Published in final edited form as:

J Clin Psychiatry. 2015 May ; 76(5): 607–613. doi:10.4088/JCP.14m09195.

Longitudinal Skeletal Effects of Selective Serotonin Reuptake Inhibitors and Risperidone in Children and Adolescents

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Abstract

Objectives: In a previous cross-sectional study, we found lower bone mass during treatment with selective serotonin reuptake inhibitors (SSRIs) and risperidone in youths. Here, we evaluate the skeletal effects of these psychotropics at follow-up.

Methods: Between 04/2005 and 07/2011, medically healthy 7 to 17 year-old males treated with risperidone for six months or more were enrolled and returned for follow-up, 1.5 years later. Treatment history was extracted from the medical and pharmacy records. Anthropometric, laboratory, and bone mass measurements were obtained. Multivariable linear regression analyses compared participants who remained on risperidone at follow-up to those who had discontinued SGA treatment as well as SSRI-treated versus SSRI-unexposed participants.

Results: The sample consisted of 94 boys with a mean age of 11.8 ± 2.7 years at study entry. The majority had an externalizing disorder and had received risperidone and SSRIs for 2.5 ± 1.7 years and 1.6 ± 1.9 years, respectively, at study entry. By follow-up, 26% ($n=24$) had discontinued risperidone. Compared to discontinuing risperidone, continuing it was associated with a decline in age-sex-height-race-specific areal bone mineral density (BMD) Z-score at the lumbar spine ($p<0.04$) and failure to increase radius trabecular volumetric BMD ($p<0.03$), after accounting for significant covariates. In addition, receiving an SSRI was associated with reduced lumbar spine

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Disclosures: None.

Previous Presentations: Aspects of the findings have been presented orally at the annual meeting of the American Society of Clinical Psychopharmacology, Hollywood, FL, June 16–19, 2014.

areal BMD Z-score and radius trabecular volumetric BMD at both study entry ($p < 0.02$ and $p < 0.03$, respectively) and follow-up ($p < 0.06$ and $p < 0.03$, respectively) but without further decline observed between the two visits.

Conclusions: Chronic SSRI treatment in children and adolescents is associated with reduced, albeit stable, bone mass for age, while chronic risperidone treatment is associated with failure to accrue bone mass.

Introduction:

Selective serotonin reuptake inhibitors (SSRIs) and second-generation antipsychotics (SGAs) are widely prescribed, often long-term. Therefore, in order to optimize patient care, attention is increasingly paid to the safety of extended use of psychotropics, particularly regarding cardiovascular risk^{1,2,3,4,5}.

One potential, but largely neglected, side effect is the risk for loss of bone mass^{6,7}, leading to osteopenia/osteoporosis. Osteoporosis is estimated to affect around 3.5% of the U.S. population, with billions of dollars in annual costs related to fractures and disability⁸. Most antipsychotics cause hyperprolactinemia, which persists in a significant proportion of patients during chronic use^{9,10} and has been linked to osteopenia in patients with prolactin-secreting pituitary adenomas¹¹. However, additional processes, perhaps more directly related to the drugs' pharmacodynamics, could also interfere with skeletal metabolism during SGA treatment^{12,13}. Similarly, SSRIs have been implicated in loss of bone mass and increased fracture risk^{6,14}. This can occur by disrupting functional serotonin signaling in bone cells peripherally^{14,15} and modulating sympathetic nervous system activity centrally, through hypothalamic serotonin 5HT_{2C} receptors^{16,17}.

