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Authors

Lee, Janet Y
Fan, Bo
Montenegro, Gabrielle
et al.

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Interpretation of Bone Mineral Density Z-Scores by Dual-Energy X-ray Absorptiometry in Transgender and Gender Diverse Youth Prior to Gender-Affirming Medical Therapy

Janet Y. Lee[1,2,3,*], **Bo Fan**[4,5], **Gabrielle Montenegro**[6], **Roger K. Long**[1,2], **Srinath Sanda**[1], **Gina Capodanno**[1], **Anne L. Schafe**[2,3,5], **Andrew J. Burghardt**[4], **Stephen M. Rosenthal**[1], **Ellen B. Fung**[7]

[1]Division of Pediatric Endocrinology, Department of Pediatrics, University of California, San Francisco, San Francisco, CA, United States

[2]Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Francisco, San Francisco, CA, United States

[3]Endocrine and Metabolism Section, San Francisco Veterans Affairs Health Care System, San Francisco, CA, United States

[4]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, United States

[5]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, United States

[6]University of California, San Francisco Benioff Children's Hospital Oakland, Oakland, CA, United States

[7]Division of Hematology, Department of Pediatrics, University of California, San Francisco Benioff Children's Hospital Oakland, Oakland, CA, United States

Introduction

Gender-affirming medical therapy for transgender and gender diverse (TGD) youth can be initiated as early as Tanner Stage 2 of puberty with gonadotropin-releasing hormone agonists (GnRHa) for puberty suppression to allow for gender exploration without concurrent progression of undesired secondary sex characteristics, followed by discontinuation of GnRHa to allow progression of endogenous puberty or initiation of gender-affirming estradiol or testosterone at a later point in adolescence (1,2). Because GnRHa therapy is prescribed at a time of skeletal vulnerability, the Endocrine Society Clinical Practice Guidelines recommend assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) for TGD youth who are treated with GnRHa monotherapy, and suggest following BMD by DXA until peak bone mass is attained (1).

*Corresponding author. janet.lee@ucsf.edu.

To date, all published studies describing BMD data by DXA in TGD youth have reported findings using BMD Z-scores of chronologic age and sex designated at birth reference standards (3–7). The International Society of Clinical Densitometry (ISCD) provided its first guidance on interpretation of BMD by DXA in TGD individuals in the 2019 adult position statement; namely, that BMD Z-scores should be interpreted using the reference standards corresponding to the gender identity if there is a binary gender identity, and to the sex designated at birth if there is a non-binary gender identity (8,9). However, there is no specific guidance for DXA interpretation of TGD youth included in the 2019 ISCD pediatric position statement.

A Dutch group reported lower pre-treatment BMD Z-scores by DXA in late pubertal transfeminine youth who initiated GnRHa at Tanner Stages 4–5 of puberty. After initiating estradiol therapy around 16 years of age, BMD Z-scores in these transfeminine individuals continued to decrease at 22 years of age, despite several years of estradiol (3). In contrast, a UK cohort of transmasculine youth had lower pre-treatment BMD Z-scores by DXA than transfeminine youth (5). A cohort of American TGD youth in Tanner Stages 2–3 of puberty had higher rates of low pre-treatment BMD Z-scores (−2) than expected, with 30% designated male at birth (DMAB) and 13% designated female at birth (DFAB) meeting the criteria for low BMD (6). Reasons for low BMD are under investigation, with one study demonstrating that TGD youth with low pre-treatment BMD had lower physical activity scores than TGD youth with normal pre-treatment BMD (6).

Given the lack of data regarding appropriate DXA reference populations in TGD youth, we sought to investigate different methods of interpreting BMD Z-scores by DXA in a cohort of early pubertal TGD youth prior to initiation of GnRHa therapy for puberty suppression. We hypothesized that BMD Z-score approaches using both sex reference standards and using chronologic and bone ages would yield similar results in early pubertal TGD youth. To further explore clinical relevance, we tabulated differences in low BMD for age categorization by each methodology.

Materials and methods

From 02/2019 to 06/2021, early pubertal TGD youth were prospectively enrolled from a single academic multi-disciplinary gender center if they were in Tanner Stage 2–3 of puberty (by breast exam if designated female at birth, DFAB, or testicular exam if designated male at birth, DMAB) and planned to initiate puberty suppression with GnRHa therapy. Exclusion criteria included abnormal puberty timing (e.g., precocious or delayed puberty), metabolic bone disease (e.g., osteogenesis imperfecta), and medical conditions or use of medications known to impact bone metabolism (e.g., anorexia nervosa, systemic glucocorticoids). Prior to GnRHa therapy, height by wallmounted stadiometer, weight, bone age radiograph, and DXA at total body less head (TBLH), lumbar spine (LS), total hip (TH), femoral neck (FN), and 1/3 radius (RAD) sites were measured. Height was obtained three times and averaged. The clinical research protocol was approved by the Institutional Review Board at our institution.

Bone age radiographs were independently read using the Gruelich and Pyle atlas for male and female reference standards (10) by two board-certified pediatric endocrinologists blinded to participant age and designated sex at birth, and reads were averaged. If there was a discrepancy between the two reads of more than 1 year and 2 months, a third board-certified pediatric endocrinologist read the blinded bone age and all three reads were averaged.

Due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic restrictions on our campus research facilities, DXA was performed at two locations in our institution, and both machines were Hologic Horizon A models (Marlborough, MA). Most scans were performed on DXA machine 1 (n = 28), and the remaining scans were performed on DXA machine 2 (n = 7). DXA machine 1 required repairs for a broken table, and no major repairs or upgrades were performed on DXA machine 2 during the study period. Both DXA machines are cross-calibrated to the same index (gold standard) machine on the same campus, but not to one another. Following the cross-calibration protocol of multiple site studies for epidemiology and clinical drug trials (9), a set of cross-calibration phantoms (Hologic Block, Hologic Femur, Hologic Whole Body, European Spine, and European Forearm) were scanned at both DXA machines to create cross-calibration correction factors that convert the machine 2 results to machine 1 results and harmonize the BMD values.

