HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

J Pediatr. 2015 June ; 166(6): 1449–1454.e1. doi:10.1016/j.jpeds.2015.03.005.

The Effect of Psychostimulants on Skeletal Health in Boys co-Treated with Risperidone

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Abstract

Objectives—To examine the skeletal effects of chronic psychostimulant treatment in children and adolescents.

Study design—Medically healthy 5 to 17 year-old males from four different clinic-based studies were combined for this analysis. They were divided by psychostimulant use into 3 groups: none to negligible, intermittent, and continuous use. Most (95%) had also received risperidone for six months or more. Treatment history was extracted from medical and pharmacy records. Anthropometric and bone measurements, using dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), were obtained at each research visit. Multivariable linear regression analysis models examined whether age-sex-specific height Z-score and skeletal outcomes differed among the three psychostimulant-use groups.

Results—The sample consisted of 194 males with a mean age of 11.7±2.8 years at study entry. The majority had an externalizing disorder. There was no significant difference across the three treatment groups in height Z-score or in skeletal outcomes at the radius, lumbar spine, or whole body. One hundred forty-four boys had valid follow-up skeletal data 1.4±0.7 years after study entry. Again, neither height Z-score nor the skeletal outcomes were different among those who remained on psychostimulants between the two visits, started psychostimulants anew, or had not taken psychostimulants.

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The authors declare no conflicts of interest.

Conclusions—Following chronic treatment, psychostimulants did not appear to significantly affect bone mass accrual in children and adolescents taking risperidone. There was a small, but statistically not significant, negative impact on longitudinal growth.

Attention deficit hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity, impairing functioning across a variety of settings.[1] Its prevalence ranges between 2.5% in adults and 5% in children.[1] Although a number of interventions are available, psychostimulants are the most effective at targeting ADHD symptoms.[2] The use of these drugs continues to grow worldwide.[3–5]

Concerns have been raised about the potential for psychostimulants to stunt longitudinal growth.[6–8] This effect appears to plateau over extended periods of treatment[7] and it remains unclear whether adult height is impacted.[9–11]

Preclinical work in 4-week-old male rats treated for 13 weeks suggests that psychostimulants may interfere with bone metabolism, resulting in reduced bone mass and increased bone fragility.[12] The femur and tibia exhibited these changes, but not the vertebrae. Further, low bone mass and increased fragility recovered within 5 weeks following medication discontinuation.[12] The mechanisms involved in the possible skeletal effects of psychostimulants have not been established, but may involve the downstream effects of dopamine transporter blockade,[13] height suppression,[7] hormonal alterations,[14, 15] or nutritional insufficiency due to medication-induced anorexia.

Aside from a small (n=10) pilot study,[16] the skeletal effects of psychostimulants have not been examined in children and adolescents. If, as suggested by preclinical findings,[12] extended psychostimulant treatment hinders bone mass accrual, then the clinical impact could be significant given that peak bone mass accrued by early adulthood is a major determinant of lifetime risk of osteoporosis and fractures.[17]

Thus, we undertook an analysis of data from several pediatric studies to examine skeletal health following chronic treatment with psychostimulants. We anticipated that psychostimulant use will be associated with a clinically-significant reduction in bone mass.

Methods

Data from four studies were combined in this analysis to maximize sample size (Table I; available at www.jpeds.com). Study 1 involved 152 participants, 7 to 17 years old, who had received risperidone for at least six months. One hundred eight (71%) returned for an additional follow-up visit, 1.5±0.3 years after study entry.[18] Study 2 was cross-sectional and involved eight 10 to 18 year-olds treated with risperidone for at least one year. Study 3 consisted of a randomized trial (n=46) examining the skeletal effects of calcium and vitamin D supplementation in 5 to 17 year-old boys taking risperidone for at least one year and exhibiting hyperprolactinemia. Study 4 consisted of a longitudinal observational study (n=17) involving 5 to 16 year-old, largely antipsychotic-naïve, participants, six of whom had initiated treatment with risperidone within the prior month. In all four studies, chronic medical or neurological conditions, concurrent treatment with more than one antipsychotic medication, or pregnancy led to exclusion.

All the studies were approved by the local Institutional Review Board. After complete description of the study, written assent was obtained from children ≤ 14 years old, and written consent was obtained from adolescents and parents or guardians.