Previously, we examined skeletal health in a group of boys in extended risperidone treatment and found an inverse association between prolactin serum concentration and trabecular volumetric bone mineral density (vBMD) at the ultradistal radius, measured using peripheral quantitative computed tomography (pQCT)¹⁸. Furthermore, SSRI use was associated with lower vBMD at the ultradistal radius as well as lower age-sex-specific areal bone mineral density (aBMD) Z-score at the lumbar spine, measured using dual-energy x-ray absorptiometry (DXA)¹⁸. DXA is the most widely-used method to assess bone mass, particularly in clinical settings, but pQCT has the additional advantages of generating a true estimate of BMD and isolating trabecular from cortical bone^{19,20}. Trabecular bone is more metabolically active and, consequently, more susceptible to the effect of various metabolic factors (e.g., hormonal, toxic, pharmacological, etc)^{19,20}. Here, we describe the outcome of the bone measures in participants who returned for follow-up 18 months later. Specifically, we examined the skeletal effects of SSRI treatment and continuing vs. discontinuing risperidone, between study entry and follow-up. We anticipated that the use of these medications would be associated with lower bone mass.

Methods

Participants:

As previously described¹⁸, 7 to 17 year-old patients treated with risperidone for six months or more were enrolled between 04/2005 and 10/2009, irrespective of the indication for risperidone. Concurrent treatment at study entry with additional psychotropics, but not with other antipsychotics, was allowed. In fact, 54% of the participants were receiving SSRIs concurrently^{18,21}. Participants with chronic medical conditions were excluded as were pregnant females and those receiving hormonal contraception. Eighteen months after study entry, the participants returned for a follow-up between 07/2007 and 07/2011, when study entry assessments were repeated. This study was 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:

All medication use was recorded from the medical and pharmacy records^{18,22}. During both research visits, anthropometric measurements were obtained following a standard protocol and pubertal stage was recorded^{18,22}.

A best-estimate diagnosis, following the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)²³, 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 NIMH Diagnostic Interview Schedule for Children (DISC-IV)²⁴, and the Child Behavior Checklist²⁵.

Daily calcium and vitamin D intake during the week prior to enrollment was estimated using the 2004 Block Kids Food Frequency Questionnaire²⁶ and physical activity was assessed by asking the parent to compare the child's usual level of physical activity to their peers', using a 5-point Likert scale²⁷.

A blood sample was obtained to measure prolactin, testosterone, two markers of bone formation (osteocalcin and bone-specific alkaline phosphatase), a marker of bone resorption (collagen type I C-telopeptide [CTX]), and trough (i.e., before morning dose) serum risperidone and 9-hydroxyrisperidone concentrations (referred to, henceforth, as risperidone concentration). Due to funding considerations, the bone turnover markers were added at a later point in the study, making them available primarily at follow-up. Only measurements from samples obtained in the morning, from participants who were fasting, were included in the analyses.

Following the same protocol described previously¹⁸, vBMD at the nondominant ultradistal radius was measured with pQCT using a Stratec XCT-2000 scanner, software version 6.0 (Stratec, Inc., Pforzheim, Germany). Trabecular vBMD was measured as the mean density of the 90% central area of the bone's cross-section, while total vBMD encompassed the entire bone mass, including the thin cortical shell. Compromised pQCT scans, e.g., by movement, were rejected. A Hologic QDR DELPHI-4500A unit (Hologic, Inc, Bedford, MA)

was used to estimate bone mineral content (BMC) and aBMD in the lumbar spine (L1-L4, LS). Quality-control and calibration of the equipment were performed daily.

Data Analysis:

Because the number of female participants who returned for follow-up was small ($n=7$) and because BMD is under a strong sex effect, we restricted the analyses to boys similar¹⁸. Three boys were excluded due to the onset of hypothyroidism ($n=2$) or type 1 diabetes by follow-up. Further, risperidone-treated participants whose risperidone serum concentration was undetectable at study entry or at follow-up were excluded due to suspected treatment non-adherence. Body mass index (BMI) was computed as weight/height² (kg/m²) and height and BMI age-sex-specific Z-scores were generated based on the 2000 Centers for Disease Control and Prevention normative data²⁸. Age-sex-height-race-specific Z-scores for LS BMC and aBMD were generated following the Bone Mineral Density in Childhood Study²⁹. Using the laboratory-determined normal ranges, hyperprolactinemia was defined as a prolactin concentration >15.2 ng/mL.

