Racial differences in skeletal fragility but not osteoarthritis among women and men with cerebral palsy☆

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ABSTRACT

Background: Adults with cerebral palsy (CP) have increased risk for skeletal fragility and osteoarthritis. However, racial differences in these outcomes have not been examined. Such knowledge could improve patient-specific clinical care for the prevention and management of these conditions. The purpose of this study was to determine if there were racial differences in the prevalence of osteoporosis, all-cause fracture, and osteoarthritis among young and middle-aged adults with CP.

Methods: Data from 2016 were extracted from a random 20% sample of the Medicare fee-for-service database. International Classification of Diseases, Tenth Revision, Clinical Modification codes were used to identify 18–64 year olds with CP, as well as osteoporosis, all-cause fracture, osteoarthritis, and neurodevelopmental and noncommunicable disease comorbidities.

Results: Of the 16,488 adults with CP, 13,334 were White, 2,477 were Black, and 677 were Hispanic. The age-standardized prevalence of osteoporosis (women: 12.9%, 9.0%, 8.3%, respectively; men: 9.2%, 4.8%, 7.9%, respectively) and fracture (women: 7.4%, 4.2%, 9.9%; men: 6.0%, 2.3%, 6.0%) was lower for Black adults with CP compared to White adults with CP (all \( p < 0.005 \)). No racial differences were observed for age-standardized prevalence of osteoarthritis (women: 13.6%, 14.4%, 9.6%; men: 10.7%, 10.4%, 12.7%). The racial differences between Black and White adults with CP remained even after adjusting for age, U.S. region, neurodevelopmental comorbidities, and several noncommunicable diseases for osteoporosis (women: OR = 0.66, 99.5% CI = 0.48–0.91; men: OR = 0.51, 99.5% CI = 0.35–0.75) and fracture (women: OR = 0.57, 99.5% CI = 0.37–0.89; men: OR = 0.39, 99.5% CI = 0.23–0.68).

Conclusions: Study findings suggest racial differences in skeletal fragility among young and middle-aged adults with CP, with White women and men with CP having greater risk compared to Black women and men with CP. This study found no evidence of racial differences in the prevalence of osteoarthritis.

1. Introduction

Cerebral palsy (CP) is the most common physical disability of childhood and affects about 3.1 per 1000 children in the U.S. (Christensen et al., 2014). The etiology of CP and the resulting clinical phenotype varies, encompassing genetic predisposition, brain lesions, and maternal/environmental exposures leading to damage or malformation of the developing brain (Villamor et al., 2017). While the health, function, and medical profiles are complex and heterogeneous, what links all individuals with CP is some degree of motor impairment, risk for restriction in activities of daily living, and low societal integration. Collectively, these factors increase susceptibility for poor growth and development, especially of the musculoskeletal system.

Children with CP have low levels of physical activity (Whitney et al., 2017; Johnson et al., 2009) and an underdeveloped musculoskeletal system (Whitney et al., 2017; Johnson et al., 2009; Modlesky et al., 2015) compared to typically developing children, regardless of the severity of CP. The result is a skeletally fragile phenotype in the trabecular (Modlesky et al., 2015) and cortical (Whitney et al., 2017; Modlesky et al., 2009) bone compartments with overall bone strength deficits ranging from 34% (milder forms of CP) (Whitney et al., 2017) to 71% (moderate-to-severe forms of CP) (Modlesky et al., 2009) compared to age, sex, and race matched typically developing children. Further, children with CP have elevated musculoskeletal (Whitney

Abbreviations: CP, cerebral palsy
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weight) (Wu et al., 2011). Racial di-
differences in the general population for these conditions. Evidence suggests racial CP, despite the well-documented literature on racial di-
ferences (i.e., osteoporosis and fracture) and osteoarthritis among adults with
lacking for determining if racial di-
been made (Whitney et al., 2019b). However, epidemiologic studies are
recommendations for earlier screening and preventive strategies have
Whitney et al., 2018d; Whitney et al., 2019b; O’Connell et al., 2019),
stantial economic burden (Xie et al., 2016; Burge et al., 2007). When
counting the recent literature regarding the magnitude of the problem of
these conditions for adults with CP (Whitney et al., 2018c; Whitney et al., 2018d; Whitney et al., 2019b; O’Connell et al., 2019),
recommendations for earlier screening and preventive strategies have
made (Whitney et al., 2019b). However, epidemiologic studies are
lacking for determining if racial differences exist for skeletal fragility 
(i.e., osteoporosis and fracture) and osteoarthritis among adults with 
CP, despite the well-documented literature on racial differences within
the general population for these conditions. Evidence suggests racial
differences in the prevalence of and risk factors for CP (e.g., birth
weight) (Wu et al., 2011). Racial differences in developing CP and the
resulting health complications experienced throughout the lifespan may
stem from behavioral factors (e.g., pre- and post-natal care), institutional
factors (e.g., healthcare disparities), socioeconomic factors (e.g.,
neighborhood poverty) (Messer et al., 2008), psychosocial stressors
(Dailey, 2009), genetics (Menon et al., 2006), and epigenetics (Crowgy
et al., 2018; Mohandas et al., 2018), which are all associated with the
pathophysiology of skeletal fragility and osteoarthritis. Taken together, 
individuals with CP may have a unique interplay between genetic, 
environmental, and behavioral constructs that lead to early develop-
ment of skeletal fragility and osteoarthritis, which may be further
fluenced by race. However, little research attention has been given to
investigating racial differences in health outcomes for this underserved
adult population. By knowing racial differences in skeletal fragility and
osteoarthritis, clinicians treating adults with CP may be better equipped
to provide clinical care by adopting earlier screening, treatment, and
preventive strategies unique to their patient to optimize skeletal and
joint health throughout the lifespan. Therefore, the primary objective of
this study was to determine if there were racial differences among
young and middle-aged White, Black, and Hispanic individuals with CP
for the prevalence of osteoporosis, all-cause fracture, and osteoarthritis.

