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Clinical bone health among adults with cerebral palsy: moving beyond assessing bone mineral density alone

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ABBREVIATIONS

BMD Bone mineral density
BMC Bone mineral content
DXA Dual energy X-ray absorptiometry

Abstract

AIM To understand associations among bone mineral density (BMD), bone mineral content (BMC), and bone area, and their association with fractures in adults with cerebral palsy (CP).

METHOD This retrospective cohort study included 78 adults with CP with a hip dual energy X-ray absorptiometry (DXA) from 1st December 2012 to 3rd May 2021 performed at the University of Michigan. Data-driven logistic regression techniques identified which, if any, DXA-derived bone traits (e.g. age/sex/ethnicity-based z-scores) were associated with fracture risk by sex and severity of CP. BMC-area associations were examined to study the structural mechanisms of fragility.

RESULTS Femoral neck area was associated with lower age-adjusted odds ratios (ORs) of fracture history (OR 0.72; 95% confidence interval [CI] 0.49–1.06; p=0.098), while higher BMD was associated with higher odds of incident fracture (OR 3.08; 95% CI 1.14–8.33; p=0.027). Females with fracture had lower area than females without fracture but similar BMC, whereas males with fracture had larger area and higher BMC than males without fracture. The paradoxical BMD-fracture association may be due to artificially elevated BMD from BMC-area associations that differed between females and males (sex interaction, p<0.05): males had higher BMC at lower area values and lower BMC at higher area values compared to females.

INTERPRETATION BMD alone may not be adequate to evaluate bone strength for adults with CP. Further research into associations (or integration) between BMC and area is needed.

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BMD as a Bone Fragility Marker *Daniel G Whitney et al.*

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What this paper adds

- Bone mineral density (BMD) can be artificially elevated by a small diameter bone.
- Small bone size may be an overlooked marker of fragility in cerebral palsy (CP).
- Bone marrow content-area disintegration may lead to fragility that BMD assessment cannot capture.
- BMD assessment alone may be insufficient to detect bone fragility in CP.

[Main text]

Is labeling cerebral palsy (CP) a low bone mass condition based on bone mineral density (BMD) sufficient for clinical assessment and management of bone strength/fragility? Defining low bone mass is primarily done through the sole interpretation of lower-than-expected BMD derived from dual energy X-ray absorptiometry (DXA). Much has been learned by utilizing BMD to understand bone development during growth and bone health in adults with CP.[1–3] However, BMD is a

ratio: bone mineral content (BMC)/area. Children and adults with CP have small diameter bones,[4,5] which could artificially inflate BMD. Further, bone size is a major determinant of fracture risk.[6,7] Smaller diameter bones are mechanically weaker owing to the restricted external distribution of skeletal material, therefore, the attributable fracture risk by bone size may be missed when examining BMD alone.

More important is that bone strength is defined by the integration of several structural traits, not just one.[8–10] In general, smaller diameter bones compensate by augmenting their mineral deposition (e.g. BMC) and relative cortical area to maximize their stiffness and strength. In contrast, wider diameter bones require lower relative cortical area, higher BMC, and lower BMD to maintain strength without excess mass.[11,12] To put it simply, bones can achieve mechanical competence (e.g. fracture resistance) through this coordinate adjustment or integration of mass and external size. This bone trait integration occurs in unique but predictable ways, based on external bone size.[13] Since the size-mass integration patterns differ across the bone size spectrum,[11–13] multi-trait, not single-trait, approaches may be needed to evaluate factors affecting bone strength. In support of this notion, a multinational, prospective study including more than 7000 adults without CP assessed if structural traits were associated with incident fracture, independent of BMD. The major finding was that the multi-trait measure, failure load, which is defined by the integration of structure (bone size) and mass (BMC), was the strongest predictor of incident fracture out of 13 bone traits, suggesting the importance of size-mass integration in fracture risk than any single trait alone.[8]