By design, all participants were taking risperidone at study entry. At follow-up, 73% were still taking it, with 18% discontinuing all SGA treatment and 9% switching to another SGA²². Participants who returned for follow-up were less likely to have had a history of child maltreatment (6% vs. 16%, $p=0.05$) but more likely to be males (93% vs. 79%, $p<0.02$), suffer from an autism spectrum disorder (18% vs. 2%, $p<0.02$), and to have been receiving an antidepressant (63% vs. 40%, $p<0.02$)²².

Because no differences in bone measurements were observed between boys discontinuing all SGA treatment and those switching to another SGA, they were combined (Risp Discont group) and compared to those who continued risperidone (Risp Cont group) using Student t-test for continuous variables and chi square test for categorical ones. To examine the skeletal effects of SSRIs, two groups were identified: 1) those who were not receiving SSRIs either at study entry or at follow-up (No SSRI, $n=37$) and 2) those who were taking SSRIs at both visits (SSRI group, $n=44$). The remainder of the participants were too few, including those who took SSRIs at study entry but not at follow-up ($n=8$) and vice versa ($n=5$).

Multivariable linear regression analysis examined the association between continuing vs. discontinuing risperidone and skeletal outcomes at study entry and follow-up, adjusting for relevant covariates as informed by our previous work¹⁸. Similar analyses examined the effect of SSRIs on skeletal health. Cohen's d effect size was generated by dividing the difference in group-specific least squares means by the residual of the relevant multivariable linear regression model. 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

Participants

Ninety-four boys, 70 (74%) of whom were in the Risp Cont group, returned for follow-up and met the criteria for inclusion in this analysis (Table 1). By far, the most common

diagnoses were attention deficit hyperactivity disorder (n=83, 88%) and disruptive behavior disorders (n=82, 87%), with depressive disorder afflicting only a minority (n=4, 4%). Risperidone was prescribed primarily (78%) for irritability and aggression.

SSRIs and Skeletal Outcomes

We first examined the skeletal outcomes in those participants who were consistently either on or off SSRIs both at study entry and follow-up (Table 2 and Figure 1). After adjusting for relevant confounders, treatment with SSRIs was associated with reduced bone mass at the lumbar spine and ultradistal radius at both study entry and follow up. These associations were not appreciably altered with further adjustment for the anxious/depressed, withdrawn/depressed, or internalizing problems t scores of the Child Behavior Checklist obtained at follow-up, none of which significantly contributed to the model (all p values>0.90). However, the change between both research visits was not significant.

After adjusting for stage of genitalia development, height Z-score, and the rate of change in height between study entry and follow-up, SSRI treatment was marginally associated with lower osteocalcin concentration at follow-up ($\beta = -23.3$, 95% confidence interval [CI]: -47.3 to 0.7 , Cohen's $d=0.54$, $p<0.06$). However, there was no significant association with CTX ($p>0.10$) or bone-specific alkaline phosphatase ($p>0.90$).

Risperidone and Skeletal Outcomes

Next, we examined the association between continuing vs. discontinuing risperidone by follow-up and the skeletal outcomes (Table 2 and Figure 1). There was no significant difference in any of the skeletal measures at study entry between the two risperidone treatment status groups (i.e., Risp Cont vs. Risp Discont). This is expected as all participants were on risperidone at that point. There were also no significant differences at follow up. However, after including study entry LS aBMD Z-score ($p<0.0001$) in the model, in addition to age, height Z-score, and BMI Z-score, the Risp Discont group had a marginally significantly higher LS aBMD Z-score at follow-up ($\beta=0.17$, 95% CI: -0.03 to 0.37 , Cohen's $d=0.42$, $p<0.10$). This is consistent with the significantly different change in LS aBMD Z-score between study entry and follow up between the two groups (Table 2 and Figure 1). In fact, LS aBMD Z-score significantly declined ($\beta = -0.13$, 95% CI: -0.23 to -0.03 , $p=0.01$) between study entry and follow-up in the Risp Cont group but did not change in the Risp Discont group ($p>0.30$). This association was attenuated when additional adjustment was made for anxious/depressed (Cohen's $d=0.45$, $p<0.09$), withdrawn/depressed (Cohen's $d=0.49$, $p<0.06$), or internalizing problems t scores (Cohen's $d=0.45$, $p<0.09$) of the Child Behavior Checklist obtained at follow-up, none of which significantly contributed to the model (all p values>0.50). Further, accounting for SSRI treatment status did not alter the findings.