2. Methods

2.1. Data source

Data were extracted from a random 20% sample of the Medicare fee-for-service database from the Centers for Medicare and Medicaid Services (CMS). Claims data from the Medicare Provider Analysis and Review, Outpatient, and Carrier files (Parts A and B), which are primarily used for reimbursement purposes, were leveraged from the year 2016. Pharmacy claims were not available for this study. Eligibility for Medicare enrollment in 2016 includes all individuals 65 years of age and older and individuals with disabilities at any age and of any income status. Since the data are de-identified, the local Institutional Review Board approved this study as non-regulated.

2.2. Sample selection

International Classification of Diseases, Tenth Revision, Clinical
Modification (ICD-10) codes were used to identify all medical condi-
tions. ICD-10 codes are entered into the billing system by health service providers. Information regarding how diagnoses were made (e.g., DXA) or by whom (e.g., primary care provider) are not available. Individuals that were covered by Health Maintenance Organization plans were excluded because of incomplete claims, thus biasing estimates. Inclusion criteria for this study were: at least one claim in any position for any CP diagnosis (G80 family codes; spastic hemiplegia, spastic diplegia, spastic quadriplegia, ataxoid, ataxic, and other/unspecified CP); between 18 and 64 years of age; 12 months of continuous enroll-
ment in a health plan in 2016; at least one medical service utilization in
2016; and the primary race was identified as White, Black, or Hispanic.
Race was identified using the information provided by CMS. Information regarding how race was identified (e.g., self-report) is not available. The single claim-based definition to identify pediatric-onset conditions has shown good accuracy using administrative claims data, with sensitivity of 99% and positive predictive value of 79% (Reeves et al., 2014).

2.3. Outcome measures

The three prevalent outcomes measures, osteoporosis, all-cause
fracture, and osteoarthritis, were identified by using at least one claim
in any position. Osteoporosis was identified as osteoporosis with (M80
family codes) or without (M81 family codes) current pathological
fracture. Fracture was identified as osteoporosis with current patholo-
gical fracture (M80 family codes) or fracture of the cervical vertebra
(S12 family codes), ribs, sternum, or thoracic spine (S22 family codes),
lumbar spine or pelvis (S32 family codes), or tibia or fibula (S82 family codes). Osteoarthritis was identi-
fied as polyosteoarthritis (M15 family codes), hip osteoarthritis (M16
family codes), knee osteoarthritis (M17 family codes), first carpome-
tacarpal joint osteoarthritis (M18 family codes), or other/unspecified
osteoarthritis (M19 family codes). The single claim-based algorithm to
identify osteoporosis, fracture, and osteoarthritis has shown excellent
ability to identify these medical conditions, as evidenced by positive
predictive values up to 92% (Leslie et al., 2011), 97%
(Narongroeknawin et al., 2012), and 94% (Shrestha et al., 2016), re-
spectively.

2.4. Covariates

Age, sex, race (White, Black, Hispanic), and state of residency were
available for analysis. A variable indicating region of U.S. (West, Midwest, South, and Northeast) was constructed to account for differ-
ences in region which may influence the outcome measures, such as
climate (e.g., sunlight exposure and vitamin D status) and cultural (e.g.,
activity, diet) factors. Other important socioeconomic status indicators
(e.g., income, education) were not available. Further, data regarding severity of CP using common clinical measures (e.g., gross motor
function classification system) are not available in administrative
claims, and > 70% of the cohort had “other” or “unspecified” CP, thus
not allowing for stratification or statistical adjustment for the clinical
subtypes of CP (e.g., spasticity/athetoid, hemiplegic). Since co-
morbidity with neurodevelopmental conditions increases the medical
complexity of CP (Reid et al., 2018), dichotomous variables were
constructed for the presence of common neurodevelopmental conditions (i.e., intellectual disabilities [F70-79 family codes], autism spectrum disorders [F840 and F843-49 family codes], and epilepsy [G40 family codes]). To get a proxy of overall health status, dichotomous variables were constructed for the presence of the following non-communicable diseases: ischemic heart diseases (I20-22 and I24-25 family codes), cerebrovascular diseases (I60-69 family codes), hypertensive (I10-16 family codes) and other cardiovascular diseases (heart failure, I50 family codes; atherosclerosis, I70 family codes), diabetes (including type 1 and 2: E08-13 family codes), mood affective disorders (F30-39 family codes), anxiety disorders (F40-48 family codes), substance abuse disorders (abuse or dependence F10-16 and F18-19 family codes including alcohol, opioid, cannabis, sedative/ hypnotic/anxiolytic, cocaine, other stimulant, hallucinogen, inhalant, and other psychoactive substance related disorders), chronic obstructive pulmonary disease (J41-44 family codes), chronic kidney disease as previously described (Muntner et al., 2015) (N03, N18, E112, I12-13, and R80 family codes), liver diseases (K70-77 family codes), and malignant cancer (C00–7B family codes).