Procedures

During the research visits, height and weight measurements were obtained following a standard protocol and pubertal stage was recorded.[19, 20] The medical and pharmacy records were reviewed to document all psychotropic treatments, including the start and stop date of each drug and its dosage.[19, 20] All dosages of psychostimulants were expressed in methylphenidate (MPH) equivalents for amphetamines (x2).[21]

A best-estimate diagnosis, following the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR),[22] was generated based on a review of the psychiatric record, often supplemented by a clinical interview (conducted by CAC), a standardized interview of the parent using the Diagnostic Interview Schedule for Children (DISC-IV) (except in Study 2),[23] and the Child Behavior Checklist.[24]

Daily calcium and vitamin D intake during the week prior to enrollment was estimated using the 2004 Block Kids Food Frequency Questionnaire,[25] and physical activity was assessed (except in Study 2) by asking the parent to compare the child's usual level of physical activity to their peers', using a 5-point Likert scale.[26]

Following the same protocol described previously,[18, 20] peripheral quantitative computed tomography (pQCT) scans were obtained at the 4% site of the nondominant radius (rich in trabecular bone), to estimate volumetric bone mineral density (vBMD), and at the 20% site to estimate cortical vBMD. A Stratec XCT-2000 scanner, software version 6.0 (Stratec, Inc., Pforzheim, Germany), was used. Trabecular vBMD was measured as the mean density of the 85% central area of the bone's cross-section, and total vBMD encompassed the entire bone mass, including the thin cortical shell.[18] pQCT scans compromised by movement were rejected. A Hologic QDR DELPHI-4500A dual-energy x-ray absorptiometry (DXA) unit (Hologic, Inc., Bedford, MA; Studies 1 and 2) or a Hologic Discovery A unit (Studies 3 and 4) was used to estimate bone mineral content (BMC) and areal bone mineral density (aBMD) in the lumbar spine vertebrae L1 through L4 (LS) or of the total body less head (TBLH). The two DXA units were cross-calibrated using a Hologic anthropomorphic spine phantom, Hologic Whole Body Phantom, Orthometrix Anthropomorphic phantom "Oscar Jr," and 12 human volunteers. Qualitycontrol and calibration of the equipment were performed daily. Although each of the four studies acquired at least one bone scan, the scan type and skeletal site varied (Table I). Studies 1, 2, and 3 measured trabecular vBMD at the 4% radius site. In addition, study 3 measured cortical vBMD at the 20% radius site. Studies 1 and 2 acquired a LS DXA scan, and studies 3 and 4 acquired a TBLH scan.

Statistical Analyses

Body mass index (BMI) was computed as weight/height^2 (kg/m^2) and age-sex-specific height and BMI Z-scores were generated based on the 2000 Centers for Disease Control and

Prevention normative data.[27] Age-sex-height-race-specific Z-scores for LS and TBLH BMC and aBMD were generated following the Bone Mineral Density in Childhood Study.[28]

Because the number of female participants with a bone scan was relatively small and because there is a strong sex effect on BMD, we restricted the analyses to boys. As the principal aim of this analysis was to examine the skeletal effects of psychostimulants, the participants were divided in three groups: 1) Boys with no exposure to psychostimulants within the two years prior to the bone scan (No-MPH, n=40). This group included participants who never received psychostimulants (n=26) as well as those who had received them but not for at least two years prior to undergoing the bone scan (n=14). The period of two years was set, somewhat arbitrarily, given that psychostimulant holidays allow the rapid recovery of longitudinal growth delays,[7, 12] in order to ensure that any potential skeletal effect of psychostimulants would have resolved. 2) The second group consisted of those who had taken psychostimulants continuously (MPH-Cont, n=91). This included boys who never discontinued psychostimulants (n=63) as well as those who may have discontinued them at some point but had taken them continuously for two years prior to undergoing the bone scan (n=28). 3) Finally, boys who took psychostimulants intermittently, including during the two years prior to the bone scan formed the third group (MPH-Intermit, n=63).

To take full advantage of the data available, two sets of analyses related to the skeletal outcomes were conducted. First, anthropometric and skeletal measures obtained at study entry were compared among the three MPH groups. Albeit cross-sectional, this analysis included the largest number of participants, optimizing statistical power. Next, a longitudinal analysis was conducted to examine whether continued psychostimulant treatment because study entry was associated with changes in anthropometric or skeletal outcomes.