After all BMD values were harmonized, BMD Z-scores were height Z-score adjusted based on the BMD in Childhood Study (BMDCS) (11) using four methodologies at the TBLH, LS, TH, FN, and RAD sites: 1. Sex designated at birth and chronologic age, 2. Sex designated at birth and bone age, 3. Gender identity and chronologic age, 4. Gender identity and bone age. For TGD youth who identified as non-binary, female reference standards were used for transfeminine non-binary gender and male reference standards were used for transmasculine non-binary gender. Black reference standards were used if participants reported at least 50% of immediate ancestry were of black race; otherwise, non-black reference standards were used. Given the knowledge that race has significant impacts on bone density and geometry (11), we chose to further delineate race by ancestry in this cohort - this designation only applied to one study participant.

All data analyses were performed using Stata/SE, v17.0 (College Station, TX) statistical package (12). After verifying that the subgroups were normally distributed with equal variances, comparisons among the four different methodologies of calculating BMD Z-scores were analyzed using analysis of variance (ANOVA) models and pairwise comparisons were done using t-tests with Bonferroni correction. Comparisons of BMD Z-scores at each site by sex designated at birth were done with two-tailed t-tests. Percentages of TGD youth who met criteria for low BMD for age with lowest BMD Z-score $\leq$ −2 were tabulated for each methodology. We set a significance level of a = 0.05 for all statistical analyses.

Results

Participant characteristics

Participant characteristics are described in Table 1, with nearly even split between sex designated at birth (48.6% DFAB), and all participants noted to be in Tanner Stage 2–3 of

puberty (65.7% Tanner Stage 2). Binary gender identities prior to GnRHa were reported by 91.4% of participants. Two participants with non-binary gender identities were DMAB with non-binary transfeminine identities and one participant with non-binary gender identity was DFAB with non-binary transmasculine identity. The majority of participants reported non-Hispanic (77.1%) and white (88.6%) backgrounds. Two participants (<6%) reported black race but only one had at least 50% of immediate ancestry of black race; therefore, black reference data were used for this participant. Bone age did not differ significantly from chronologic age when determined using sex designated at birth, and differences between chronological age and bone age determined by gender identity reflect the known sex-based differential timing of puberty (e.g., average female puberty starts between 8–13 years old and average male puberty starts between 9–14 years old).

DXA bone mineral density Z-scores

BMD Z-scores using all four methodologies at all sites for all participants were not statistically significantly different, either by ANOVA or t-tests with Bonferroni correction, except at LS for DFAB participants by ANOVA (p = 0.04) (Table 2). However, at the TBLH (Fig. 1), LS (Fig. 2), TH (Fig. 3), and FN (Fig. 4) sites, DMAB were noted to have lower BMD Z-scores than DFAB. There were statistically significant differences between DMAB and DFAB BMD Z-scores at TBLH and TH sites when calculated using sex designated at birth and chronologic age, at the TBLH site when calculated using sex designated at birth and bone age, at TBLH and LS sites when calculated using gender identity and chronologic age, and at the LS site when calculated using gender identity and bone age. No statistically significant differences between DMAB and DFAB were seen at the non-weight bearing RAD (Fig. 5) site.

When BMD Z-scores were calculated by bone age and gender identity, the trend at all sites except for lumbar spine showed higher BMD Z-scores in DMAB and lower BMD Z-scores in DFAB when compared with BMD Z-scores calculated by chronologic age and sex, although these differences were not statistically significant.

Low BMD for age determination and clinical relevance

There were differences among BMD Z-score methodologies in the number of study participants who fulfilled criteria for low BMD for age with at least one BMD Z-score −2: calculating BMD Z-scores based on gender identity increased the number of TGD youth considered to have low BMD for age (Table 3). These proportions of low BMD for age were not statistically significantly different when compared via ANOVA and by paired t-tests with Bonferroni correction; clinically, however, three more participants would have shifted from normal to low BMD for age category if BMD Z-scores were calculated based on gender identity and chronologic age.

Similar to our previously reported data on early pubertal TGD youth (6), the percentages of pre-treatment low BMD (44.4%–55.6%) in DMAB were more than triple that of DFAB (11.8%–17.7%) in this cohort regardless of methodology used to calculate BMD Z-scores. Overall, there were higher percentages of pre-treatment low BMD in all TGD youth than would be expected in the general population.

We examined whether any individuals had larger discrepancies between chronological age and bone age for sex designated at birth. For instance, one study participant experienced menarche prior to the study visit due to insurance delays and two other participants experienced onset of puberty at the extremes of the puberty timing window and were found to have differences in BMD Z-score among the four methodologies, particularly between BMD Z-scores as determined by chronologic age versus bone age (Table 4). Notably, the BMD Z-scores by bone age were more similar in these participants.

Discussion

We compared BMD Z-scores calculated using chronologic and bone ages as well as female and male reference standards in a cohort of early pubertal TGD youth prior to initiating gender-affirming hormone therapy with GnRHa. Differences in BMD Z-scores among approaches did not reach statistical significance except by ANOVA at LS for DFAB participants, and there were notable trends. In particular, when BMD Z-scores for DFAB were calculated based on the male reference ranges, BMD Z-scores were generally lower. Similarly, the BMD Z-scores for DMAB were higher when calculated based on female reference ranges. The only exception to this trend was the largely trabecular LS site, in which the opposite trend was noted. Because higher incidence of low BMD has been observed in cohorts of transfeminine TGD youth (3,4,6,7), utilizing the female reference ranges in DMAB TGD youth may shift the categorization of individuals into the normal BMD range. Indeed, in our cohort there were some differences in which participants were categorized as having low BMD for age depending on which methodology was used to calculate BMD Z-scores. We also found that youth who initiated puberty at the extremes of the puberty timing windows may have greater differences between BMD Z-scores calculated by chronologic versus bone age.