Similarly, after adjusting for study entry trabecular vBMD ($p<0.0001$), in addition to age, BMI Z-score, and physical activity, the Risp Cont group had a significantly lower trabecular vBMD ($\beta = -19.7$, 95% CI: -33.8 to -5.6 , Cohen's $d=1.03$, $p<0.008$). In fact, trabecular vBMD was unchanged between study entry and follow-up in the Risp Cont group ($p>0.80$) but increased in the Risp Discont group ($p<0.002$). This association was not appreciably

altered by adjusting for the anxious/depressed, withdrawn/depressed, or internalizing problems t scores obtained at follow-up, none of which significantly contributed to the model (all p values>0.20). Further, taking SSRI treatment status into account did not alter the findings. A similar, albeit attenuated, pattern of findings emerged when ultradistal radius total vBMD was examined.

No significant associations were found between the risperidone treatment status groups and the bone turnover markers at follow-up, after adjusting for stage of genitalia development, height Z-score, and the rate of change in height between study entry and follow-up (all p values>0.50).

Prolactin and Skeletal Outcomes

None of the Risp Discont participants exhibited hyperprolactinemia at follow-up while 48% of the Risp Cont group did. After adjusting for LS aBMD Z-score at study entry, height and BMI Z-scores at follow-up, and risperidone treatment status at follow-up, prolactin concentration at follow-up was positively associated with LS aBMD Z-score ($\beta=0.009$, $p<0.02$). Of note, the effect of risperidone treatment status that was marginally significant in the more reduced model described earlier, became significant when prolactin concentration was added to the model ($p<0.02$). In contrast, prolactin concentration at follow-up was not significantly associated with radius trabecular vBMD at follow-up, after accounting for trabecular vBMD at study entry and age, BMI Z-score, physical activity, and risperidone treatment status at follow-up. Adjusting for SSRI exposure does not alter the results.

Discussion:

To our knowledge, this is the first study to prospectively examine the skeletal effects of commonly-used psychotropics in youths. Using DXA and pQCT, focused on trabecular bone sites, we found that risperidone and SSRIs are both associated with reduced bone mass but with differing trajectories. In fact, while SSRIs were associated with reduced bone mass at both study entry and follow-up without an apparent worsening over time, risperidone was associated with increasingly significant failure to accrue bone mass, as would otherwise be expected for the age of the participants.

Attention is increasingly focused on promoting preventive medicine. At the same time, it has become widely recognized that many chronic diseases have their onset in childhood and adolescence. This would certainly apply to osteopenia and osteoporosis, particularly as age-related bone loss is directly related to peak BMD achieved by young adulthood⁸. The concern is that even a moderate reduction in peak BMD could significantly increase the incidence of osteoporotic fractures^{8,30,31}. Therefore, the reduction in BMD we observed could have significant long-term health implications as continued treatment, beyond a certain age³², may prevent psychotropic-treated youths from reaching their optimal peak bone mass. This is especially troublesome as these medications are widely used, often for extended periods, leaving those who care for psychiatrically-ill youths in a difficult position, having to choose between treating an ongoing distressing and impairing condition or placing the child at risk for long-term sequelae.