We also examined whether psychostimulant treatment was associated with a reduction in height Z-score, reflecting longitudinal growth suppression. We extracted, from the medical records, the “baseline” height measurements collected within 90 days before or 15 days after the initiation of psychostimulants. This range was selected to maximize the sample size as the primary health care providers may not have documented height the day a psychostimulant was started. Because the No-MPH group consisted largely of participants who had never received psychostimulants, we estimated a “baseline” height by selecting a measurement obtained at a date preceding study entry by an interval comparable with that in the other two MPH groups.

Differences among the three MPH groups were compared using one-factor analysis of variance (ANOVA) for continuous variables and chi square or Fisher’s Exact test for categorical ones. Multivariable linear regression analysis examined the association between the MPH groups and anthropometric and skeletal outcomes, adjusting for relevant covariates. Specifically, change in risperidone treatment was controlled for, where appropriate, due to its potentially confounding effect.[18] We then repeated the analyses after substituting the cumulative weight-adjusted dose of psychostimulants for the MPH groups. This latter set of analyses excluded participants in the MPH-Intermit group because their intermittent use of psychostimulants in the two years prior to study entry could mask any

potential effect of these medications on the skeleton. All hypothesis tests were two-tailed with a significance level of $p < 0.05$ and analyses utilized procedures from SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC).

Results

The demographic and clinical data of the 194 male participants are presented in Tables II and III, for the entire sample and divided by MPH treatment status.

Cross-sectional Analyses

Psychostimulant Use and Height at Study Entry—At study entry, age-sex-specific height Z-score was significantly higher in the No-MPH group compared with the two other groups (Table II). In order to determine whether this was caused by psychostimulants (ie, growth suppression) or predated their use, we compared "baseline" (ie, pre-psychostimulants) height Z-score between the three groups. The No-MPH group was non-significantly taller than the other two groups at "baseline" (Table II). Similarly, the change in height Z-score between "baseline" and study entry was not significantly different among the groups, although it was in the expected direction (ie, a trend for reduced height Z-score in both MPH-treated groups; Table II). When the cumulative weight-adjusted psychostimulant dose was substituted for MPH treatment groups, there was no association between it and change in height Z-score among participants in the No-MPH or MPH-Cont groups ($p>0.40$).

Psychostimulants and Skeletal Outcomes at Study Entry—Table IV (available at www.jpeds.com) summarizes the unadjusted skeletal outcomes across the three MPH treatment groups. Using multivariable linear regression analysis adjusting for age ($\beta=5.0$, $p<0.05$), forearm length ($p>0.20$), BMI Z-score ($\beta=13.3$, $p<0.0001$), and the use of selective serotonin reuptake inhibitors (SSRIs, $\beta= -16.2$, $p<0.008$), there was no significant difference in trabecular vBMD at the ultradistal radius site (ie, 4%) either between the No-MPH and the MPH-Cont groups ($p>0.90$) or between the No-MPH and the MPH-Interm group ($p>0.90$). Further adjustment for physical activity ($\beta=8.6$, $p<0.03$) did not alter these results. Similarly, after adjusting for the same variables, no significant associations were found between the MPH treatment groups and either total vBMD or strength index at the ultradistal radius (both $p>0.60$).

A smaller group of participants had valid pQCT scan data at the 20% radius site (Table IV). After adjusting for age ($p>0.50$), BMI Z-score ($p<0.04$), forearm length ($p>0.70$), physical activity ($p>0.50$), and SSRI use ($p>0.30$), there was no significant association between the MPH treatment groups and cortical vBMD ($p>0.70$). After adjusting for the same variables, we also failed to find any significant association with cortical thickness ($p>0.40$), periosteal or endosteal circumference ($p>0.60$ and >0.40, respectively), or polar section modulus ($p>0.80$).