2.5. Statistical analysis

Descriptive characteristics were summarized and racial differences in descriptive characteristics were examined using the independent t-test or Chi-square test. \( P \leq 0.005 \) (two-tailed) was used to determine statistical significance for this large sample, as recommended by a coalition of methodologists to detect new discoveries (Benjamin et al., 2018; Ioannidis, 2018). To be consistent with the \( p \)-value threshold, 99.5\% binomial confidence intervals (CI) were calculated for the prevalence estimates of neurodevelopmental and noncommunicable disease comorbidities as the sample proportion \( \pm \) the margin of error using a \( z \)-value of 2.807.

Direct age-standardization (Age Standardization and Population Counts and National Center for Health Statistics, 2014) for osteoporosis, fracture, and osteoarthritis was performed for each racial group and by sex. The 2016 U.S. adult population was used as a standard population. The U.S. Census Bureau released a table on age (5-year age brackets) and sex composition in the U.S. for 2016 (Age and Sex Composition in the United States: 2016, 2018). In order to make use of the population table in 5-year age groups, it was assumed that age was evenly distributed within the 15–19 year age bracket. Therefore, since 6.8\% of U.S. males were 15–19 years old, it was assumed that 2.722\% males were 18–19 years old (6.8\% \times (2/5)). A similar approach was performed for females.

Multivariable logistic regression models were developed separately for women and men with the outcome as osteoporosis in one set of analyses, fracture in another set of analyses, and osteoarthritis in the final set of analyses. The primary exposure variable for all models was race (reference: White). Model 1 adjusted for age, U.S. region, and neurodevelopmental comorbidities. Model 2 adjusted for the variables in model 1 and all noncommunicable diseases noted above. The main effect of race was interpreted. Effect estimates were reported as odds ratios (OR) with 99.5\% CI.

A sensitivity analysis was performed that required at least two claims on separate days to identify CP and all neurodevelopmental and noncommunicable disease comorbidities to determine the main effect of race on the outcome measures using the fully adjusted model.

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

3. Results

Unadjusted descriptive characteristics of 18–64 year olds with CP (\( n = 16,488 \)) stratified by White (\( n = 13,334 \)), Black (\( n = 2477 \)), and Hispanic (\( n = 677 \)) are presented in Table 1. White adults with CP were older than Black and Hispanic adults with CP and Black adults with CP were older than Hispanic adults with CP. There was a significant difference in the distribution of U.S. region by race (all \( p < 0.005 \)) with 54.3\% of Black adults with CP residing in the South and 35.0\% of Hispanic adults with CP residing in the West. White adults with CP were more likely to have intellectual disabilities compared to Hispanic adults with CP (\( p < 0.005 \)). White adults with CP had higher prevalence of mood affective disorders, anxiety disorders, and cancer compared to Black and Hispanic adults with CP, and hypertensive and other cardiovascular diseases compared to Hispanic adults with CP (all \( p < 0.005 \)). Black adults with CP had higher prevalence of cerebrovascular diseases, diabetes, and chronic kidney disease compared to White adults with CP, and hypertensive and other cardiovascular diseases compared to White and Hispanic adults with CP (all \( p < 0.005 \)).

3.1. Osteoporosis

The age-standardized prevalence of osteoporosis by sex is presented in Fig. 1. White women and men with CP had higher prevalence compared to Black women and men with CP (both \( p < 0.005 \)). No other statistical differences were observed across racial groups.

The adjusted odds for osteoporosis by sex is presented in Table 2. After adjusting for U.S. region and neurodevelopmental comorbidities (model 1) and compared to White adults with CP, the odds of osteoporosis was significantly lower for Black women (OR = 0.68; 99.5\% CI = 0.49–0.93) and men (OR = 0.51; 99.5\% CI = 0.35–0.74) with CP, but not for Hispanic women (OR = 0.61; 99.5\% CI = 0.29–1.29) or men (OR = 0.61; 99.5\% CI = 0.29–1.30) with CP. After further adjusting for all noncommunicable diseases (model 2), the odds were largely unchanged and remained significantly lower for Black women (OR = 0.66; 99.5\% CI = 0.48–0.91) and men (OR = 0.51; 99.5\% CI = 0.35–0.75) with CP.

3.2. Fracture

The age-standardized prevalence of fracture by sex is presented in Fig. 2. White women and men with CP had higher prevalence compared to Black women and men with CP (both \( p < 0.005 \)). No other statistical differences were observed across racial groups.

