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WHITNEY ET AL.

ADULTS WITH CEREBRAL PALSY HAVE HIGHER PREVALENCE OF FRACTURE

Adults With Cerebral Palsy Have Higher Prevalence of Fracture Compared With Adults Without Cerebral Palsy Independent of Osteoporosis and Cardiometabolic Diseases[1]

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ABSTRACT

Individuals with cerebral palsy (CP) have an increased risk of fracture throughout their lifespan based on an underdeveloped musculoskeletal system, excess body fat, diminished mechanical loading, and early development of noncommunicable diseases. However, the epidemiology of fracture among adults with CP is unknown. The purpose of this cross-sectional study was to determine the prevalence of fracture among a large sample of privately insured adults with CP, as compared with adults without CP. Data were from the Optum Clinformatics Data Mart (Eden Prairie, MN, USA), a deidentified nationwide claims database of beneficiaries from a single private payer. Diagnostic codes were used to identify 18- to 64-year-old beneficiaries with and without CP and any fracture that consisted of osteoporotic pathological fracture as well as any type of fracture of the head/neck, thoracic, lumbar/pelvic, upper extremity, and lower extremity regions. The prevalence of any fracture was compared between adults with (n = 5,555) and without (n = 5.5 million) CP. Multivariable logistic regression was performed with all-cause fracture as the outcome and CP group as the primary exposure. Adults with CP had a higher prevalence of all-cause fracture (6.3% and 2.7%, respectively) and fracture of the head/neck, thoracic, lumbar/pelvic, upper extremity, and lower extremity regions compared with adults without CP (all $p < 0.01$). After adjusting for sociodemographic and socioeconomic variables, adults with CP had higher odds of all-cause fracture compared with adults without CP (OR 2.5; 95% CI, 2.2 to 2.7). After further adjusting for cardiometabolic diseases, adults with CP had higher odds of all-cause fracture compared with adults without CP (OR 2.2; 95% CI, 2.0 to 2.5). After further adjusting for osteoporosis, adults with CP still had higher odds of all-cause fracture compared with adults without CP (OR 2.0; 95% CI, 1.8 to 2.2). These findings suggest that young and middle-aged adults with CP have an elevated prevalence of all-cause fracture

compared with adults without CP, which was present even after accounting for cardiometabolic diseases and osteoporosis.

KEY WORDS: FRACTURE; CEREBRAL PALSY; EPIDEMIOLOGY; OSTEOPOROSIS; CARDIOMETABOLIC DISEASE

Introduction

Cerebral palsy (CP) arises from damage or malformation of the developing brain, and is the most common pediatric-onset physical disability.[1–5] The etiology of CP leads to neurological[6] and neuromuscular[7,8] alterations, which prevent optimal fulfillment of motor function capacity and mechanical loading.[7–10] Children with CP are therefore predisposed to an inadequate development of muscle and bone during growth,[9–13] with the underdevelopment of the musculoskeletal system apparent prior to their 2nd birthday.[14] The result is a structurally weak musculoskeletal system,[9,11,12] which helps to explain the heightened susceptibility for acquiring low-energy fractures among this pediatric population.[15–17] Importantly, as children with CP transition into and throughout adulthood, there is a further loss of ambulatory ability with resultant decrease in weight-bearing,[18] which increases fracture risk throughout the lifespan. However, knowledge of fracture epidemiology among adults with CP is lacking.

Previous fracture epidemiology research has led to important contributions towards understanding the burden of fracture and informing health-related policies.[19] Among the general population of older adults, fracture is a major cause of acquired functional disability,[20] morbidity,[21,22] lower quality of life,[23,24] and early mortality,[20,25–28] and represents a substantial economic burden.[29] However, limiting the focus of fracture epidemiology to older adults

represents a problem because many rehabilitation populations, such as adults with CP, have an early development of noncommunicable diseases[30] and a lower life expectancy[31,32] compared with the general population. Therefore, this population is likely underrepresented in fracture epidemiology and surveillance, resulting in insufficient clinical information, which may potentially misguide approaches to policy reform and systems-level decision-making processes. This is reflected in the updated 2018 evidence-based guidelines set forth by the U.S. Preventive Services Task Force,[19] which recommends screening for fracture in all adults ≥65 years of age, with no recommendations for the growing adult CP population[33,34] or other pediatric-onset disabilities.