Our data also redemonstrate that TGD youth who are DMAB have lower BMD Z-scores than TGD youth who are DFAB, except at the non-weight bearing forearm site, reinforcing the potential that differences in weight-bearing physical activity may be an important factor (6). Interpretation of the BMD Z-score differences in TGD youth based on sex designated at birth could also be impacted by methodology chosen to determine BMD Z-scores. In addition, the differences in trends between cortical and mixed cortical/trabecular sites (TBLH, TH, FN, RAD) and the primarily trabecular site (LS) could be explained by cisgender male children having a larger range in BMD at those cortical sites, as well as development of bone mass and strength at later ages, in comparison to cisgender female children (13,14). The BMD range at the LS during the pubertal age windows are also similar, with very little difference in values between male and female references (14).

While there is guidance on how to interpret BMD by DXA for TGD adults, more data are needed to help guide DXA interpretation in TGD youth. Because puberty timing can be so variable, with usual initiation in a six-year age window and subsequent manipulation of timing with gender-affirming hormone therapy, bone age radiographs may be useful in providing a more accurate assessment of bone mass status in these youth, particularly in those who initiate endogenous puberty at the extremes of the typical timing window. Bone age radiographs are relatively inexpensive and easily obtained, and could be collected prior

to DXA imaging to allow for BMD Z-score adjustment based on skeletal age. While minor variations may occur in assessment of bone age, pediatric endocrinologists and radiologists all receive training on interpretation of bone age radiographs.

Data regarding hip bone geometry indicate that TGD adults who initiated pubertal suppression in early puberty resemble the reference curves of the affirmed gender, but those who initiated gender-affirming medical therapy in middle to late puberty more closely followed the hip geometry reference curves of the sex designated at birth (15). Over time, if these early pubertal TGD youth go on to initiate gender-affirming hormone therapy with estradiol or testosterone, it would especially make sense to compare BMD Z-scores using the reference standards of the affirmed gender rather than by the sex designated at birth; in fact, this would be congruent with the recommendations included in the 2019 ISCD Adult Position Statement (8,9). Given the ongoing uncertainties in interpretation of DXA in TGD youth, these topics should be considered at the next ISCD Pediatric Position Development Conference.

While our study utilized standardized imaging measures, limitations include a small sample from a single center with majority White and non-Hispanic/Latinx background. Thus, our findings may not be generalizable to the larger population of TGD youth. In addition, DXA data reported here only include pre-treatment values, and the larger context of bone accrual trajectories and ultimate peak bone mass attainment remains to be seen. The forthcoming longitudinal data will be more informative, after the participants either stop GnRHa or elect to initiate gender-affirming sex hormones.

Conclusions

Based on our findings, it may be useful to utilize skeletal age, especially in those initiating puberty at the extremes of usual timing, as well as both sex reference standards to interpret BMD by DXA prior to and during GnRHa monotherapy, and then utilize reference standards of the affirmed gender when either GnRHa therapy is ceased to allow for endogenous puberty to progress or gender-affirming hormone therapy with estradiol or testosterone is started. More longitudinal data are needed on approach to interpreting BMD by DXA in TGD youth, as various methodologies can yield different conclusions which in turn may impact clinical approach, such as decisions on the timing of discontinuation of GnRHa or initiation of gender-affirming sex hormones.