Recently, using data from this same sample, we reported that those who continued on risperidone maintained their moderate increase in BMI Z-score ($\sim 0.32 \pm 1.11$) compared to pre-risperidone values while those who discontinued all SGAs returned to their pre-treatment BMI Z-score, despite having taken risperidone for years²². The absence of pre-risperidone skeletal measurements and of an unmedicated control group makes it impossible to determine whether the Risp Discont group saw its skeletal outcomes return to normal after discontinuing risperidone. It is hoped that full recovery is possible in the absence of clinical relapse requiring reinstitution of psychotropic treatment³². Notably, discontinuing risperidone not only removes the detrimental direct effect of the drug on the skeleton but also that of associated weight gain.

Elsewhere, we have reviewed the complex mechanisms potentially involved in the skeletal effects of risperidone¹². Elegant research has also shed light on the skeletal effects of SSRIs¹⁴. Our findings suggest that these medications may impact bone mass accrual differently, following long-term use. In fact, continued risperidone treatment led to failure to increase trabecular vBMD at the radius. At the lumbar spine, this process translated into a decline in aBMD Z-score between study entry and follow-up. Of note, trabecular vBMD measurements are raw values while aBMD measurements are adjusted for age and height (as well as for sex and race). This explains why we observed an increase in the former in those who discontinued risperidone but a decrease in the latter among those who continued risperidone. In contrast, SSRI use was consistently associated with lower bone mass at both visits but this deficit did not worsen over time. The study, however, did not examine the mechanisms that account for our observations. Preclinical data suggest that psychotropics may interfere with both bone formation and resorption^{12,14,16}. We found a trend for osteocalcin to be lower during SSRI treatment, consistent with what has been reported¹⁴. However, no associations were found between risperidone use and bone turnover markers.

In our previous work, using data collected at study entry, we found prolactin to be inversely associated with trabecular vBMD¹⁸. Bone loss associated with hyperprolactinemia is thought to be mediated primarily by hypogonadism¹¹. However, the discovery of functional prolactin receptors on bone cells suggests that a direct effect is likely^{12,33}. Surprisingly, after accounting for risperidone treatment status, we found prolactin concentration to be positively associated with LS aBMD Z-score but not with trabecular vBMD. This may be due to the complex role prolactin plays in controlling bone metabolism during development^{33,34,35}.

Elsewhere, we describe an inverse association between major depressive disorder, but not generalized anxiety disorder, and low bone mass in older adolescents³⁶. This is consistent with published data linking the two³⁷, although ours is the first study to examine this question in nearly psychotropic-naïve patients. In the present study, adjusting for depressive and anxiety symptom severity, as captured by the child behavior checklist, did not alter the overall pattern of the findings, exhibiting limited to no impact. Further, the rate of major depressive disorder in our participants was low. Nonetheless, we cannot rule out the possibility that the association we found between SSRI use and low bone mass reflects rather an underlying association between depression and skeletal health.

Although this study presents novel findings, it suffers from several limitations. First, the participants were enrolled having already initiated treatment with psychotropics. Therefore, pre-treatment measurements are lacking. Further, while this study is focused on risperidone because of its propensity to cause hyperprolactinemia, other antipsychotics have overlapping mechanisms of action³⁸. Therefore, it is unclear to what extent our findings extend to other psychotropics. We combined in a single group those who discontinued all SGA treatment by follow-up with those who switched to other SGAs as no differences in the skeletal outcomes were detected between them. Nonetheless, each SGA was represented by one to three patients, making it impossible to draw reliable conclusions about their individual skeletal effects. We measured bone mass at sites rich in trabecular bone, but examining the skeletal effects of psychotropics on whole body bone mineral content as well as on cortical bone, specifically, can also be informative. Finally, examining the skeletal effects of psychotropics in females and in a more racially and ethnically diverse population is necessary, particularly as women are at the highest risk for osteoporosis and psychotropics are also widely used in individuals from diverse backgrounds.

In sum, the chronic use of risperidone in youths is associated with a progressive decline in trabecular bone mass while the use of SSRIs is associated with significantly lower, but static, bone mass. Future studies should examine these findings in more representative individuals and identify interventions to reverse or attenuate the skeletal effects of psychotropics as their use is necessary in order to alleviate the distress and impairment associated with psychopathology.