The lack of fracture epidemiology among individuals with CP is concerning. Young adults (18 to 30 years) with CP have an elevated prevalence of musculoskeletal diseases, which is 10 times higher compared with young adults without CP.[30] In particular, the prevalence of osteoporosis in young adults with CP (8%)[30] was recently shown to be similar to the general population of adults ≥50 years of age (10%).[35] Moreover, the prevalence of osteoporosis becomes more pronounced throughout the adult lifespan among individuals with CP.[36] Therefore, evaluating fracture risk among adults with CP prior to reaching their older adult years is urgently needed, as this knowledge could inform strategies to prevent or lessen the burden of fracture among these patients. Accordingly, the primary objective of this study was to determine the prevalence of fracture among young and middle-aged adults with CP compared with adults without CP, using a large, nationwide insurance database. We hypothesized that adults with CP would have higher prevalence of fracture compared with adults without CP. The secondary objective was to determine if the elevated prevalence of noncommunicable diseases, including cardiometabolic diseases and osteoporosis, moderates the association between CP and fracture.

Materials and Methods

Data source

Data came from the Clinformatics Data Mart Database (OptumInsight, Eden Prairie, MN, USA). This is a nationwide deidentified single private payer administrative claims database of 79 million beneficiaries that have commercial or Medicare Advantage health plans from 2001 to 2017. These private-payer administrative claims data include service utilization throughout enrollment on their insurance plan. This database has been used to examine trends of cardiometabolic diseases and conditions among adults with CP,[37] as well as other conditions and their associated complications.[38-40] Data are deidentified and the University of Michigan Institutional Review Board approved this study as nonregulated.

Sample selection

Data were obtained from the most recent available year, 2016, which contained more than 16 million beneficiaries. Beneficiaries that were between 18 and 64 years of age, had 12 full months of continuous enrollment, and had at least one service utilization in 2016 were considered for this investigation. All conditions, including CP, outcome measures, cardiometabolic diseases, and osteoporosis were identified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes, and are presented in Table 1. The final sample comprised 5.5 million young and middle-aged adults, including 5555 with CP.

Fracture

The primary outcome measure was all-cause fracture, which was represented as any type of fracture based on any cause (eg, unspecified, pathological fracture associated with osteoporosis) at any anatomical location in 2016. Identifying all-cause fracture for populations

with other pediatric-onset disabilities using ICD-10 codes has been previously described.[41] The secondary outcome measure was the prevalence of all-cause fracture based on anatomical location, including the head/neck, thoracic, lumbar/pelvic, upper extremity (shoulder/arms, forearm, wrist/hand), and lower extremity (femur, tibia/fibula, ankle, foot) regions.

Covariates

Covariates were selected based on their relevance to adults with CP, fracture, and availability in the administrative claims database.[30,36,42,43] Sociodemographic and socioeconomic variables included age, sex, ethnic group, and education level. We have previously reported that adults with CP had a higher prevalence of cardiometabolic diseases and osteoporosis compared with adults without CP.[30] Cardiometabolic diseases and osteoporosis are associated with skeletal fragility in the non-CP population,[42,43] and were therefore included as covariates grouped in the following categories: ischemic heart disease (eg, atherosclerotic heart disease); cerebrovascular disease (eg, cerebral infarction); hypertensive and other cardiovascular disease (eg, hypertension, heart failure); type 2 diabetes; and osteoporosis.

Statistical analysis

Descriptive characteristics were summarized as mean (SD) for continuous variables and percentage (frequency) for categorical variables. Group differences in fracture variables were examined using χ^2 tests with $p < 0.01$ to detect statistical significance between groups. To examine the prevalence of all-cause fracture across age and by sex, age was stratified into the following groups to reflect different stages of the adult lifespan, as guided by previous studies for adults with CP[30,36]: 18 to 30, 31 to 40, 41 to 50, and 51 to 64 years of age. Group differences for

each age group and sex were examined using χ^2 tests with $p < 0.01$ to detect statistical significance between groups.