Acknowledgments

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Fig. 1.
Total Body Less Head BMD Z-scores, Boxplots of areal BMD Z-scores calculated using four different methodologies are shown for designated females at birth (left) and designated males at birth (right). Boxes represent the interquartile ranges (IQR, 25th-75th percentile), horizontal lines within the box mark the median values, the whiskers show minimum (quartile 1 – 1.5* IQR) and maximum values (quartile 3 + 1.5 * IQR), and points show outliers.
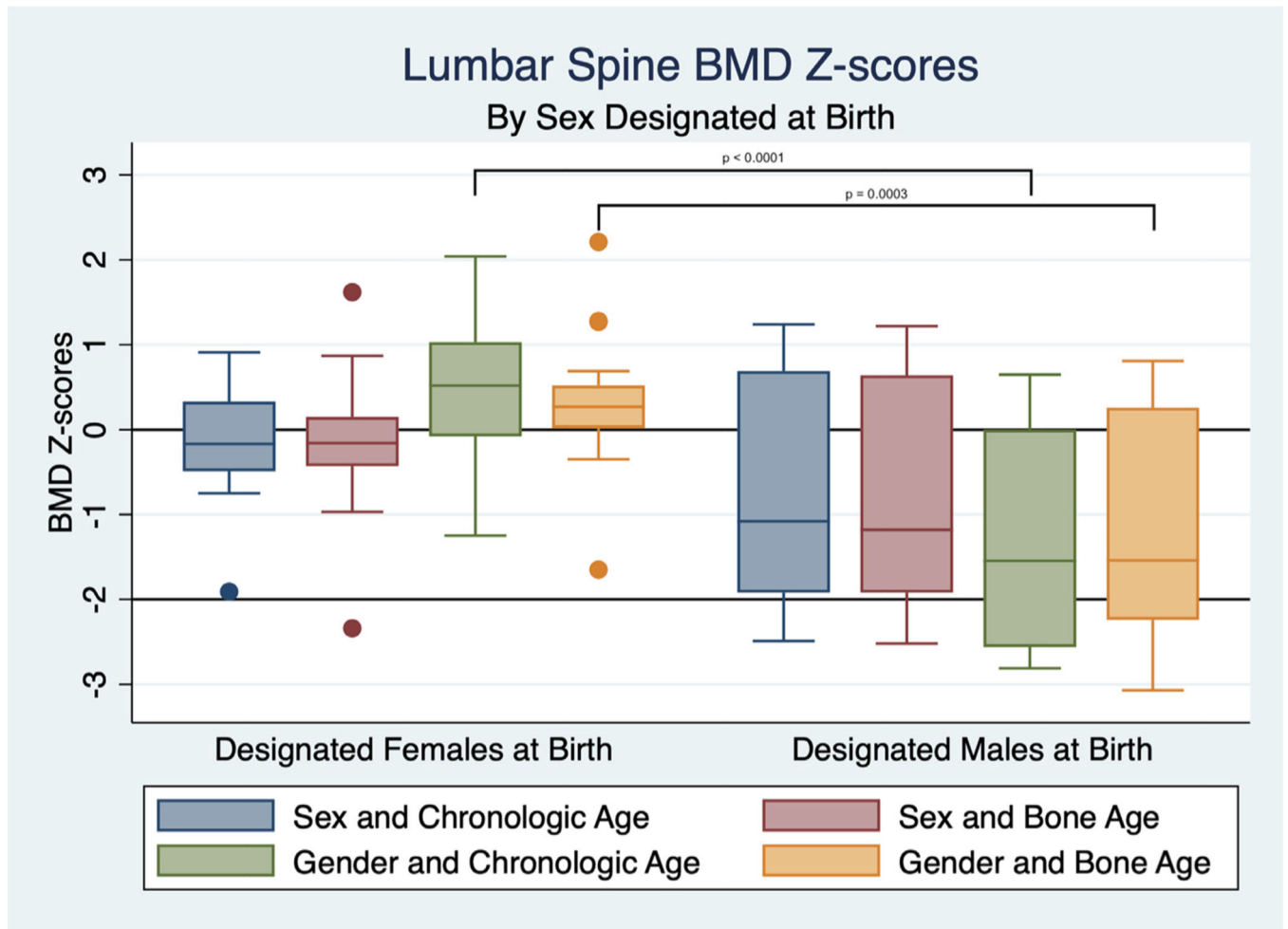
Fig. 2.
Lumbar Spine BMD Z-scores, Boxplots of areal BMD Z-scores calculated using four different methodologies are shown for designated females at birth (left) and designated males at birth (right). Boxes represent the interquartile ranges (IQR, 25th-75th percentile), horizontal