The adjusted odds for fracture by sex is presented in Table 3. After adjusting for U.S. region and neurodevelopmental comorbidities (model 1) and compared to White adults with CP, the odds of fracture was significantly lower for Black women (OR = 0.57; 99.5\% CI = 0.37–0.88) and men (OR = 0.38; 99.5\% CI = 0.22–0.65) with CP, but not for Hispanic women (OR = 1.09; 99.5\% CI = 0.53–2.23) or men (OR = 0.87; 99.5\% CI = 0.44–1.74) with CP. After further adjusting for all noncommunicable diseases (model 2), the odds were largely unchanged and remained significantly lower for Black women (OR = 0.57; 99.5\% CI = 0.37–0.89) and men (OR = 0.39; 99.5\% CI = 0.23–0.68) with CP.

3.3. Osteoarthritis

The age-standardized prevalence of osteoarthritis by sex is presented in Fig. 3. No statistical differences were observed across racial groups.

The adjusted odds for osteoarthritis by sex is presented in Table 4. After adjusting for the variables in model 1 and 2, there was no difference in the odds of osteoarthritis for Black or Hispanic women or men with CP compared to White adults with CP.

3.4. Sensitivity analysis

The sensitivity analyses (\( n = 12,613 \); women, \( n = 5938 \); men, \( n = 6675 \)) that required at least two claims to identify CP and all neurodevelopmental and noncommunicable disease comorbidities found the same conclusions as the primary analysis for racial
4. Discussion

The main finding of this study is that there were racial differences in skeletal fragility but not osteoarthritis among young and middle-aged adults with CP. Specifically, even after adjusting for potential confounding factors, White women and men with CP had higher prevalence of osteoporosis and fracture compared to Black women and men with CP. Study findings significantly add to the growing body of literature by providing large, national-level data documenting racial differences in skeletal fragility, but not osteoarthritis, among adults with CP. This is important because there are substantial racial differences in non-CP populations for screening for skeletal fragility, osteoporosis diagnoses (Cheng et al., 2009), and osteoporosis-related treatment rates (Cauley, 2011; Hamrick et al., 2006). Therefore, understanding the differences in skeletal fragility and osteoarthritis across racial groups among adults with CP is a fundamental step towards developing successful interventions to optimize skeletal and joint health for this underserved population. Moreover, the prevalence estimates of osteoporosis, fracture, and osteoarthritis observed in this study were markedly elevated. Recent studies leveraging private insurance claims data from 2016 found that the general population without CP of the same age group had an osteoporosis prevalence of 1.3%, fracture prevalence of 2.7% (Whitney et al., 2019b), and osteoarthritis prevalence of 7.9% (Whitney et al., 2019c). Therefore, despite the low absolute prevalence (e.g., < 15%), these estimates are still much higher than what would be expected for this younger age group. Importantly, early development of these conditions can significantly increase personal, disease, and economic burden (Burge et al., 2007; Tatangelo et al., 2019; Turkiewicz et al., 2014), and should be aggressively treated and prevented to minimize the cost to public health.

In the general population, White individuals, and particularly women, have greater risk of skeletal fragility compared to other racial groups (Cauley, 2011). However, mortality rate following a hip fracture is higher for Black women than White women (Jacobsen et al., 1992). Black individuals tend to have greater risk for osteoarthritis, but this

**Table 1**

Descriptive characteristics of 18–64 year olds with cerebral palsy.

| Descriptive characteristics | White | Black | Hispanic | p-Value |
|----------------------------|-------|-------|----------|---------|
| Sample size, n             | 13,334| 2477  | 677      |         |
| Age, mean (SD)             | 46.3 (11.3) | 43.1 (12.3) | 37.2 (11.0) | < 0.001 |
| 18–40 years, %             | 31.9  | 43.4  | 67.4     |         |
| 41–64 years, %             | 68.1  | 56.6  | 32.6     |         |
| Sex, %                     |       |       |          | 0.023   |
| Women                      | 46.8  | 45.7  | 41.7     |         |
| Men                        | 53.2  | 54.3  | 58.4     | < 0.001 |
| Region, %                  |       |       |          |         |
| West                       | 15.4  | 7.4   | 35.0     |         |
| Midwest                    | 30.6  | 21.4  | 12.4     |         |
| South                      | 32.3  | 54.3  | 34.1     |         |
| Northeast                  | 21.8  | 16.8  | 18.5     |         |

**Fig. 1.** Age-standardized prevalence of osteoporosis for 18–64 years olds with cerebral palsy. Error bars represent 99.5% confidence intervals. *p-value < 0.005.
association may be sex- and joint-specific and accounted for, at least in part, by confounding factors (Nelson et al., 2013; Wright et al., 2008). Further, Black individuals are less likely to receive hip or knee replacement than White individuals (Smith et al., 2017). Reasons for these racial differences in skeletal fragility and osteoarthritis have been attributed to differences in bone mineral density, geographic properties of bone and joints, geographic region, health disparities, and other socioeconomic factors (e.g., poverty) (Cauley, 2011; Wright et al., 2008; Nelson et al., 2016; Cauley et al., 2005; Tsai, 2019). Poor overall health status, as indicated by presence of noncommunicable diseases, is also associated with increased risk for skeletal fragility (Silverman et al., 2016). In the current study, the racial difference in skeletal fragility between Blacks and Whites remained even after accounting for U.S. region and comorbid neurodevelopmental conditions, which are each associated with skeletal fragility (Schrager et al., 2007; Neumeyer et al., 2017; Sheth et al., 2008). Further, the addition of all non-communicable diseases to the model (i.e., model 2), which provided a proxy of overall health status, had little-to-no effect on the association of race with each outcome as evidenced by small or no deviations in the adjusted OR, suggesting a robust association between race and skeletal fragility among young and middle-aged adults with CP. However, this study was unable to directly assess other important indicators of socioeconomic status (e.g., income, education), CP severity, and physical activity levels, which are all associated with the outcomes. Whether there are differences in these measures among adults with CP and if they are associated with development of skeletal fragility or osteoarthritis requires further investigation.