We then performed multivariable logistic regression with the outcome as all-cause fracture and the primary exposure variable as CP group (CP, without CP) for the entire sample. Models were introduced in a serial stepwise order: Model 1 adjusted for age (as continuous), sex, and education level; Model 2 adjusted for the variables in Model 1, ischemic heart disease, cerebrovascular disease, hypertensive and other cardiovascular disease, and type 2 diabetes; Model 3 adjusted for the variables in Model 2 and osteoporosis. We examined for an interaction between group (CP, without CP) with sex and education level for each model. If the interaction was not significant, subsequent analyses were performed. The main effect of the CP group was interpreted. We did not initially include ethnicity in the model as to avoid truncation of the data because of the extent of missingness/unknown (approximately 25%). However, we performed a sensitivity analysis among individuals with complete/known data for ethnicity by further adjusting the multivariable logistic regression models for ethnicity. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) using two-sided 95% CIs.

Results

Descriptive characteristics and prevalence of cardiometabolic diseases and osteoporosis for young and middle-aged adults with CP (n = 5,555) and without CP (n = 5.5 million) are presented in Table 2. The prevalence of all-cause fracture and by the anatomical location for adults with CP and without CP are presented in Table 3. Adults with CP had higher prevalence of all-cause fracture at any location (6.3%, 2.7%), and all-cause fracture of the head/neck (0.8%, 0.2%), thoracic (0.7%, 0.3%), lumbar/pelvic (0.5%, 0.2%), upper extremity (1.6%, 1.0%), and

lower extremity (3.3%, 1.2%) regions (all $p < 0.01$). Figure 1 shows the prevalence of all-cause fracture at any location across age groups and by sex. For all age groups and sex, individuals with CP had a higher prevalence of all-cause fracture at any location compared with individuals without CP (all $p < 0.01$).

The adjusted odds ratios of all-cause fractures are presented in Table 4. After adjusting for age, sex, and education level (Model 1), adults with CP had higher odds of all-cause fracture compared with adults without CP (OR 2.5; 95% CI, 2.2 to 2.7). After further adjusting for cardiometabolic diseases (ie, ischemic heart disease, cerebrovascular disease, hypertensive and other cardiovascular disease, and type 2 diabetes; Model 2), the odds of all-cause fracture remained significantly elevated among adults with CP compared with adults without CP (OR 2.2; 95% CI, 2.0 to 2.5). Finally, with further adjustment for osteoporosis (Model 3), the odds of all-cause fracture remained significantly elevated among adults with CP compared with adults without CP (OR 2.0; 95% CI, 1.8 to 2.2).

The results of the sensitivity analysis revealed that ethnicity had no effect on all-cause fracture for the CP group variable (n = 4,128,412) for Model 1 (OR 2.5; 95% CI, 2.2 to 2.8), Model 2 (OR 2.3; 95% CI, 2.0 to 2.6), or Model 3 (OR 2.0; 95% CI, 1.8 to 2.3).

Discussion

The chief finding of this investigation is that young and middle-aged adults with CP had a higher prevalence and odds of all-cause fracture compared with adults without CP, even after accounting for their higher prevalence of cardiometabolic diseases and osteoporosis. This is a critical finding because fractures represent a major source of economic burden,[29] disease,[21,22] and mortality[20,25–28] in the general population of older adults. The findings from the current

investigation highlight the need for improvement of screening strategies to allow for earlier detection of fracture risk among individuals with CP. These efforts could improve future health outcomes for individuals with CP, as previous randomized control trials involving screening for fracture risk[44] and other interventions[44–46] have shown promise in minimizing fractures and their associated burdens among other at-risk populations.

To our knowledge, the surveillance of fracture burden among adults with CP has not been reported. Identifying the prevalence of fracture is an important first step towards understanding secondary chronic disease trajectories and mortality profiles among this underserved population, which is projected to expand over the coming decades. Poor overall health status is a strong predictor of functional and survival outcomes postfracture for the general population of older adults.[20] Our previous work has shown that individuals with CP do indeed have poor overall health status prior to reaching their older adult years, as evidenced by an early development of noncommunicable diseases (eg, cardiometabolic diseases) and multimorbidity.[30,36,37,47,48] Fractures among this population may represent a more devastating burden of adverse health and shorter survival, and therefore requires further attention.