lines within the box mark the median values, the whiskers show minimum (quartile 1 – 1.5* IQR) and maximum values (quartile 3 + 1.5 * IQR), and points show outliers.
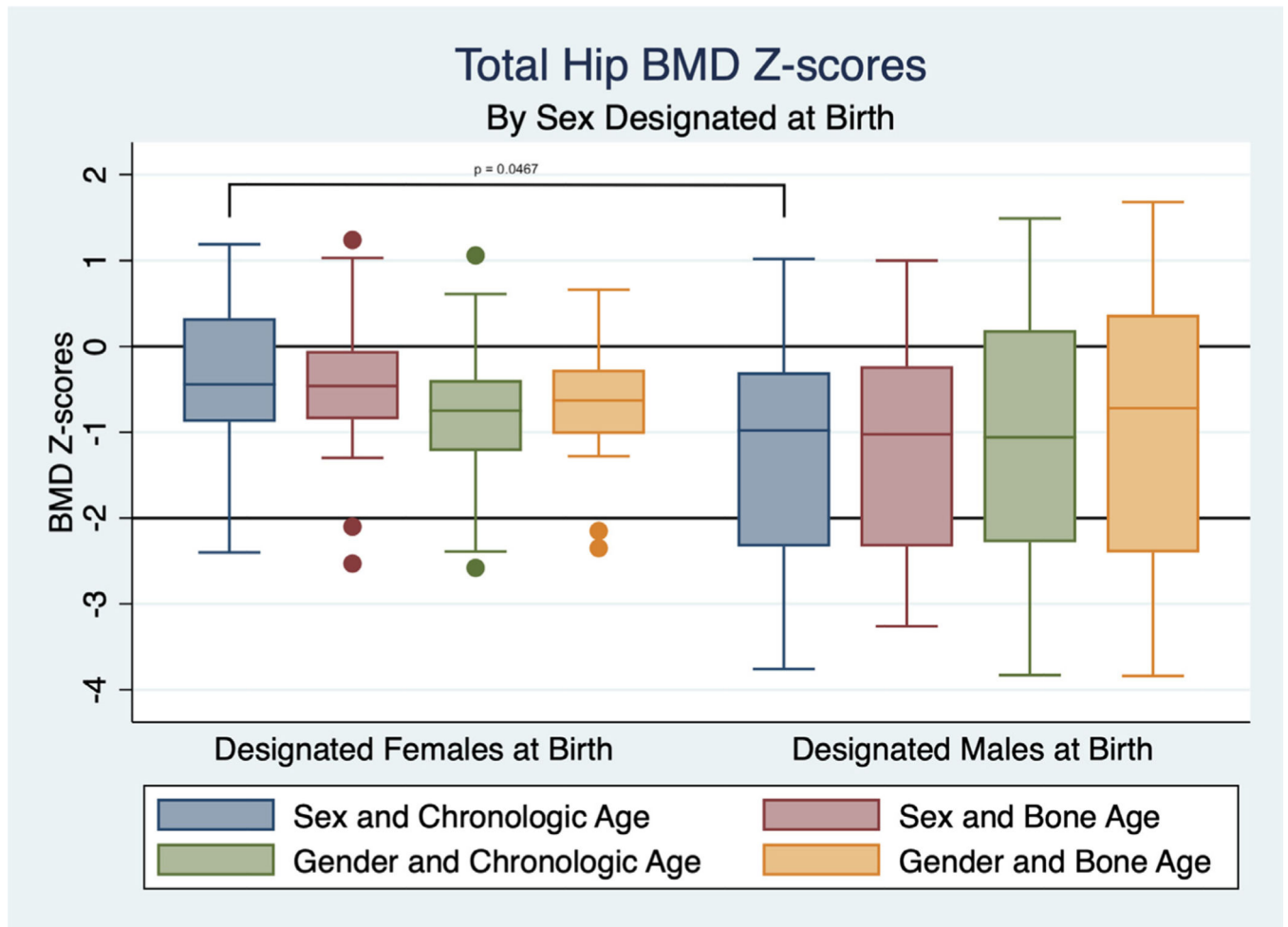
Fig. 3.
Total Hip BMD Z-scores, Boxplots of areal BMD Z-scores calculated using four different methodologies are shown for designated females at birth (left) and designated males at birth (right). Boxes represent the interquartile ranges (IQR, 25th-75th percentile), horizontal lines within the box mark the median values, the whiskers show minimum (quartile $1 - 1.5*$ IQR) and maximum values (quartile $3 + 1.5 *$ IQR), and points show outliers.
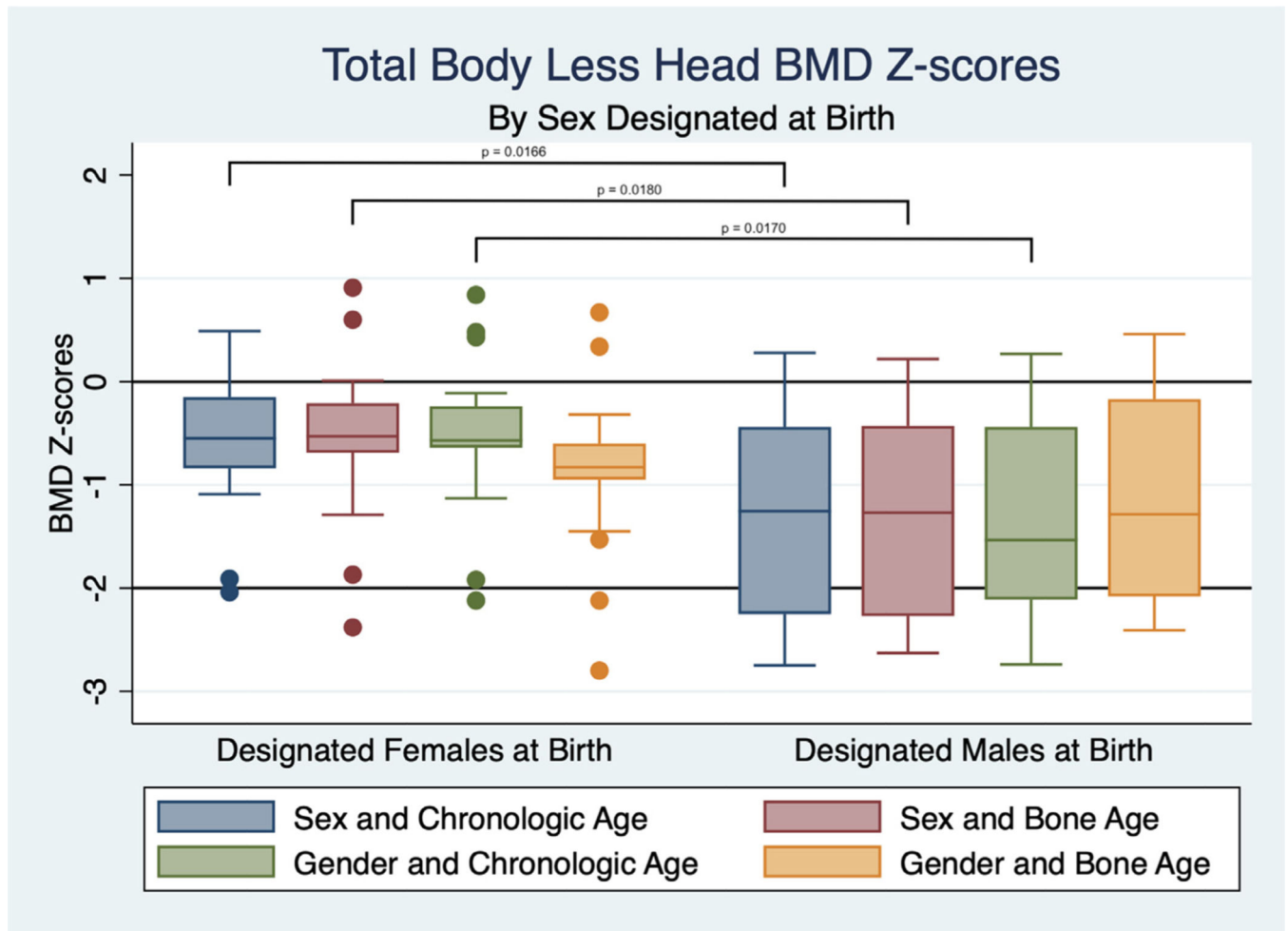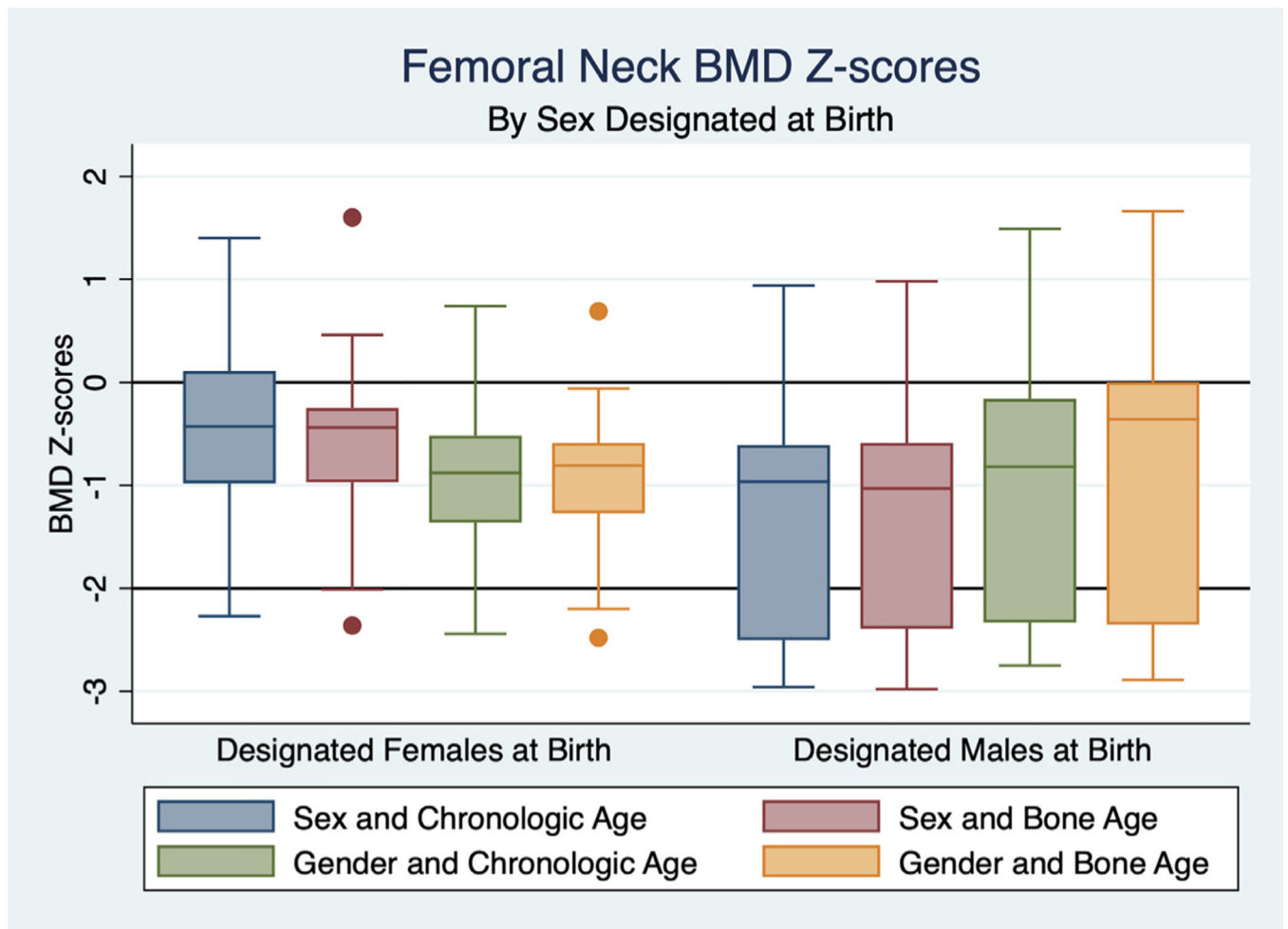
Fig. 4.