There are many factors associated with the pathophysiology of skeletal fragility and osteoarthritis among individuals with CP. Whether and how these factors differ by racial group could provide insight into patient-specific care for skeletal fragility and osteoarthritis. Low levels of physical activity reported in children with CP predispose inadequate accrual of muscle and bone throughout growth and development (Whitney et al., 2017). Concomitant with reduced physical activity levels as these children age into and throughout their adult years (Day et al., 2007) is the emergence of a concerning musculoskeletal profile (Whitney et al., 2018c; Whitney et al., 2019b; O’Connell et al., 2019) that gets worse throughout the lifespan (Whitney et al., 2018d). There are also various skeletal deformities and malalignments of the lower extremities present among individuals with CP (Robin et al., 2008; Noonan et al., 2004; Miller et al., 1997), including femoral

Table 2
Multivariable logistic regression for osteoporosis among 18–64 year olds with cerebral palsy.

|                      | Women Model 1 | Women Model 2 | Men Model 1 | Men Model 2 |
|----------------------|---------------|---------------|-------------|-------------|
| Sample size, n       | 7657          | 7657          | 8831        | 8831        |
| Race                 |               |               |             |             |
| White                | Reference     | Reference     | Reference   | Reference   |
| Black                | 0.68 (0.49, 0.93) | 0.66 (0.48, 0.91) | 0.51 (0.35, 0.74) | 0.51 (0.35, 0.75) |
| Hispanic             | 0.61 (0.29, 1.29) | 0.61 (0.29, 1.30) | 0.88 (0.48, 1.62) | 0.90 (0.49, 1.65) |
| Age (as continuous)  | 1.07 (1.06, 1.08) | 1.06 (1.05, 1.08) | 1.04 (1.03, 1.06) | 1.05 (1.03, 1.06) |
| Region               |               |               |             |             |
| Northeast            | Reference     | Reference     | Reference   | Reference   |
| West                 | 0.50 (0.36, 0.70) | 0.50 (0.36, 0.69) | 0.71 (0.51, 0.98) | 0.70 (0.50, 0.97) |
| Midwest              | 0.58 (0.45, 0.75) | 0.59 (0.46, 0.76) | 0.53 (0.40, 0.71) | 0.53 (0.40, 0.71) |
| South                | 0.59 (0.46, 0.76) | 0.59 (0.46, 0.76) | 0.59 (0.45, 0.78) | 0.59 (0.45, 0.78) |
| Intellectual disorders | 1.87 (1.52, 2.29) | 1.91 (1.55, 2.35) | 2.69 (2.13, 3.40) | 2.70 (2.13, 3.42) |
| Autism spectrum disorders | 1.48 (0.96, 2.27) | 1.49 (0.97, 2.30) | 0.75 (0.47, 1.19) | 0.78 (0.49, 1.23) |
| Epilepsy             | 2.01 (1.64, 2.46) | 1.96 (1.59, 2.40) | 2.23 (1.78, 2.80) | 2.20 (1.75, 2.76) |
| Ischemic heart diseases | 1.25 (0.81, 1.92) | 1.00 (0.68, 1.49) | 0.86 (0.68, 1.09) | 0.82 (0.51, 1.31) |
| Cerebrovascular diseases | 1.17 (0.83, 1.66) | 1.00 (0.68, 1.49) | 0.86 (0.68, 1.09) | 0.82 (0.51, 1.31) |
| Hypertensive and other cardiovascular diseases | 1.09 (0.88, 1.35) | 1.00 (0.68, 1.49) | 0.86 (0.68, 1.09) | 0.82 (0.51, 1.31) |
| Diabetes             | 0.93 (0.71, 1.22) | 0.93 (0.68, 1.27) | 0.93 (0.68, 1.27) | 0.93 (0.68, 1.27) |
| Mood affective disorders | 0.90 (0.72, 1.13) | 0.74 (0.57, 0.97) | 0.74 (0.57, 0.97) | 0.74 (0.57, 0.97) |
| Anxiety disorders    | 1.01 (0.80, 1.27) | 1.00 (0.77, 1.30) | 1.00 (0.77, 1.30) | 1.00 (0.77, 1.30) |
| Substance abuse disorders | 1.16 (0.57, 2.33) | 0.76 (0.35, 1.67) | 0.76 (0.35, 1.67) | 0.76 (0.35, 1.67) |
| Chronic obstructive pulmonary disease | 1.46 (1.03, 2.07) | 1.37 (0.93, 2.02) | 1.37 (0.93, 2.02) | 1.37 (0.93, 2.02) |
| Chronic kidney disease | 0.98 (0.64, 1.48) | 1.36 (0.88, 2.09) | 1.36 (0.88, 2.09) | 1.36 (0.88, 2.09) |
| Liver diseases       | 1.30 (0.84, 2.00) | 1.34 (0.86, 2.09) | 1.34 (0.86, 2.09) | 1.34 (0.86, 2.09) |
| Cancer               | 1.58 (1.08, 2.31) | 1.40 (0.87, 2.27) | 1.40 (0.87, 2.27) | 1.40 (0.87, 2.27) |

OR, odds ratio; CI, confidence interval.