While it is important to understand risk factors for bone fragility in adults with CP, we first need to understand the structural mechanisms underlying their bone fragility. Currently, little is known about how the underdeveloped skeletal framework during growth influences bone fragility other than BMD across the adult lifespan for individuals with CP. As DXA-derived BMD may not provide sufficient information on bone size, BMC, or other structural traits, the structural mechanisms underlying bone fragility in CP may not be detected when assessing BMD alone, leading to missed opportunities for bone fragility treatment and prevention. As an early step to begin

understanding the relevance of size and mass traits, the objective of this study was to identify the relationships among DXA-derived femoral neck BMD, BMC, and bone area (e.g. trait integration) and determine if these DXA-derived bone traits were associated with fracture risk in a clinical sample of adults with CP. The femoral neck was selected as it is a better predictor of systemic fragility compared to other skeletal sites.[14]

METHOD

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Data source

This retrospective, cohort study analyzed medical records from adults (≥18y) with CP who had a hip DXA scan from the University of Michigan Health System between 1st December 2012 and 3red May 2021. The University's institutional review board approved this study.

DXA

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Hip DXA scans were collected from a GE Lunar iDXA bone densitometer using standard methods (GE Healthcare, Chicago, IL, USA). Femoral neck BMD, BMC, and bone area were examined before and after transforming to age-, sex-, and ethnicity-based z-scores.[15] The GE Lunar iDXA scanner had excellent precision at the femoral neck palsy (e.g. BMD coefficient of variation=1.4%)[16] and good-to-excellent test–retest reliability among nine adults with mild to severe CP from the current study cohort (*n*=3 males; age range 29–57y) who had two DXA scans, on average 2 years 1 month apart (i.e. femoral neck BMD, BMC, and area intraclass correlations 0.94, 0.88, and 0.93 respectively).

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Fracture

History of fracture was the outcome for statistical modeling as there were too few incidents fracture (*n*=7). The majority (>80%) of those with a fracture history had inadequate information on the number, location, or date of previous fractures.

Therefore, fracture history was examined as a dichotomous variable of 'yes' or 'no', consistent with previous reports.[2,17–19]

Non-bone variables

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Informed by clinician notes and the Gross Motor Function Classification System (GMFCS), severity of CP was dichotomized as mild-to-moderate (GMFCS level I–III) and severe (GMFCS level IV or V). Age, sex, and ethnic group were ascertained. Data on height, body mass, and body mass index (BMI) on the day or the date closest to the participant's DXA were collected. Information on osteoporosis medications and calcium and/or vitamin D supplements within 1-year prior to the DXA date was collected.

Statistical analysis

Variables were summarized by sex and severity of CP. Group differences were tested using the χ^2 or Fisher's exact test for categorical variables or the one-way analysis of variance or Kruskal–Wallis test, based on normality of distribution (determined by the Shapiro–Wilk test) for continuous variables. Bivariate linear regressions were visually depicted among the DXA-derived bone traits in the z-score forms (to mitigate effects by age, sex, and ethnicity). If outliers or influential observations were detected (e.g. Cook's distance >0.50), regressions were redone after removing the observation(s).

Logistic regression analyses were performed with the outcome as fracture history using stepwise regression for variable selection. The goal of this analysis was to take a data-driven approach to identify which, if any, DXA-derived bone traits were associated with fracture history. In this context, stepwise regression is ideal for preliminary screening and hypothesis testing as there is limited evidence of variable contribution to the outcome.[20] Based on the number of outcome events (as events-per-variable), up to seven independent variables were able to be examined in a single model.[21] There were 13 variables initially considered to have clinical relevance to fracture history (three bone traits and all non-bone variables listed above). Logistic regression models examined the association between fracture history with age, sex, severity of CP, BMI, body mass, and height separately (unadjusted models), and then in a single adjusted model with BMI or

body mass+height, but not BMI+body mass+height, to avoid redundancy (and multicollinearity) with BMI (other variables had too few cases for analysis). If the unadjusted and adjusted association had a $p<0.25$ (this threshold guards against premature variable exclusion), the variable was carried forward to the stepwise regression. The stepwise regression included the variable(s) from the pre-analysis step and the bone traits. Following recommendations, we used a p-value of <0.25 to allow a variable to enter the model and a p-value of <0.157 for a variable to remain in the model.[22] For logistic regression models, we assessed the model fit using the Hosmer–Lemeshow goodness-of-fit test.