Femoral Neck BMD Z-scores, Boxplots of areal BMD Z-scores calculated using four different methodologies are shown for designated females at birth (left) and designated males at birth (right). Boxes represent the interquartile ranges (IQR, 25th-75th percentile), horizontal lines within the box mark the median values, the whiskers show minimum (quartile 1 – 1.5* IQR) and maximum values (quartile 3 + 1.5 * IQR), and points show outliers.
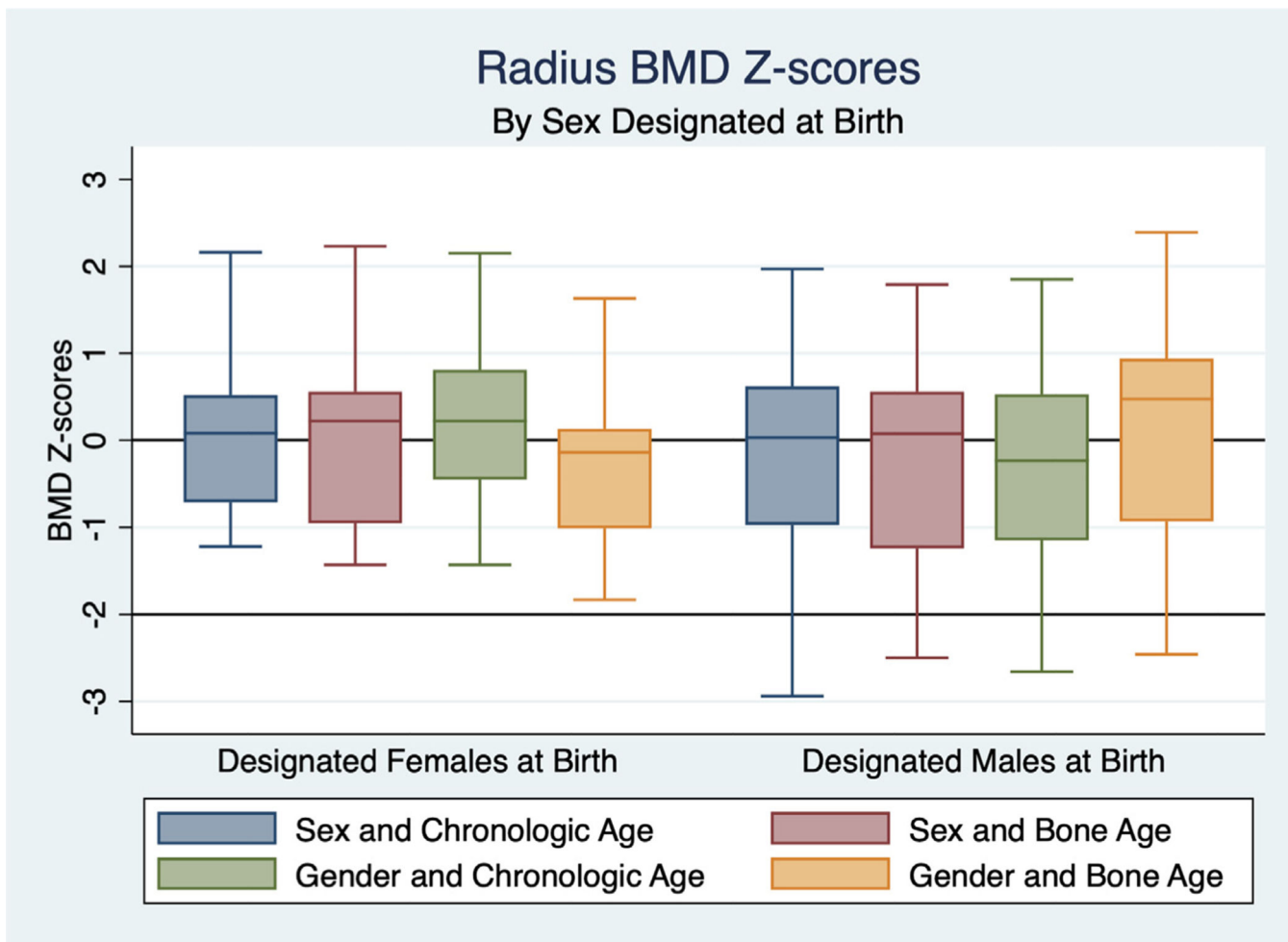
Fig. 5.
1/3 Radius BMD Z-scores, Boxplots of areal BMD Z-scores calculated using four different methodologies are shown for designated females at birth (left) and designated males at birth (right). Boxes represent the interquartile ranges (IQR, 25th-75th percentile), horizontal lines within the box mark the median values, the whiskers show minimum (quartile 1 − 1.5* IQR) and maximum values (quartile 3 + 1.5 * IQR), and points show outliers.