In the current study, we found that adults with CP had a higher prevalence of fracture across all regions of the body compared with adults without CP. We also found that the odds of any fracture was more than 2 times higher among adults with CP, even after adjusting for cardiometabolic diseases, which are more prevalent in the adult CP population[30] and are associated with skeletal fragility in the non-CP population.[42,43] Another important factor for fracture risk is osteoporosis. We have previously reported that the prevalence of osteoporosis is similar among young adults with CP (18 to 30 years) as compared with the general population of adults ≥50 years of age,[35] and becomes progressively more prevalent throughout the adult CP

lifespan.[36] In the current study, after further adjusting for osteoporosis, the higher odds of any fracture persisted, and were 2 times higher among adults with CP compared with adults without CP (Table 4). However, the lack of association between osteoporosis and elevated fracture risk among adults with CP may be in part because of underdetection of osteoporosis in this population within the clinical setting, given that the data for this study were derived from diagnostic codes. Fracture would be less sensitive to bias based on underdetection because, except for some vertebral fractures, most fractures result in a hospital visit. Screening for fracture risk and osteoporosis among younger adults is not common clinical practice, even among populations with known skeletal fragility.[19] Therefore, interpretation should be made with caution. Moreover, factors other than osteoporosis may contribute to the elevated fracture risk among adults with CP. The pathogenesis of heightened fracture susceptibility can be largely accounted for by the status of fall risk, in addition to poor musculoskeletal health.[49] CP is a neuromuscular condition, so gait abnormalities and muscle weakness may increase the likelihood of falls in this population,[50] thus increasing the risk of low-energy fracture. Unfortunately, in the current investigation, we were unable to ascertain cause of fracture, which may have provided unique insights into the mechanisms of fracture risk among adults with CP.

It is important to note that our sample of privately insured young and middle-aged adults is suspected to be a higher-functioning segment of the CP population, leading to a likely underrepresentation of the true extent of the fracture prevalence for this population. Using claims-based data, it is not possible to determine the severity of disabilities or the level of motor impairment. Therefore, our suspicion is based on the premise that to be enrolled in private insurance, one must purchase their own insurance, be covered through employment, or be married to someone who has private insurance. Both employment and marriage rates are lower

among adults with pediatric-onset disabilities compared with the general population,[51] which is likely more pronounced among individuals with more-severe forms or more medically complex disabilities. Evidence to support the likelihood that our sample reflects a higher functioning segment of the CP population is that the osteoporosis prevalence estimate found in this study (5.5%) is about half that of what we have previously reported from adults with CP from the southeastern Michigan region.[36] In our previous study,[36] over half of the sample had moderate-to-severe forms of CP. There is a substantial difference in the prevalence of osteoporosis among milder versus more severe forms of CP.[30] Therefore, the finding from the current investigation of an elevated prevalence of fracture is likely a conservative estimate.

The burden of poor musculoskeletal health among individuals with CP is a long-standing pathophysiological process that starts in early childhood. Concomitant with the underdeveloped musculoskeletal system leading to increased low-energy fracture risk in childhood,[15–17] children with CP also have elevated bone marrow fat infiltration.[9] Elevated bone marrow fat may impede skeletal acquisition independent of or synergistic with their low levels of physical activity[9,10] and inadequate mechanical loading in children with CP.[52] Although the mechanisms are unknown,[52] the elevated bone marrow fat infiltration in children with CP may positively associate with sclerostin, which is an osteocyte-derived molecule that prevents bone formation and stimulates bone marrow adipogenesis.[53,54] In a study by Shin and colleagues,[55] nonambulatory adults with CP had higher sclerostin levels compared with ambulatory adults with CP. This is consistent with findings that sclerostin is regulated by mechanical loading.[53,56] There is also some evidence that hypogonadism in adults with CP may lead to detrimental changes in body composition and BMD.[57] Taken together, there is a complex intricacy of mechanical and endocrine/metabolic factors that negatively impact skeletal development and

preservation, thus increasing fracture risk throughout the lifespan among individuals with CP. Importantly, sustaining a fracture may be a salient factor initiating or exacerbating musculoskeletal and nonmusculoskeletal diseases among this population; however, these pathways have yet to be elucidated.