Bone trait z-scores were compared across groups after further stratifying by history of fracture. Cohen's *d* (difference in means/pooled standard deviation) was computed to estimate the effect size, with 0.2, 0.5, and 0.8 representing a small, medium, and large effect respectively.

Exploratory analysis

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Interactions in regression analyses were tested separately between bone area z-score with age, sex, severity of CP, BMI, body mass, height, and history of fracture in predicting BMC z-score.

Logistic regression models were developed with incidence of fracture as the outcome. The exposure was the standard deviation (SD) of each bone trait relative to that individual's group mean (group determined by sex and severity). Given the few outcome events, we applied the Firth correction, which is a penalized likelihood regression technique used to minimize analytic bias caused by few outcome events among small samples.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and $p<0.05$ was considered statistically significant.

RESULTS

Descriptive characteristics and DXA-derived bone traits for adults stratified by sex and severity of CP (total $n=78$) are presented in Table 1.

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Correlations among DXA-derived bone traits

As expected, BMD z-scores showed strong positive correlations with BMC z-scores for the entire sample and subgroups (all $p<0.001$) (Fig. 1a; Table S1, online supporting information). The BMD z-scores did not correlate with bone area z-scores for the entire sample or subgroups (all $p>0.05$), suggesting that deficits in BMD and bone area z-scores were unrelated (Fig. 1b). The bone area z-scores showed moderate positive correlations with BMC z-scores for the female subgroups (both $p<0.05$), but not for the male subgroups (both $p>0.05$) (Fig. 1c). Notably, the severe groups for each sex showed lower BMC z-scores for a given area z-score.

There was evidence of influential observations in six of the 15 relationships, but the conclusions about the six relationships did not alter when the influential observations were removed. In fact, after removing influential observations, some of the relationships became stronger. For example, by removing two females with severe CP resulting in very high area z-scores, the area-BMC z-score relationship strengthened ($y=0.96x-0.36$, $r^2=0.48$, $p<0.001$), and by removing one male with severe CP resulting in a very low BMC z-score, the area-BMC z-score relationship strengthened ($y=0.42x-1.31$, $r^2=0.36$, $p=0.012$).

The patterns were similar when bone traits were examined in their raw form (Fig. S1, online supporting information).

Clinical relevance of DXA-derived bone traits

In the pre-analysis (Table S2, online supporting information), age and sex were associated with fracture history. In the stepwise regression analysis, only age and bone area z-score were retained in the final model (findings were unchanged when height, body mass, BMI, and severity of CP were included). Bone area z-score was associated with a lower age-adjusted odds of fracture history, which was marginally statistically insignificant ($p=0.098$) (Fig. 2), suggesting that smaller area bones were more likely to have had a fracture history. The associations among bone traits with fracture history were similar after removing adults that had exposure to osteoporosis medication and

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calcium/vitamin D supplements (model *n*=64), except the association with bone area z-score became stronger (OR 0.66; 95% CI 0.43–1.02; *p*=0.061). The *p*-value for the Hosmer–Lemeshow test for all logistic regression models ranged from 0.213 to 0.979, indicating good calibration.

Bone traits by fracture history

Bone traits and non-bone variables were compared between those with and those without a fracture history (Table S3, online supporting information). These analyses were done for each sex separately as the findings were consistent for mild-to-moderate and severe CP, but in a unique way for females and males. For females, those with a fracture history (*n*=23) had a smaller bone area z-score than those without (*n*=27), but no difference in BMC or BMD z-score (Fig. 3a). For males, those with a fracture history (*n*=17) had a larger bone area z-score, higher BMC z-score, and higher BMD z-score than those without a fracture history (*n*=11) (Fig. 3b).

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Exploratory analysis

After removing three outliers with exceedingly high bone area z-scores (two females, one males), there was a sex interaction for the association between bone area and BMC in both the z-score and raw form (for interaction, *p*=0.044 and *p*=0.024 respectively). To put it simply, compared to females, males had higher BMC for a lower bone area and lower BMC for a higher bone area (Fig. S2, online supporting information).