Fig. 2. Age-standardized prevalence of fracture for 18–64 years olds with cerebral palsy. Error bars represent 99.5% confidence intervals. *p-value < 0.005.
The musculoskeletal pathological phenotype in childhood is also governed by several CP-related factors (Chan and Miller, 2014), such as the type of CP (e.g., spastic, dyskinetic, ataxic), anatomical distribution of affected areas (e.g., hemiplegia, diplegia, quadriplegia), and the level of gross motor functional ability (e.g., independent ambulation, wheelchair user). Further, the degree to which muscles are affected (e.g., severity), how they are affected (e.g., spasticity), and the number of affected muscles and sites plays a foundational role on joint health by altering articular surface stresses during movement; all of which may lead to localized joint damage and increased risk for skeletal fragility and osteoarthritis.

In addition to the more established and recognized functional, anatomical, and physiological factors, epigenetics may have a unique or multiplicative role on the burden of skeletal fragility and osteoarthritis among individuals with CP, which is also influenced by race. Recent evidence suggests an altered epigenome between children with and without CP (Crowgey et al., 2018; Mohandas et al., 2018) and between preterm Black and non-Black infants (Salihu et al., 2016). Pre- and peri-natal factors and early life stressors can alter DNA methylation patterns in offspring (Roth et al., 2009) that remain sustained throughout the lifespan and are associated with chronic diseases later in life (Hao et al., 2018; Nieratschker et al., 2014). Unique DNA methylation profiles have been observed from tissue of postmenopausal women with osteoporosis (Reppe et al., 2017) and human osteoarthritic cartilage (Alvarez-Garcia et al., 2016) compared to their respective control group. Whether the causes of CP, subsequent poor psychosocial development (Whitney et al., 2019d; Whitney et al., 2018e; Whitney et al., 2019e), and race lead to DNA methylation patterns that predispose to early development of chronic diseases, including skeletal fragility and osteoarthritis, requires further investigation.

The limitations of this study must be discussed. First, CP-specific data (e.g., clinical subtypes and severity measures), other socioeconomic status indicators (e.g., income, education), and physical activity were not available or were inadequately coded in the CMS dataset, resulting in the inability to stratify or statistically adjust for these relevant constructs. In light of this limitation, this study adjusted for neurodevelopmental conditions that are commonly comorbid with CP and several high-burden noncommunicable diseases, which provides a proxy of the overall health status of the individual. Second, there is risk for unmeasured confounding which is inherent to observational research designs. E-values were therefore computed to determine the

### Table 3
Multivariable logistic regression for fracture among 18–64 year olds with cerebral palsy.

| Race       | Model 1 OR (99.5% CI) | Model 2 OR (99.5% CI) | Model 1 OR (99.5% CI) | Model 2 OR (99.5% CI) |
|------------|-----------------------|-----------------------|-----------------------|-----------------------|
| White      | 1.00 (reference)      | 1.00 (reference)      | 1.00 (reference)      | 1.00 (reference)      |
| Black      | 0.57 (0.37, 0.88)     | 0.57 (0.37, 0.89)     | 0.38 (0.22, 0.65)     | 0.39 (0.23, 0.68)     |
| Hispanic   | 1.09 (0.53, 2.23)     | 1.10 (0.54, 2.26)     | 0.87 (0.44, 1.74)     | 0.85 (0.42, 1.70)     |
| Age (as continuous) | 1.03 (1.02, 1.05) | 1.03 (1.02, 1.04) | 1.02 (1.01, 1.03) | 1.02 (1.01, 1.03) |

OR, odds ratio; CI, confidence interval.

### Fig. 3
Age-standardized prevalence of osteoarthritis for 18–64 years olds with cerebral palsy. Error bars represent 99.5% confidence intervals. *p-value < 0.005.

anteverversion, hip subluxation, and joint dislocation. The musculoskeletal pathological phenotype in childhood is also governed by several CP-related factors (Chan and Miller, 2014), such as the type of CP (e.g., spastic, dyskinetic, ataxic), anatomical distribution of affected areas (e.g., hemiplegia, diplegia, quadriplegia), and the level of gross motor...
extent of unmeasured confounding (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 (Mathur et al., 2018; VanderWeele and Ding, 2017). Using the fully adjusted model for Black vs. White since Hispanic race was not different, the E-value (lower 95% CI) for women and men was 2.40 (1.43) and 3.33 (2.00) for osteoporosis, respectively, and 2.90 (1.50) and 4.57 (2.80) for fracture, respectively. Given the large E-values, it seems unlikely that unmeasured confounding largely biased these estimates.