Table 1

Participant characteristics ($n = 35$).

Sex Designated at Birth	
Female	17 (48.6%)
Male	18 (51.4%)
Gender Identity	
Female	16 (45.7%)
Male	16 (45.7%)
Non-binary	3 (8.6%)
Race [*]	
Native American or American Indian	0 (0.0%)
Asian	2 (5.7%)
Native Hawaiian or Other Pacific Islander	1 (2.9%)
Black or African-American	2 (5.7%)
White	31 (88.6%)
More than One Race	6 (17.1%)
Unknown/Not Reported	2 (5.7%)
Ethnicity	
Hispanic/Latinx	6 (17.1%)
Non-Hispanic/Latinx	27 (77.1%)
Unknown/Not Reported	2 (5.7%)
Tanner Stage	
2	23 (65.7%)
3	12 (34.3%)
Chronologic Age, years, mean ± SD (range)	
Designated Females at Birth	11.18 ± 1.06 (9.73–13.18)
Designated Males at Birth	11.44 ± 0.96 (9.77–13.10)
Bone Age (Female Reference Standards), years, mean ± SD (range)	
Designated Females at Birth	11.12 ± 1.36 (8.33–14.5)
Designated Males at Birth	9.31 ± 1.28 (7.33–11.5)
Bone Age (Male Reference Standards), years, mean ± SD (range)	
Designated Females at Birth	13.22 ± 1.19 (11–16.5)
Designated Males at Birth	11.56 ± 1.28 (9–13.25)

[*] multiple options could be marked for each participant, "More than One Race" was a discrete option.

Table 2

DXA bone mineral density Z-scores.

Total Body Less Head Bone Mineral Density Z-scores (mean ± SD)

	Designated Females at Birth (n = 17)					Designated Males at Birth (n = 18)				
	Sex		Gender		p-value*	Sex		Gender		p-value
	Chronologic Age	Bone Age	Chronologic Age	Bone Age		Chronologic Age	Bone Age	Chronologic Age	Bone Age	
	−0.55 ± 0.69 (−2.04 to 0.49)	−0.57 ± 0.79 (−2.38 to 0.91)	−0.54 ± 0.76 (−2.12 to 0.84)	−0.87 ± 0.81 (−2.8 to 0.67)	0.54	−1.29 ± 1.00 (−2.75 to 0.28)	−1.32 ± 0.99 (−2.63 to 0.22)	−1.29 ± 0.99 (−2.74 to 0.27)	−1.14 ± 1.01 (−2.41 to 0.46)	0.95

Lumbar Spine Bone Mineral Density Z-scores (mean ± SD)

	Designated Females at Birth (n = 17)					Designated Males at Birth (n = 18)				
	Sex		Gender		p-value	Sex		Gender		p-value
	Chronologic Age	Bone Age	Chronologic Age	Bone Age		Chronologic Age	Bone Age	Chronologic Age	Bone Age	
	−0.11 ± 0.71 (−1.91 to 0.91)	−0.16 ± 0.84 (−2.34 to 1.62)	0.53 ± 0.81 (−1.25 to 2.04)	0.31 ± 0.82 (−1.65 to 2.21)	0.04	−0.76 ± 1.30 (−2.49 to 1.24)	−0.79 ± 1.28 (−2.52 to 1.22)	−1.27 ± 1.27 (−2.81 to 0.65)	−1.18 ± 1.29 (−3.07 to 0.81)	0.51