There were six females (two metacarpal, one fibula, three [multi-]metatarsal) and one male (nasal) who sustained an incident fracture (average time to fracture, 3y 2mo; range, 7mo–6y 6mo), and all but one had a higher BMD z-score compared to their sex and severity group (Table S4, online supporting information). A higher unadjusted OR (with Firth correction) of incident fracture was associated with a higher BMD z-score SD (OR 3.08; 95% CI 1.14–8.33; *p*=0.027; HL *p*=0.574) and BMC z-score SD (OR 3.83; 95% CI 1.37–10.71; *p*=0.011; HL *p*=0.525), but not bone area z-score SD (OR 1.69; 95% CI 0.81–3.53; *p*=0.165; HL *p*=0.474).

DISCUSSION

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This study found that adults with CP compared to those without a fracture history generally had the same or higher BMD, which was supported by the exploratory analysis examining fracture incidence. These data suggest that BMD may not be able to accurately distinguish fracture from non-fracture cases for adults with CP.

Bone traits integrate with one another in a manner to achieve mechanical competence, often predicted by external bone size.[13] The association between higher BMD and fractures in this study may, therefore, be due to disintegration among size and mass traits, but possibly in different ways for females and males. Additionally, the deficit in BMD was not related to the deficit in bone area, suggesting that BMD is not a proxy of area for adults with CP. Importantly, bone area emerged in this study as the DXA-derived bone trait with the strongest association with fracture history (smaller bones more likely to have a fracture history). Fracture resistance of long bones is proportional to the 4th power of the distance from the neutral axis.[7] Therefore, bone fragility may be more sensitive to bone size than mass. While more research is needed, BMD alone may not be an adequate marker to evaluate bone fragility for adults with CP.

Consistent with previous reports,[18,23] severity of CP was not associated with fracture history. Sustaining a fracture is a complex, multi-faceted event. While bones in those with more severe CP may be more structurally fragile, the variability in motor function and societal integration can create stark differences in daily activities and exposure to situations that may lead to a fracture.[24] Contrary to this study, pediatric studies in CP have found that lower BMD at the distal femur and lumbar spine was associated with fracture history.[2,17] However, work by Trinh et al.[3] found that fracture history among adolescents and young adults with CP was associated with a greater annual BMD gain, but area or BMC were not reported. It is, therefore, unknown if the BMD gain was due to higher mineralization or loss in bone size, which is important as each structural adaptation has an opposite effect on fracture risk, potentially explaining their paradoxical finding. It cannot be understated that there are a wide variety of

confounders that may impact fracture risk by severity of CP, such as unique medical complexities (e.g. comorbidity profiles, epilepsy), feeding tubes, medications, and duration of medication exposure (e.g. prolonged bisphosphonate use), among other factors. These factors may also uniquely impact bone trait integration for adults with CP. Unfortunately, this study was not positioned to capture these potentially important effects but serves as the foundation to support further research into this area.

While preliminary, this study suggests considerable interindividual variation and disintegration among bone traits, with a possible sex effect in the pattern of BMC-area integration, collectively pointing to the complexity of labeling CP a low bone mass condition based on BMD alone. Females with a fracture history versus those without trended towards having, on average, a smaller bone size without an associated higher BMC, resulting in fragility via a small and less stiff skeletal framework. For males, the pattern of size-mass integration was less clear. Males with a fracture history had a larger bone area and higher BMC and BMD than those without. Although, bone fragility has an earlier onset and is more prevalent among females in the general population, the sex difference in fracture risk is less pronounced among adults with CP.[25,26] In this study, the raw DXA-derived bone traits were similar across sex and severity groups, which is unusual as males have, on average, larger and more mineralized bones compared to females in the general population. Once the bone traits were z-transformed, males in this study had greater deficits in bone traits compared to females. This may have biased our male sample by not having the range of bone phenotypes to capture associations. However, femoral neck raw and z-score BMD,[18,19] BMC, and bone area[27] values are consistent with previous studies in adults with CP.

The size-mass integration may be complicated in males with CP. Bone trait integration differs by sex.[28] Here, we observed a significant interaction for the area-BMC association. For males compared to females, there was higher BMC at the lower end of bone area, but less BMC at the higher end of bone area. Whether this finding is a unique sex effect, a biological compensatory mechanism, or confounded by pathophysiology (e.g. due to low testosterone/estrogen, loading, iatrogenic effects) requires further investigation. Importantly, the concepts proposed here are best

interpreted based on the reminder that this study used a convenience sample of those with a hip DXA scan performed primarily for clinical decision-making. Therefore, while the basic theoretical concepts proposed are generally supported by this study, the clinical sample may not be representative of the greater population of adults with CP.