As for the DXA-based variables, after adjusting for BMI Z-score ($p<0.0001$), physical activity ($p>0.10$), and SSRI use ($\beta= -0.28$, $p=0.10$), there was no significant association between the three MPH treatment groups and age-sex-height-ethnicity-specific LS aBMD

(p>0.20). However, after adjusting for the same variables, LS BMC Z-score was marginally higher in the MPH-Interm group compared with the No-MPH group (LS Means: 0.31 vs. −0.16, LS Means difference: 0.48, 95% confidence interval: −0.05, 1.00, p<0.09). In addition, after adjusting for BMI Z-score (p=0.0002), physical activity (p<0.03), and SSRI use (β= −0.32, p<0.08), there was no significant association between the three MPH treatment groups and age-sex-height-ethnicity-specific TBLH BMC Z-score (p>0.10). Similarly, after adjusting for BMI Z-score (p<0.003), physical activity (p>0.20), and SSRI use (β= −0.32, p<0.03), there was no significant association between the three MPH treatment groups and TBLH BMD Z-score (p>0.60).

After adjusting for the same covariates, the cumulative weight-adjusted psychostimulant dose was not significantly associated with any of the skeletal measures among participants in the No-MPH or MPH-Cont groups (all p values >0.20).

Longitudinal Analyses

Psychostimulants and Change in Height between Study Entry and Follow-up

—One hundred fifty boys returned for at least one follow-up visit during which a bone scan was collected. Six who had developed hypothyroidism (n=3) or type 1 diabetes (n=1) or received an extensive course of corticosteroids (n=2) prior to the follow up visit were excluded. For those with multiple follow-up visits, the visit most distant from study entry was selected for the longitudinal analysis. The mean±SD interval between the two visits was 1.4±0.7 years during which time 68 participants continued to receive psychostimulants (Chronic-MPH group), 34 started psychostimulants anew (New-MPH), and 24 remained psychostimulant-naïve (No-MPH). Another 17 took psychostimulants intermittently and one, who had been on psychostimulants at study entry, discontinued them.

There was no significant difference in height Z-score change between study entry and the last visit across the Chronic-MPH, New-MPH, and No-MPH groups (p>0.70), after accounting for the time interval between the two visits (p>0.50).

Psychostimulants and Change in Skeletal Outcomes between Study Entry and Follow-up—

Valid pQCT data at the ultradistal radius were available for 84 boys. After adjusting for study entry trabecular vBMD (p>0.10), age (p>0.50), forearm length (p>0.30), and BMI Z-score (p>0.40), as well as change in forearm length and in BMI Z-score between study entry and follow-up (both p>0.30), the interval between the two visits (p>0.60), and whether the participants had remained on risperidone by follow-up or not (p>0.40), MPH treatment status (i.e., Chronic-MPH vs. New-MPH vs. No-MPH) was not associated with change in trabecular vBMD between study entry and follow-up (p>0.30). Similarly, using comparable regression models, there was no significant association between MPH treatment status and change in total vBMD (p>0.40) or in strength index (p>0.10). Only 22 participants had valid pQCT data at the 20% radius site both at study entry and follow-up, restricting statistical power. After adjusting for relevant variables, MPH treatment status was not associated with change between study entry and follow-up in any of the skeletal outcomes at this site (all p>0.50).

Eighty-one participants had two DXA scans at the lumbar spine. After adjusting for agesex-height-ethnicity-specific LS aBMD at study entry ($p<0.06$), height and BMI Z-score at study entry ($p<0.07$ and $p<0.06$, respectively), change in height and BMI Z-score between study entry and follow-up ($p>0.20$ and $p=0.01$, respectively), and whether participants had remained on risperidone or not ($\beta= -0.26$, $p<0.03$), there was no significant association between MPH treatment status and change in LS aBMD Z-score between study entry and follow-up ($p>0.20$). Similarly, after adjusting for the same relevant variables, no association was found with change in LS BMC Z-score ($p>0.30$), TBLH BMC Z-score ($p>0.50$), or TBLH aBMD Z-score ($p>0.10$).

Discussion

We found no significant impact on bone mass at the ultradistal radius or the lumbar spine. Preliminary analyses, involving a smaller sample, also failed to show an effect on overall bone mass or on cortical bone in the radius.

