strategies could be immediately implemented to reduce the burden of fracture for adults with NDDs, or if population- or patient-specific modifications are needed, requires further investigation.

Findings from the current study found no difference in crude post-fracture mortality rate between adults with and without NDDs. However, as individuals with NDDs have compromised health at younger ages and are more likely to be male, age and sex adjustment is needed to better understand post-fracture mortality risk beyond group differences in these characteristics. After statistically accounting for age, sex, and other demographic variables using Cox regression, the HR for post-fracture mortality was greater for adults with vs. without NDDs for the 3-, 6-, and 12-month time points. The greater mortality risk for these time points remained elevated after further adjustment for pre-

fracture chronic diseases.

When analyses were stratified by fracture location, results suggest site-specific effects on mortality risk for adults with NDDs. Specifically, lower extremity fractures were associated with 69% greater unadjusted mortality rate and 141% greater adjusted mortality risk for adults with vs. without NDDs. Upper extremity fractures were associated with 39% greater unadjusted mortality rate, but this was not statistically significant (95% CI = 0.97–1.98). However, after adjusting for age, sex, and other demographic variables, adults with NDDs had 76% greater mortality risk following an upper extremity fracture. Moreover, there was a group by sex interaction for the upper extremities, with the difference in mortality risk present among men, but not women, with vs. without NDDs. This study did not find evidence of difference in mortality rate or risk between adults with and without NDDs based on low-trauma fracture of the vertebral column or hip. The differential association of site-specific fracture location with post-fracture complications may be due to many factors. Individuals with NDDs exhibit inadequate development of bone and altered biomechanical loading patterns (e.g., due to physical disabilities) throughout growth, and adults with NDDs have poor skeletal preservation. The chronic burden of skeletal fragility throughout the lifespan may lead to site-specific

**Table 5**  
Crude 12-month post-fracture mortality rate and rate ratio (RR) and adjusted hazard ratio (HR) between adults with neurodevelopmental disabilities (NDDs) and without NDDs (reference) by fracture location.

	Mortality cases	Crude mortality rate	Mortality RR	Model 1	Model 2
	N	N per 100 person years	RR (95% CI)	HR (95% CI)	HR (95% CI)
Vertebral column					
Without NDDs	9397	7.38	Reference	Reference	Reference
With NDDs	52	6.87	0.93 (0.71, 1.22)	1.17 (0.89, 1.54)	1.16 (0.88, 1.52)
Hip					
Without NDDs	8779	11.00	Reference	Reference	Reference
With NDDs	56	9.39	0.85 (0.66, 1.11)	1.25 (0.96, 1.63)	1.26 (0.97, 1.65)
Lower extremities					
Without NDDs	2790	2.07	Reference	Reference	Reference
With NDDs	36	3.51	1.69 (1.22, 2.35)	2.41 (1.73, 3.35)	<sup>a</sup>
Upper extremities					
Without NDDs	3760	2.48	Reference	Reference	Reference
With NDDs	31	3.45	1.39 (0.97, 1.98)	1.76 (1.23, 2.50)	<sup>a</sup>

ID, intellectual disabilities; CP, cerebral palsy; ASD, autism spectrum disorders; CI, confidence interval. Model 1 adjusted for age, sex, race, and US region. Model 2 adjusted for age, sex, race, US region, cardiovascular diseases (i.e., ischemic heart diseases, heart failure, cerebrovascular diseases, and/or hypertension), diabetes (i.e., type 1 or 2, primary or secondary), chronic obstructive pulmonary diseases, and cancer. Vertebral column, N = 148,310; hip, N = 96,878; lower extremities, N = 152,274; upper extremities, N = 169,546.

<sup>a</sup> Number of mortality cases insufficient for analysis (N < 40).

vulnerability to fractures unique to these populations (e.g., distal femur fractures most common for cerebral palsy [48]), which may in turn impact health and survival outcomes. Better understanding site-specific effects of fracture on health outcomes requires further research, as this may lead to more targeted interventions to mitigate fracture and its disease sequela for adults with NDDs.

When analyses were stratified by the NDD subgroups, adults with ID only had greater crude post-fracture mortality rate compared to adults without NDDs at the 6- and 12-month time points. However, after statistically accounting for age, sex, and other demographic variables using Cox regression where analyses were able to be performed, the HR for post-fracture mortality was greater for adults with ID only and ASD only, but not CP only, compared to adults without NDDs. Although, stratifying by NDD subgroups resulted in a small number of mortality cases for some groups, possibly leading to unreliable point estimates and CI. Therefore, interpretations for the NDD subgroups should be done so with caution.

The finding of similar mortality risk between adults with CP only and adults without NDDs raises an important issue, in that the post-fracture mortality rates in this study may be underestimating the extent of the problem for these adult NDD populations. Study findings were derived from a nationwide private insurance database, which represents a healthier segment of the NDD populations [29,49]. To support this notion, we found that the prevalence of comorbidity among the NDD groups, which increases the medical complexity and needs of the individual [50], was only 9.8%. This estimate is lower than expected based on other population-based studies [50,51]. Further, the average age of death for our sample of adults with NDDs that sustained a low-trauma fracture was 69.8 years, which is higher than previously reported from large-scale studies [30–32]. In regards to CP, the study sample may have been disproportionately biased to reflect a less skeletally fragile patient population, relative to ID and ASD. Part of the severity spectrum for CP includes motor function deficits and ranges from independent ambulation (i.e., no need for assistive walking devices) to using an electric-powered wheelchair for mobility. This considerable range in mechanical loading ability leads to large variation in the extent of skeletal fragility for this population. In previous studies, we have found the prevalence of osteoporosis, a predictor of low-trauma fracture, among privately-insured adults aged 18–64 years with CP ( $n = 5555$ ; osteoporosis prevalence, 5.5%) [29] was higher than adults without CP (1.3%), but considerably lower than what we previously published from a clinical-based sample of adults with CP ( $n = 1395$ ; osteoporosis prevalence,  $\sim 10\%$  for 18–40 year olds,  $\sim 15\%$  for 41–50 year olds,  $\sim 26\%$  for  $> 50$  year olds) [52]. In that clinical-based study [52], over half of the sample had moderate to severe forms of CP, and the prevalence of musculoskeletal morbidities among adults with moderate to severe forms of CP are about double compared to adults with milder forms [26]. Therefore, study findings with regard to CP should be interpreted with caution. Further research is required that leverages data that better represents the diversity of the CP population.