The complex adaptive nature of bone is often underappreciated and cannot be detected by BMD alone. While children and adults with CP have, on average, a smaller diameter bone, there is still a considerable interindividual range from very narrow to wide sizes (e.g. large coefficient of variation percentage from this study and others[4,5]), that creates challenges for a 'one size fits all' approach to screening, monitoring, and treating bone fragility in this population. For screening bone fragility, smaller diameter bones will present with an artificially elevated BMD leading to under-detection. Whereas larger diameter bones may present with an artificially lower BMD that may be paradoxically fracture resistant owing to the wider size, consistent with findings in this study. However, fracture resistance of larger diameter bones can be compromised when other traits are deficient, such as a thin cortex (common in CP[29]) or high cortical porosity, which DXA is unable to directly measure.[6,7] For monitoring bone fragility, a rise or fall in BMD may or may not enhance bone strength, depending on what aspect of bone changes in what direction, which is tied to the bone size. For example, smaller diameter bones increase outer bone size and lose less BMC to maintain strength with aging compared to wider diameter bones, but the resultant BMD loss is similar across the spectrum of bone size.[10] The unique structural compensations by bone size (and shape) can differentially impact the skeletal framework and long-term fracture risk, which is clinically masked by assessing BMD alone.[10,11,13] While DXA has limitations, it is more widely accepted and used to assess bone strength in the clinical setting. However, there are other imaging modalities that can assess BMD and other salient structural bone traits, such as computed tomography techniques. With further refinement in these methodologies and more widespread use, non-DXA imaging modalities in the future may help to better understand bone fragility and fracture prevention in addition to, or instead of, DXA.

There are limitations to this study. The sample size was small relative to the wide age range, large variation in measures, and the need to examine subgroups by sex and severity of CP to mitigate confounding. To accommodate these and other limitations as best as possible, this study focused on z-scores to account for age, sex, and ethnicity. Still, significant or marginally insignificant findings were observed, but should nevertheless be considered as preliminary evidence to supplement ongoing research for the need to treat bone in CP as a complex adaptive system. Fracture history may not be representative of future fracture risk. Data were from routine clinical care and not from controlled research settings. Patient positioning for DXA is unknown, but plays a minor role for DXA measurement at the femoral neck (e.g. 10° internal rotation results in 0.9% lower bone area[30]). This sample includes mostly White, non-Hispanic adults, and lacks diversity. Future studies are needed to study outcomes among a more diverse sample.

BMD alone may not be sufficient to assess bone strength/fragility among adults with CP. Future studies are needed to identify how bone traits integrate across the lifespan for individuals with CP and how risk factors, such as antiseizure medications and bisphosphonates and treatment duration, impact bone trait integration, which can reveal the unique ways in which their bones become fragile.

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Supporting information

The following additional material may be found online:

Figure S1: Correlations between bone mineral density with bone mineral content and bone area, and between bone area with BMC.

Figure S2: Correlations between bone area with bone mineral content as z-score and non-transformed values.

Table S1: Linear regression equation and coefficient of determination for the relationships among femoral neck bone mineral density, bone mineral content, and bone area z-score for adults with cerebral palsy

Table S2: Unadjusted and adjusted logistic regression to determine associations between demographic and anthropometric variables with fracture history among adults with cerebral palsy

Table S3: Descriptive characteristics of adults with cerebral palsy stratified by fracture history and sex

Table S4: Descriptive characteristics of adults with cerebral palsy who sustained an incident fracture

Table S5: Final dataset used in the study

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Table 1: Descriptive characteristics of adults stratified by sex and severity of CP