The impact of psychostimulants on longitudinal growth is well-established.[7] The effect is relatively modest and reversible with medication holidays or discontinuation.[7] We failed to find a significant difference in the change in height Z-score between boys in continuous treatment (i.e., MPH-Cont) and those who had never received psychostimulants or had not received them two years or more prior to study entry (i.e., No-MPH). Several reasons could explain this observation. First, although the difference between the two groups was not statistically significant, the MPH-Cont boys showed a reduction in height Z-score between treatment onset and study entry, and the No-MPH boys exhibited an increase (LS Means= −0.15 vs 0.11, respectively; Table II). The difference, however, did not reach statistical significance (Cohen's $d=0.38$, $p>0.20$) perhaps due to the relatively small sample size. In fact, the group difference in height Z-score we found is comparable with what has been reported.[7] Second, growth suppression may have been attenuated by the fact that 95% of our participants were taking risperidone, causing them to gain weight.[21] Further, because medication holidays might reverse growth deficit,[7] it is possible that partial treatment adherence, not fully captured by our review of medical and pharmacy records, could have also attenuated the delay in longitudinal growth. The fact that no additional growth delay was observed by the follow-up visit is consistent with the plateauing of this adverse event over time.[7]

Similarly, after taking into account relevant confounding variables, we failed to find any significant association between the continuous use of psychostimulants and skeletal outcomes whether at the lumbar spine, the radius, or overall (although TBLH data were available for only a subgroup of the participants). Both the lumbar spine and the ultradistal radius are rich in trabecular bone. This being more metabolically active than cortical bone, it is more susceptible to the potentially detrimental effects of medications or disease.[29] Thus, it is somewhat reassuring that, following several years of continuous treatment, psychostimulants did not seem to have a measurable skeletal impact. This is in contrast to findings in rats where 13 weeks of treatment reduced bone mass and increased bone fragility.[12] The discrepancy is perhaps due to an interaction effect between psychostimulant exposure, weight bearing, and skeletal site as the hindlimbs, but not the vertebrae, exhibited

these changes in the rats.[12] In four-legged rats, appendicular bones bear most of the weight, unlike in humans were both appendicular and axial bones do so. We did not measure bone mass in the lower extremities as we included trabecular bone-rich sites that are weight and non-weight bearing. Future preclinical studies should examine the skeletal effects of psychostimulants while minimizing the confounding effect of weight bearing (ie, tail suspension paradigms) and future clinical studies should examine the effects on the lower extremities. An alternative explanation for the failure to find reduced bone mass in our psychostimulant-treated males is that, as may have been the case with height, partial medication adherence allowed normal bone mass accrual. In fact, as reviewed earlier, treatment discontinuation was followed by relatively rapid skeletal recovery in rats.[12]

Elsewhere, using data from a sample that partially overlaps with this one, we report that SSRI use was associated with a significant, but static, detrimental effect on bone mass, and risperidone treatment appeared to increasingly hamper bone mass accrual over time.[18] Our results here are largely consistent with these earlier findings.

This study has several shortcomings. First, it is an observational study. Males who may have exhibited clinically significant growth delay could have been placed on intermittent psychostimulant treatment (i.e., medication holidays), given lower dosages, or taken off the medication to avoid this side effect. Consequently, any potential detrimental impact on bone mass accrual could have been also attenuated. Many of the participants had taken risperidone and SSRIs (95 and 46%, respectively; Table III). These medications affect bone metabolism,[18, 30] which could have masked an independent effect of psychostimulants. Thus, future studies should consider examining the skeletal effects of psychostimulants in the absence of polypharmacy. Further, future studies should also measure bone mass at the onset of psychostimulant treatment and include females and more racially/ethnically diverse participants. Finally, we examined whether psychostimulant treatment interacted with pubertal development to affect bone mass but found no significant interaction effect (data available upon request). Nonetheless, larger studies should explore the presence of a period of skeletal development that may be more sensitive to the effects of psychostimulants, such as during rapid bone accretion (typically in Tanner stages 4 and 5).

Acknowledgments

We thank the families and staff from the University of Iowa Clinical Research Unit, as well as the research team members.

Funded by Young Investigator Awards (2005 and 2007), Fraternal Order of Eagle Diabetes Research Center (pilot grant), and the National Institutes of Health (RR024979, R21MH080968, and K23MH085005). The content is solely the responsibility of the authors, and does not necessarily represent the official views of the funding agencies.

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J Pediatr. Author manuscript; available in PMC 2016 June 01.

Table 1

Description of Studies Contributing Data from Boys (n) to the Main Analysis.