One limitation of this study is that as previously mentioned, the overall sample of adults with CP included here may not represent the entire CP population, but rather a higher-functioning segment of this population. Therefore, study findings are likely underreporting the extent of the fracture prevalence among adults with CP. Another limitation is that we were unable to determine fracture history or cause of fracture from cross-sectional data. The pathophysiological processes leading to heightened fracture susceptibility in adulthood starts early in the childhood years. Fracture among individuals with CP may predict subsequent fractures,[58] thus leading to unmeasured confounding. Future studies are needed to examine the causes of fracture, as this may provide novel insight for informing target-specific interventions for the prevention of fracture among individuals with CP.

In conclusion, study findings suggest that adults with CP have an increased prevalence of fracture, even after accounting for their higher prevalence of cardiometabolic diseases and osteoporosis. Fracture in the general population of older adults represents a major cause of noncommunicable disease development,[21,22] poor quality of life,[23,24] and early mortality.[20,25–28] Future work is needed to identify fracture-related morbidity and mortality trajectories among individuals with CP throughout the lifespan. Knowing this information could assist in planning and developing interventions (eg, physical activity programs) to increase fracture resistance and decrease morbidity among individuals with CP. Further, work is needed to identify strategies to

improve prevention, treatment, and management of fracture and its subsequent complications among individuals with CP.

Disclosures

All authors state that they have no conflicts of interest.

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Fig. **1.** Prevalence of all-cause fracture at any location for men (*A*) and women (*B*) with and without cerebral palsy (CP).

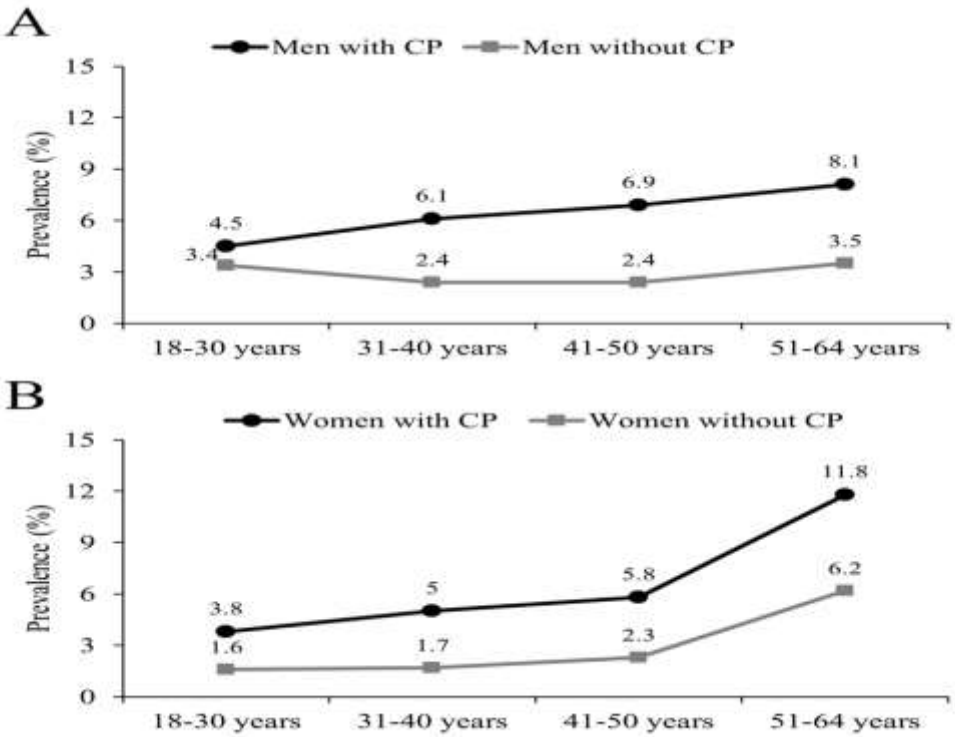

Figure 1