	Females, mild-to-moderate CP (*n*=24)	Males, mild-to-moderate CP (*n*=10)	Females, severe CP (*n*=26)	Males, severe CP (*n*=18)
Demographic and anthropometric measures, mean (SD)				
Age, y:mo	47:11 (15:6)	41:6 (13:4)	36:10 (14:1)	37:2 (15:10)
18–40y, %	41.7	60.0	69.2	72.2
41–64y, %	41.7	30.0	23.1	16.7
≥65y, %	16.6	10.0	7.7	11.1
Ethnic group, %				
White	100	100	96.2	94.4
Black	0	0	3.8	5.6
BMI (kg/m^2)	28.2 (7.9)	22.4 (4.6)	23.9 (8.1)	22.3 (4.6)
Body mass (kg)	69.9 (21.2)	62.8 (18.2)	54.4 (21)[1]	59.2 (15)
Height (cm)	157.3 (9.6)	166.1 (9.5)	150.5 (11.3)	162.3 (10.1)[b]
Fracture history, %				

No	50.0	40.0	57.7	38.9
Yes	50.0	60.0	42.3	61.1
Osteoporosis medication, %	4.2	0 (0)	11.5	5.6
Calcium/vitamin D, %	8.3	20.0	7.7	16.7
DXA-derived femoral neck bone traits, mean (SD)				
BMD	0.81 (0.13)	0.75 (0.13)	0.68 (0.22)[a]	0.65 (0.21)
BMD z-score	0.39 (1.07)	–0.87 (1.19)	–1.14 (1.82)[a]	–1.74 (1.56)
BMC	3.75 (0.78)	3.96 (0.78)	3.17 (1.15)	3.01 (1.00)
BMC z-score	0.04 (0.94)	–1.11 (0.92)[c]	-0.95 (1.44)[a]	–2.14 (1.11)[b]
Area	4.63 (0.48)	5.29 (0.51)[a]	4.65 (1.08)	4.77 (1.10)
Area z-score	–0.42 (0.74)	–0.86 (0.64)	-0.26 (1.71)	–1.54 (1.63)

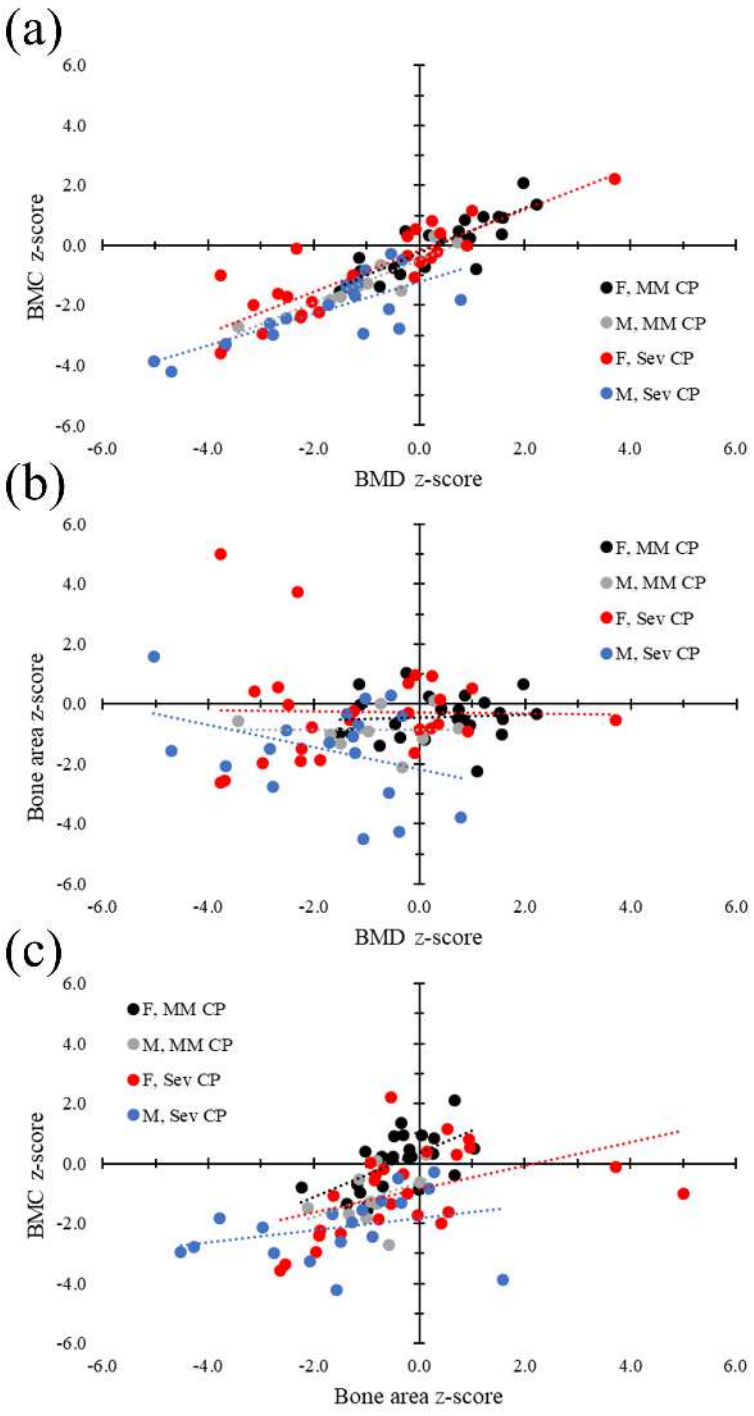
[a]$p<0.05$, compared to females with mild-to-moderate cerebral palsy (CP). [b]$p<0.05$, compared to females with severe CP. [c]$p=0.050$, compared to females with mild-to-moderate CP. SD, standard deviation; BMI, body mass index; DXA, dual energy x-ray absorptiometry; BMD, bone mineral density; BMC, bone mineral content.