Study	n	Age Range	Description	Follow-up	pQCT		DXA	
					49%	20%	LS	TBLH
Study 1: Longitudinal	139	7 to 17 yrs	Observational study in participants who had received risperidone for at least six months	94 had follow-up at 1.5±0.3 yrs	X	---	X	---
Study 2: Crosssectional	7	10 to 18 yrs	Observational study in participants who had received risperidone for at least one year	none	X	---	X	---
Study 3: Longitudinal	46	5 to 17yrs	Randomized placebo-controlled trial of calcium and vitamin D supplementation in participants who had received risperidone for at least one year and exhibited hyperprolactinemia	Mean follow up period: 1.4±1.1 yrs	X	X	---	X
Study 4: Longitudinal	16	5 to 16 yrs	Longitudinal observational study of largely antipsychotic-naïve participants: six initiated treatment with risperidone within the prior month.	Mean follow up period: 0.4±0.1 yrs	---	---	---	X

n is the number of males at study enrollment. Females were excluded from the analysis as explained in the Methods section. pQCT: Peripheral quantitative computed tomography. DXA: Dual-energy x-ray absorptiometry.

Table 2

Demographic and Clinical Characteristics of the Entire Sample (mean±sd, unless noted otherwise) and Split Based on MPH Treatment Status (mean±se, unless noted otherwise)

	Entire Sample n=194	**No-MPH n=40**	**MPH-Cont n=91**	**MPH-Intermit N=63**	**Statistic**	**p-value**
Age, yrs	11.7±2.8	12.9±0.4	12.1±0.3	10.4±0.3	F=11.93	**<0.0001**
Tanner Stage (%)						
I/II/III/IV/V	39/16/14/18/12	56/19/10/8/6	33/17/14/27/9	25/10/23/15/28	χ^2= 28.87	**0.0003**
Race/Ethnicity, n (%)					Fisher's Exact	>0.10
White	161 (84)	36 (90)	73 (81)	52 (84)		
African American	23 (12)	1 (3)	15 (17)	7 (11)		
Hispanic	5 (3)	2 (5)	1 (1)	2 (3)		
Other	3 (2)	1 (3)	1 (1)	1 (2)		
Height Z-score[¶]						
At Baseline (n=126)	0.28±1.02	0.57±0.18	0.21±0.14	0.17±0.16	F=1.63	>0.20
At Study Entry	0.19±0.96	0.70±0.15	0.06±0.10	0.05±0.12	F=7.60	**0.0007**
Change (n=126)	−0.05±0.65	0.11±0.12	−0.15±0.09	−0.05±0.10	F=1.52	>0.20
BMI Z-score[¶]	0.55±1.00	0.62±0.16	0.42±0.10	0.69±0.13	F=1.53	>0.20
Physical Activity	2.4±1.1	2.1±0.2	2.6±0.1	2.5±0.1	F=1.94	>0.10
Daily Calcium, mg	1011±376	1007±60	1011±42	1015±50	F=0.01	>0.90
Daily Vitamin D, IU	274±152	254±24	267±17	299±20	F=1.21	>0.30

MPH: psychostimulants.

[¶]Age-sex-specific height and body mass index (BMI) Z-scores generated based on the 2000 Centers for Disease Control and Prevention normative data. Baseline height measurements were collected within 90 days before or 15 days after the initiation of psychostimulants. For the No-MPH group, height measurements obtained at a date preceding study entry by an interval comparable to that in the other two MPH groups were selected (see Methods).

Significant results ($p<0.05$) are bolded and marginally significant results ($p<0.10$) are bolded and italicized.

Table 3

Psychiatric Characteristics of the Entire Sample (mean±sd, unless noted otherwise) and Split Based on MPH Treatment Status (mean±se, unless noted otherwise)