### 5. Conclusion

Young and middle-aged White individuals with CP have higher risk for skeletal fragility compared to Black individuals with CP. This study found no evidence of racial differences in osteoarthritis. While previous studies have recommended earlier screening strategies to detect musculoskeletal frailty for individuals with CP (Whitney et al., 2019b), study findings can assist development of detection and preventive services by considering the contribution of sex and race on skeletal fragility.

### References

Age and Sex Composition in the United States: 2016, 2018. United States Census Bureau (2016).

Alvarez-Garcia, O., Fisch, K.M., Wineinger, N.E., Akagi, R., Saito, M., Sasho, T., Su, A.I., Lotz, M.K., 2016. Increased DNA methylation and reduced expression of transcription factors in human osteoarthritis cartilage. Arthritis Rheumatol 68 (8), 1876-1886.

Benjamin, D.J., Berger, J.O., Johannesson, M., Nosek, B.A., Wagenmakers, E.J., Berk, R., Bollen, K.A., Brems, B., Brown, L., Caines, E., Cesario, D., Chambers, C.D., Clyde, M., Cook, T.D., De Boeck, P., Dienes, Z., Dreber, A., Easwaran, K., Efferson, C., Fehl, E., Figler, F., Field, A.P., Forster, M., George, E.I., Gonzalez, R., Goodman, S., Green, E., Green, D.P., Greenwald, A.G., Hadfield, J.D., Hedges, L.V., Held, L., Hua Ho, T., Hoxhajt, H., Hruschka, B.J., Imam, K., Imbens, G., Ioannidis, J.P.A., Jeon, M., Jones, J.H., Kichler, M., Linvson, B., List, J., Little, P., Lupia, A., MacIntyre, E., Maxwell, S.L., McCarthy, M., Moore, D.A., Morgan, S.L., Munafò, M., Nakagawa, S., Nyhan, B.,
Parker, T.H., Perichic, L., Perugini, M., Rouder, J., Rousseau, J., Savalei, V., Schiebrottd, F.D., Sellke, T., Sinclair, B., Tingley, D., Van Zandt, T., Vazire, S., Watts, D.J., Winship, C., Wolpert, R.L., Xie, Y., Young, C., Ziman, J., Johnson, V.E., 2018. Redefine statistical significance. Nat. Hum. Behav. 2 (1), 6–10.

Brauer, C.A., Coca-Paredes, A., Cudler, D.M., Guo, R., Haase, A., 2017. Incidence and mortality of hip fractures in the United States. JAMA 302 (14), 1573–1579.

Burge, R., Dawson-Hughes, B., Solomon, D.H., Wong, J.B., King, A., Tosteson, A., 2007. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. J. Bone Miner. Res. 22 (3), 460–475.

Cauley, J.A., 2011. Defining ethnic and racial differences in osteoporosis and fragility fractures. Clin. Orthop. Relat. Res. 469 (7), 1891–1899.

Dailey, D.E., 2009. Social stressors and strengths as predictors of infant birth weight in low-income African American women. J. Am. Geriatr. Soc. 53 (2), 183–189.

Christensen, D., Van Naarden Braun, K., Doernberg, N.S., Maenner, M.J., Arneson, C.L., Cauley, J.A., Lui, L.Y., Stone, K.L., Hillier, T.A., Zmuda, J.M., Hochberg, M., Beck, T.J., Ryan, J.M., 2015. Incidence of osteoporosis after diagnosis. Osteoporos. Int. 17 (11), 1653–1658.

Doktorchik, C., Patten, S., Eastwood, C., Peng, M., Chen, G., Beck, C.A., Jette, N., Crowgey, E.L., Marsh, A.G., Robinson, K.G., Yeager, S.K., Akins, R.E., 2018. Epigenetic activity of the promoter of ESR1 with respect to risk for osteoporosis in the Johnston county osteoarthritis project. Arthritis Rheum. 65 (2), 249–258.

Murphy, S.L., Schepens Niemiec, S., Lyden, A.K., Kratz, A.L., 2016. Pain, fatigue, and physical activity in osteoarthritis: the moderating effects of pain and fatigue-related activity interference. Arch. Phys. Med. Rehabil. 97 (9 Suppl.), S201–S209.

Mangood, P., Patkar, N.M., Shakoory, B., Jain, A., Curtis, J.R., Delzer, E., Lander, P.H., Lopez-Ben, R.K., Pitt, M.J., Safford, M.M., Volgas, D.A., Saag, K.G., 2015. Validation of diagnostic codes for subchondral, diaphyseal, and atypical femoral fractures using administrative claims data. J. Clin. Densitom. 18 (1), 92–102.

Nelson, A.E., Golightly, Y., Renner, J.B., Schwartz, T.A., Kraus, V.B., Helming, C.G., Ford, J.M., 2013. Brief report: differences in multisjoint symptomatic osteoarthritis phenotypes by race and sex on the Johnston county osteoarthritis project. Arthritis Rheum. 65 (2), 373–377.