[Figure legends]

Figure 1: Correlations between bone mineral density (BMD) with (a) bone mineral content (BMC) and (b) bone area and between (c) bone area with BMC for 78 adults with cerebral palsy (CP) stratified by sex (F, females; M, males) and severity of CP (MM, mild-to-moderate; Sev, severe). BMD, BMC, and bone area are from the femoral neck and transformed to age-, sex-, and ethnicity-based z-scores. Dotted lines represent the linear regression per subgroup.

Figure 2: Forest plot of odds ratio (square) with 95% confidence intervals (horizontal lines) of fracture history for femoral neck bone mineral density (BMD), bone mineral content (BMC), and bone area as age-, sex-, and ethnicity-based z-scores before (black) and after (gray) adjusting for age among adults with cerebral palsy ($n=78$).

Figure 3: Group differences (as Cohen's *d*) in means standard deviation of femoral neck bone mineral density (BMD), bone mineral content (BMC), and bone area as age-, sex-, and ethnicity-based z-scores between those with (light gray) and without (dark gray) a fracture history for (a) females (*n*=50) and (b) males (*n*=28) with cerebral palsy. Fx, fracture.



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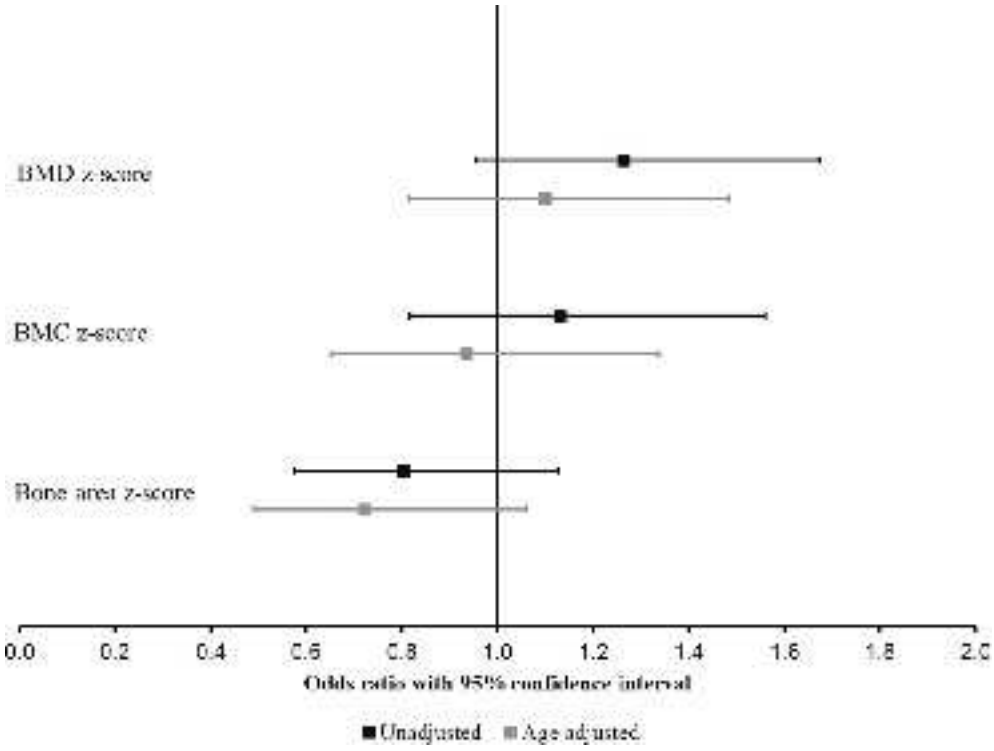