Total Hip Bone Mineral Density Z-scores (mean ± SD)

	Designated Females at Birth (n = 17)					Designated Males at Birth (n = 18)				
	Sex		Gender		p-value	Sex		Gender		p-value
	Chronologic Age	Bone Age	Chronologic Age	Bone Age		Chronologic Age	Bone Age	Chronologic Age	Bone Age	
	−0.42 ± 0.97 (−2.4 to 1.19)	−0.46 ± 0.98 (−2.53 to 1.24)	−0.77 ± 0.98 (−2.58 to 1.06)	−0.65 ± 0.82 (−2.35 to 0.66)	0.66	−1.24 ± 1.33 (−3.76 to 1.02)	−1.21 ± 1.27 (−3.26 to 1.00)	−1.04 ± 1.48 (−3.83 to 1.49)	−0.95 ± 1.58 (−3.84 to 1.68)	0.92

Femoral Neck Bone Mineral Density Z-scores (mean ± SD)

	Designated Females at Birth (n = 17)					Designated Males at Birth (n = 18)				
	Sex		Gender		p-value	Sex		Gender		p-value
	Chronologic Age	Bone Age	Chronologic Age	Bone Age		Chronologic Age	Bone Age	Chronologic Age	Bone Age	
	−0.54 ± 0.94 (−2.27 to 1.4)	−0.57 ± 0.94 (−2.36 to 1.6)	−0.92 ± 0.88 (−2.44 to 0.74)	−0.94 ± 0.77 (−2.48 to 0.69)	0.38	−1.24 ± 1.19 (−2.62 to 0.94)	−1.25 ± 1.17 (−2.98 to 0.98)	−0.97 ± 1.29 (−2.75 to 1.49)	−0.84 ± 1.39 (−2.89 to 1.66)	0.71

1/3 Radius Bone Mineral Density Z-scores (mean ± SD)

	Designated Females at Birth (n = 17)					Designated Males at Birth (n = 18)				
	Sex		Gender		p-value	Sex		Gender		p-value
	Chronologic Age	Bone Age	Chronologic Age	Bone Age		Chronologic Age	Bone Age	Chronologic Age	Bone Age	
	0.06 ± 1.01 (−1.22 to 2.16)	0.03 ± 0.98 (−1.43 to 2.23)	0.17 ± 1.07 (−1.43 to 2.15)	−0.37 ± 0.90 (−1.83 to 1.63)	0.42	−0.18 ± 1.18 (−2.94 to 1.97)	−0.22 ± 1.09 (−2.5 to 1.79)	−0.34 ± 1.12 (−2.66 to 1.85)	0.14 ± 1.18 (−2.46 to 2.39)	0.63

*
All BMD Z-scores were height Z-score adjusted; p-values shown for ANOVA of all four methodologies.

Table 3

Low BMD by BMD Z-score calculation methodology.

BMD Z-score Calculation Methodology	Low BMD,[1] n (%sex designated at birth)
Sex and chronologic age	
Designated females at birth	2/17 (11.8%)
Designated males at birth	8/18 (44.4%)
Sex and bone age	
Designated females at birth	2/17 (11.8%)
Designated males at birth	8/18 (44.4%)
Gender and chronologic age	
Designated females at birth	3/17 (17.7%)
Designated males at birth	10/18 (55.6%)
Gender and bone age	
Designated females at birth	2/17 (11.8%)
Designated males at birth	10/18 (55.6%)

[1] At least one BMD Z-score –2.

Table 4

BMD Z-scores of three participants (designated female at birth) with differences between bone and chronologic ages.

Participant Characteristics	Chronologic Age, years	Bone Age (female), years	Chronologic Age, years	Bone Age (male), years
	12.84	14.5	12.84	16.5
	Sex		Gender	
	Chronologic Age	Bone Age	Chronologic Age	Bone Age
Total Body Less Head BMD Z-scores	0.41	0.01	0.84	−0.60
Lumbar Spine BMD Z-scores	0.19	−0.43	1.51	0.02
Total Hip BMD Z-scores	0.78	0.46	1.06	0.12
Femoral Neck BMD Z-scores	0.33	−0.08	0.43	−0.47
1/3 Radius BMD Z-scores	1.51	0.84	2	−0.1

Participant Characteristics	Chronologic Age, years	Bone Age (female), years	Chronologic Age, years	Bone Age (male), years
	9.73	11.0	9.73	13.25
	Sex		Gender	
	Chronologic Age	Bone Age	Chronologic Age	Bone Age
Total Body Less Head BMD Z-scores	−0.91	−1.07	−1.13	−1.53
Lumbar Spine BMD Z-scores	0.48	0.27	0.86	0.69
Total Hip BMD Z-scores	−0.35	−0.45	−1.04	−0.63
Femoral Neck BMD Z-scores	0.31	0.11	−0.35	−0.38
1/3 Radius BMD Z-scores	−1.22	−1.43	−1.43	−1.83

Participant Characteristics	Chronologic Age, years	Bone Age (female), years	Chronologic Age, years	Bone Age (male), years
	13.18	10.5	13.18	12
	Sex		Gender	
	Chronologic Age	Bone Age	Chronologic Age	Bone Age
Total Body Less Head BMD Z-scores	0.27	0.91	0.48	0.67
Lumbar Spine BMD Z-scores	0.83	1.62	2.04	2.21
Total Hip BMD Z-scores	0.66	1.03	0.61	0.66
Femoral Neck BMD Z-scores	−0.8	−0.59	−1.03	−1.0
1/3 Radius BMD Z-scores	−0.71	0.1	−0.34	−0.14

*
All BMD Z-scores were height Z-score adjusted.