Acknowledgments:

The authors would like to thank the participants and their families, the research team, and staff of the Clinical Research Center at the University of Iowa.

Funding: This study was funded by 2005 and 2007 Young Investigator Awards and by the National Institutes of Health (RR024979, R21MH080968, R21MH080968-S1, and K23MH085005). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies. The funding agencies played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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Clinical Points:

1. Following extended treatment, risperidone was associated with progressive bone loss while SSRIs were associated with reduced, but stable, bone mass.
2. While the long-term impact on fracture risk is presently unknown, clinicians should continue to monitor the long-term safety of psychotropics, particularly in youths, and promote healthy lifestyle habits, including nutrition and physical activity.

Figure 1: Least squares means for standardized radius trabecular volumetric bone mineral density (vBMD) Z-scores and lumbar spine age-sex-height-race-specific areal bone mineral density (aBMD) Z-scores at study entry (T1), follow up (T2), and of their change between study entry and follow up, across those who were taking a selective serotonin reuptake inhibitor (SSRI) at study entry and follow up vs. at neither visits (panels a and c) and across those who continued vs. discontinued risperidone by follow up (panels b and d).

‡ adjusted for age, physical activity, and age-sex-specific BMI Z-score at T1 and T2, respectively.

† adjusted for vBMD and BMI Z-scores at T1 as well as change in BMI Z-score and time interval between T1 and T2.

‡ adjusted for vBMD and BMI Z-scores at T1, age, and change in age-sex-specific BMI Z-score and time interval between T1 and T2.

§ adjusted for age and age-sex-specific height Z-score and BMI Z-score at T1 and T2, respectively.

¶ adjusted for aBMD, height, and BMI Z-scores at T1 as well as change in height and BMI Z-scores between T1 and T2.

* adjusted for aBMD and BMI Z-scores at T1 and change in age-sex-specific BMI Z-score and in daily calcium intake between T1 and T2.

Table 1:

Demographic, Anthropometric, and Laboratory Characteristics of All the Participants, and Divided by Whether Risperidone was Continued vs. Discontinued by Follow-up. [mean±sd unless noted otherwise]

	Total Sample N=94	Risp Cont N=70	Risp Discont N=24	p-value [†]
Race/Ethnicity, n (%)				>0.70
White	78 (83)	57 (81)	21 (88)	
African American	11 (12)	9 (13)	2 (8)	
Other	3 (3)	2 (3)	1 (4)	
Hispanic	2 (2)	2 (3)	0	
Age, years				
At Study Entry	11.8±2.7	11.9±2.7	11.4±2.4	>0.40
At Follow-up	13.3±2.7	13.4±2.8	13.0±2.4	>0.50
Tanner Stage, % I/II/III/IV/V				
At Study Entry	33/20/19/23/4	35/17/19/23/6	29/29/21/21/0	>0.50
At Follow-up	15/21/15/18/30	15/21/19/13/32	17/21/4/33/25	>0.10
Body Mass Index Z-score				
At Study Entry	0.51±1.08	0.39±1.13	0.86±0.85	<0.07
At Follow-up	0.44±1.10	0.37±1.11	0.66±1.08	>0.20
Risperidone Treatment Duration, years				
At Study Entry	2.48±1.66	2.66±1.69	1.96±1.47	<0.08
At Follow-up	3.66±1.83	4.07±1.73	2.47±1.58	<0.0001
SSRI Treatment Group, n (%) [§]				>0.20
SSRI Group	44 (47)	31 (44)	13 (54)	
No SSRI Group	37 (39)	31 (44)	6 (25)	
Inconsistent SSRI Group	13 (14)	8 (11)	5 (21)	
SSRI Treatment Duration, years				
At Study Entry	1.63±1.89	1.65±2.03	1.57±1.46	>0.80
At Follow-up	2.39±2.37	2.34±2.51	2.53±1.92	>0.70