While factors that explain fracture-induced premature mortality still need to be elucidated, there may be a different set of risk factors contributing to short- and long-term post-fracture mortality [53], which may be further confounded by the NDD condition and fracture site. Among older adults, pre-fracture presence of chronic diseases [54], functional ability [55], and physical capacity (e.g., muscle strength) [56] are predictors of early post-fracture mortality, and a subsequent fracture exacerbates premature mortality [56]. In general, the overall physiological stress induced by a low-traumatic fracture may create an unfavorable biological environment that increases risk for post-fracture complications and premature death, either through direct or indirect mechanisms [53]. This places individuals with NDDs at particular risk for post-fracture complications because of the greater lifetime burden of unhealthful aging caused by low fitness levels [12,13], excess health problems experienced in childhood (e.g., excess body fat) [14–17,20,22–24], and elevated prevalence of chronic diseases in

adulthood [26,29,34,57]. Therefore, adults with NDDs may already have a vulnerable physiological environment and skeletal fragility (e.g., history of fractures), and sustaining a low-trauma fracture may increase susceptibility to post-fracture complications. Unfortunately, we were not able to ascertain lifetime fracture history.

Further, each NDD group has a considerable spectrum of severity, concomitant with a range of health complications and medical needs. For example, the multimorbidity prevalence ( $\geq 2$  chronic diseases) among 18–30 year olds with severe forms of cerebral palsy is more than double that of 18–30 year olds with mild to moderate forms (33.9% vs. 15.2%, respectively) [26], and the mortality rate is increased among lower vs. higher functioning individuals with autism spectrum disorders [32]. In summary, the risk factors for immediate and long-term post-fracture premature mortality among adults with NDDs may encompass general risk factors, such as pre-fracture chronic diseases, but there may also be risk factors unique to these NDD populations, such as the type and severity of the NDD condition, use of assistive walking device or wheelchair, and medications/polypharmacy. Future studies are needed to disentangle the general and patient-specific risk factors that may differentially associate with post-fracture premature mortality, and to what extent the fracture-mortality association is mediated by post-fracture complications, such as chronic diseases, pneumonia, for example.

The limitations of this study must be discussed. First, as noted above, the sample may reflect a higher functioning and healthier segment of the NDD population, which may explain the relatively small number of deaths and older than expected age of death. It is therefore possible that there is a bigger population health issue than the current database can capture. Study conclusions, especially for CP, should be considered within the scope of this particular population of privately-insured adults. Second, we were unable to reliably determine severity of these NDD conditions, which could have provided further clinical interpretation with stratification by severity levels. Third, the observational design of the study introduces inherent bias due to unmeasured confounding. We therefore computed e-values to estimate the extent of unmeasured confounding, which determines the minimum strength of association with the exposure and outcome needed to fully explain away a specific exposure-outcome association, conditional on the set of covariates [58,59]. The highest level covariate-adjusted Cox models for the 12-month time point were used for the NDD groups where appropriate (e.g., model 2 for NDDs; model 1 for ASD only). The estimated e-value (lower 95% CI) needed to fully explain away the effect for the NDD group variable was 2.28 (1.86) for the entire sample of adults with NDDs, 3.00 (2.34) for adults with ID only, and 2.64 (1.49) for adults with ASD only. For fracture locations, it was 4.25 (2.85) for the lower extremities and 2.92 (1.76) for the upper extremities. Given the large e-values, it appears unlikely that unmeasured confounding largely biased effect estimates for the exposure variable. Fourth, this study was underpowered to examine differences in post-fracture mortality rate for adults with NDDs by race and for many of the NDD subgroups, such as comorbid NDDs. Studies of the general population have shown racial differences for post-fracture mortality rates [60]; whether adults with NDDs follow a similar racial pattern requires further investigation. Fifth, there may be other factors or comorbidities associated with premature mortality among adults with NDDs that were not assessed in the current study. Sixth, while the medical conditions examined have shown good accuracy, it is unknown if there are substantive differences in the diagnostic accuracy of these conditions between groups.

## 5. Conclusion

We report for the first time that adults with NDDs have greater mortality risk within 12 months following a low-trauma fracture compared to adults without NDDs, despite an age difference of about a decade for those that died. Of the fracture sites, lower and upper

extremities may be more strongly associated with 12-month mortality risk for adults with vs. without NDDs. Conducting similar analyses using a more general (i.e., not privately insured) population may reveal larger disparities and we suggest such an investigation is warranted given our findings. Further research is needed to identify risk factors for excess premature mortality post-fracture and post-fracture complications that may exacerbate premature mortality among adults with NDDs.

### Declaration of competing interest

None.

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