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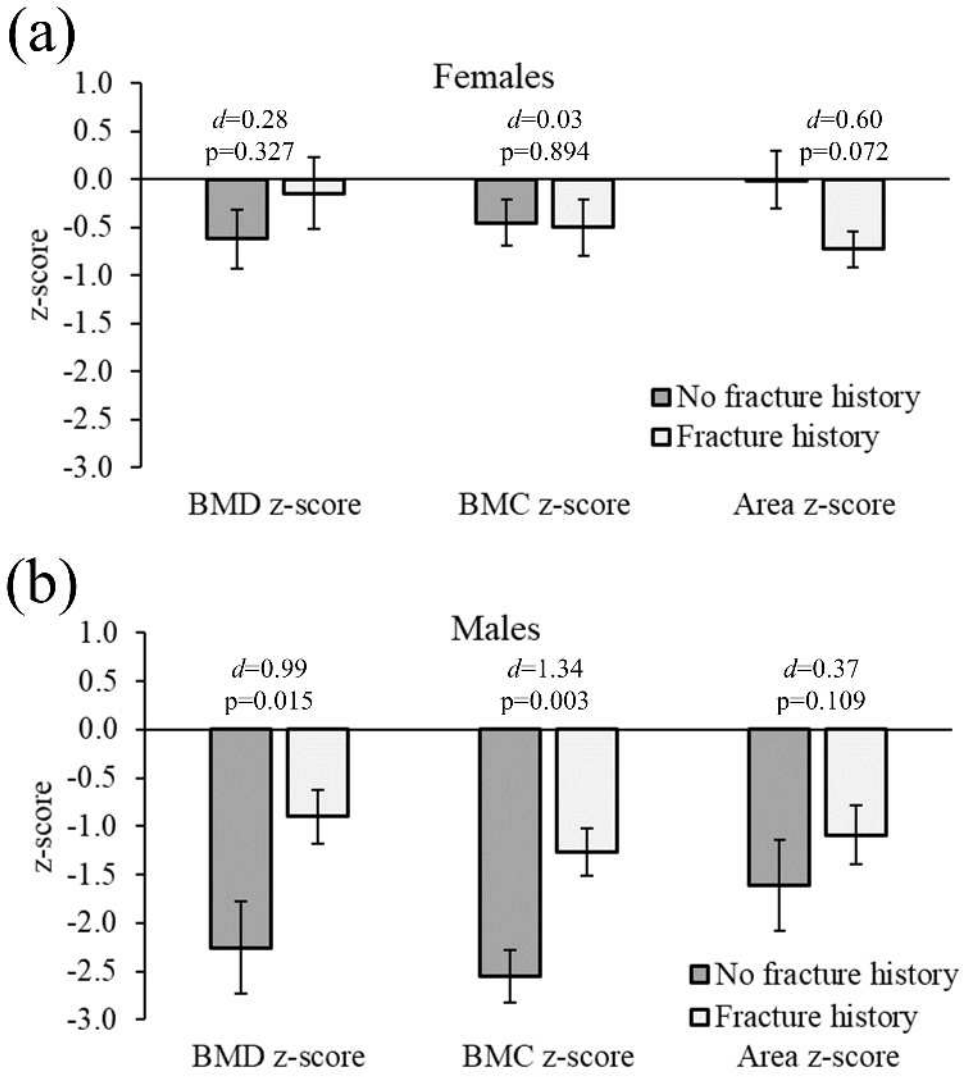

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