	Entire Sample n=194	**No-MPH n=40**	**MPH-Cont n=91**	**MPH-Intermit N=63**	**Statistic**	**p-value**
ADHD, n (%)	174 (90)	21 (53)	91 (100)	62 (98)	χ^2= 75.48	**<0.0001**
DBD, n (%)	173 (89)	31 (78)	87 (96)	55 (87)	χ^2= 9.92	**<0.008**
Depressive Disorder, n (%)	9 (5)	5 (13)	4 (4)	0	χ^2= 8.66	**<0.02**
Anxiety Disorder, n (%)	62 (32)	14 (35)	27 (30)	21 (33)	χ^2= 0.44	>0.80
PDD, n (%)	32 (16)	8 (20)	13 (14)	11 (17)	χ^2= 0.72	>0.60
Tic Disorder, n (%)	39 (20)	8 (20)	16 (18)	15 (24)	χ^2= 0.90	>0.60
Pharmacotherapy						
MPH Tx Duration, yrs¶	4.1±2.8	0.0±0.5	5.3±0.2	3.4±0.2	F=77.63	**<0.0001**
SSRI, n (%)	89 (46)	23 (58)	42 (46)	24 (38)	χ^2= 3.72	>0.10
SSRI Tx Duration, yrs¶	2.0±1.8	1.8±0.3	2.1±0.2	2.0±0.3	F=0.47	>0.60
Risperidone, n (%)	185 (95)	35 (88)	89 (98)	61 (97)	Fisher's Exact	**<0.05**
Risperidone Tx Duration, yrs¶	2.8±2.0	2.3±0.3	3.0±0.2	2.8±0.2	F=1.58	>0.20

MPH: psychostimulants, ADHD: attention deficit hyperactivity disorder, DBD: disruptive behavior disorder, PDD: pervasive developmental disorder, SSRI: selective serotonin reuptake inhibitors.

¶: Adjusted for age.

Significant results ($p<0.05$) are bolded and marginally significant results ($p<0.10$) are bolded and italicized.

Table 4

Skeletal Measures (Unadjusted) for the Entire Sample (mean±sd, unless noted otherwise) and Split Based on MPH Treatment Status (mean±se, unless noted otherwise)

	Entire Sample	No-MPH	MPH-Cont	MPH-Intermit	Statistic	p-value
Dual-Energy X-ray Absorptiometry-Based Measures						
LS BMC Z-score, n=140	0.11±0.89	−0.25±0.16	0.10±0.11	0.38±0.13	F=4.61	**<0.02**
LS aBMD Z-score, n=140	0.24±0.98	−0.01±0.18	0.16±0.12	0.53±0.15	F=3.18	**<0.05**
Low LS aBMD Z-score, n (%), n=140¶	2 (1)	1 (3)	1 (1)	0	Fisher's Exact	>0.40
TBLH BMC Z-score, n=54	0.09±0.77	−0.27±0.23	0.07±0.15	0.34±0.17	F=2.28	>0.10
TBLH aBMD Z-score, n=54	0.25±0.77	0.06±0.23	0.27±0.16	0.33±0.18	F=0.43	>0.60
Low TBLH aBMD	0	0	0	0	---	---
Z-score, n (%), n=54¶						
Peripheral Quantitative Computed Tomography-Based Measures						
Trabecular vBMD, mg/cm^3, n=150	201±39	200±7	201±5	202±6	F=0.04	>0.90
Total vBMD, mg/cm^3, n=150	322±54	322±10	320±6	326±8	F=0.18	>0.80
Strength Index, mg^2/mm^4, n=150	22.9±11.1	26.4±2.0	23.0±1.3	20.6±1.6	F=2.49	***<0.09***
Cortical vBMD, mg/cm^3, n=35	1060±31	1064±13	1058±8	1062±9	F=0.11	>0.80
Cortical Thickness, mm, n=35	2.3±0.4	2.6±0.2	2.1±0.1	2.2±0.1	F=3.17	***<0.06***
Endosteal Circumference, mm, n=35	17.4±3.9	18.4±1.6	16.9±1.0	17.4±1.1	F=0.31	>0.70
Periosteal Circumference, mm, n=35	31.5±5.1	34.8±2.1	30.4±1.2	31.4±1.5	F=1.65	>0.20
Polar Section Modulus, mm^3, n=35	142±70	192±28	128.7±16	137±19	F=2.02	>0.10

MPH: psychostimulants, LS: lumbar spine, BMC: bone mineral content, aBMD: areal bone mineral density, TBLH: total body less head, vBMD: volumetric bone mineral density. Age-sex-height-race-specific Z-scores for LS and TBLH BMC and aBMD were generated following the Bone Mineral Density in Childhood Study [30].

¶Defined as a Z-score ≤ −2.0.

Significant results ($p<0.05$) are bolded and marginally significant results ($p<0.10$) are bolded and italicized.