Nelson, A.E., Still, J.L., Shi, X.A., Leyland, K.M., Renner, J.B., Schwartz, T.A., Arden, N.K., Jordan, J.M., 2016. Measures of hip morphology are related to development of worsening radiographic hip osteoarthritis over 6 to 13 years follow-up: the Johnston county osteoarthritis project. Osteoarthr. Cartil. 24 (3), 443–450.

Neumann, M.D., Silber, J.H., Magaziner, J.S., Passarell, M.A., Mehta, S., Wener, R.M., 2014. Survival and functional outcomes after hip fracture among nursing home residents. JAMA Intern. Med. 174 (8), 1273–1280.

Reeves, S., Garcia, E., Kleyn, M., Housey, M., Stottlemyer, R., Lyon-Callo, S., O’Connor, S.M., Smith, J.C., Peterson, M.D., Rynn, L., Ryan, N., 2018. Comparison of Medicare fee-for-service and Medicare advantage benefits and implications for quality measurement and improvement. Jt Comm. J. Qual. Improv. 44 (4), 213–224.

Reid, S.M., Amor, D.J., Reddihough, D., Craig, J.M., 2018. Epigenome-wide analysis of the promoter of ESR1 with respect to risk for osteoporosis in the Johnston county osteoarthritis project. J. Gerontol. A Biol. Sci. Med. Sci. 70 (3), 339–346.

Reid, S.M., Meehan, E.M., Arnup, S.J., Reddihough, D.S., 2018. Intellectual disability in children with cerebral palsy using CMR imaging. Osteoporos. Int. 21 (11), 1835–1840.

Salkeld, G., Cameron, I.D., Cumming, R.G., Easter, S., Seymour, J., Kurrle, S.E., Quine, S., 2011.: a secondary analysis of administrative data. PLoS Med. 8 (5), e1002952.

Schönbrodt, F.D., Sellke, T., Sinclair, B., Tingley, D., Van Zandt, T., Vazire, S., Watts, D.J., Winship, C., Wolpert, R.L., Xie, Y., Young, C., Ziman, J., Johnson, V.E., 2018. Redefine statistical significance. Nat. Hum. Behav. 2 (1), 6–10.

Skegg, D.K., National Joint, W., 2017. Registry for England, I. Northern, rates of hip fractures using administrative claims data. J. Clin. Densitom. 15 (1), 92–104.
Whitney, D.G., Hurvitz, E.A., Devlin, M.J., Caird, M.S., French, Z.P., Ellenberg, E.C., Peterson, M.D., 2018d. Age trajectories of musculoskeletal morbidities in adults with cerebral palsy. Bone 114, 285–291.

Whitney, D.G., Peterson, M.D., Warschausky, S.A., 2018e. Mental health disorders, participation, and bullying in children with cerebral palsy. Dev. Med. Child Neurol. 61 (8), 937–942 In Press.

Whitney, D.G., Miller, F., Pohlig, R.T., Modlesky, C.M., 2019a. BMI does not capture the high fat mass index and low fat-free mass index in children with cerebral palsy and proposed statistical models that improve this accuracy. Int. J. Obes. 43 (1), 82–90.

Whitney, D.G., Alford, A.I., Devlin, M.J., Caird, M.S., Hurvitz, E.A., Peterson, M.D., 2019b. Adults with cerebral palsy have higher prevalence of fracture compared with adults without cerebral palsy independent of osteoporosis and cardiometabolic diseases. J. Bone Miner. Res. 34, 1246–1247.

Whitney, D.G., Kamdar, N.S., Ng, S., Hurvitz, E.A., Peterson, M.D., 2019c. Prevalence of high-burden medical conditions and healthcare resource utilization and costs among adults with cerebral palsy. In: Clinical Epidemiology, In Press.

Whitney, D.G., Warschausky, S.A., Peterson, M.D., 2019d. Mental health disorders and physical risk factors in children with cerebral palsy: a cross-sectional study. Dev. Med. Child Neurol. 61 (5), 579–585.

Whitney, D.G., Warschausky, S.A., Ng, S., Hurvitz, E.A., Kamdar, N.S., Peterson, M.D., 2019e. Prevalence of mental health disorders among adults with cerebral palsy: a cross-sectional analysis. Ann. Intern. Med. Still in press.

Wright, N.C., Rigg, G.K., Lisse, J.R., Chen, Z., I. Women’s Health, 2008. Self-reported osteoarthritis, ethnicity, body mass index, and other associated risk factors in post-menopausal women-results from the women’s health initiative. J. Am. Geriatr. Soc. 56 (9), 1736–1743.

Wright, N.C., Looker, A.C., Saag, K.G., Curtis, J.R., Delzell, E.S., Randall, S., Dawson-Hughes, B., 2014. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J. Bone Miner. Res. 29 (11), 2520–2526.

Wu, Y.W., Xing, G., Fuentes-Afflick, E., Danielson, B., Smith, L.H., Gilbert, W.M., 2011. Racial, ethnic, and socioeconomic disparities in the prevalence of cerebral palsy. Pediatrics 127 (3), e674–e681.

Xie, F., Kovic, B., Jin, X., He, X., Wang, M., Silvestre, C., 2016. Economic and humanistic burden of osteoarthritis: a systematic review of large sample studies. Pharmacoeconomics 34 (11), 1087–1100.