	Total Sample N=94	Risp Cont N=70	Risp Discont N=24	p-value [†]
Calcium Intake, mg/d				
At Study Entry	1059.8±360.7	1097.5±357.0	951.7±356.7	<0.09
At Follow-up	1010.1±389.9	1024.0±397.3	969.9±373.2	>0.50
Vitamin D Intake, IU/d				
At Study Entry	319.4±164.3	332.0±166.4	283.0±156.0	>0.20
At Follow-up	296.4±187.0	316.2±268.4	239.5±181.7	<0.05
Prolactin, ng/mL				
At Study Entry	21.8±14.2	20.7±13.4	24.9±16.2	>0.20
At Follow-up	14.2±12.8	17.4±13.5	5.5±3.4	<0.0001
Testosterone, ng/mL				
At Study Entry	180.2±188.8	174.7±192.9	195.4±180.4	>0.60
At Follow-up	298.9±219.0	295.3±217.0	307.9±228.6	>0.60
Skeletal Variables [‡]				
LS BMC Z-score				
At Study Entry	0.03±0.92	0.06±0.97	-0.05±0.79	>0.60
At Follow-up	-0.03±0.90	-0.01±0.96	-0.10±0.71	>0.60
LS aBMD Z-score				
At Study Entry	0.22±0.99	0.23±1.01	0.17±0.92	>0.80
At Follow-up	0.15±1.00	0.12±1.01	0.25±0.98	>0.50
Radius Trabecular vBMD, mg/cm ³				
At Study Entry	214.5±40.4	215.8±40.1	210.5±42.5	>0.60
At Follow-up	218.5±42.7	217.0±42.6	224.1±44.3	>0.50
Radius Total vBMD, mg/cm ³				
At Study Entry	327.9±55.3	330.1±54.6	320.6±58.9	>0.50
At Follow-up	335.5±54.4	333.4±51.7	343.1±65.1	>0.50
Follow-up Osteocalcin, ng/mL	78.9±53.2	75.6±50.7	88.3±59.8	>0.30

	Total Sample N=94	Risp Cont N=70	Risp Discont N=24	p-value [†]
Follow-up Collagen type I C-telopeptide, ng/mL	2.62±0.91	2.57±0.93	2.77±0.85	>0.30
Follow-up Bone-specific Alkaline Phosphatase, U/L	161.0±64.7	160.7±68.5	161.7±55.9	>0.90

[†]Significant findings are bolded and findings that are marginally significant are bolded and italicized.

[§]SSRI: selective serotonin reuptake inhibitors. Three groups were generated based on whether participants were taking SSRIs at study entry and follow-up (SSRI Group), at neither visits (No SSRI Group), or at only one of the two visits (Inconsistent SSRI Group).

[¶]LS: lumbar spine. BMC: bone mineral content. aBMD: areal bone mineral density. vBMD: volumetric bone mineral density. Age-sex-height-race-specific Z-scores were generated using published normative data (29). vBMD data are available for 69 participants at study entry and 62 at follow-up, after excluding compromised scans.

Table 2:

Results of multivariable linear regression analyses examining the skeletal impact of SSRI treatment and of continuing vs. discontinuing risperidone by follow up.

	SSRI Treatment Status		Risperidone Treatment Status	
	β estimate (95% Confidence Interval)	Cohen's d	β estimate (95% Confidence Interval)	Cohen's d
Dual-Energy X-ray Absorptiometry- or DXA-Based Measures [¶]				
LS aBMD Z-score				
At Study Entry	-0.48 (-0.88 to -0.08)	0.44	0.13 (-0.30 to 0.56)	0.15
At Follow up	-0.38 (-0.78 to 0.01)	0.44	0.15 (-0.33 to 0.45)	0.17
Change [‡]	0.08 (-0.11 to 0.26)	0.21	-0.20 (-0.40 to -0.00)	0.52
LS BMC Z-score				
At Study Entry	-0.35 (-0.74 to 0.03)	0.42	0.13 (-0.29 to 0.54)	0.15
At Follow up	-0.40 (-0.75 to -0.04)	0.51	0.06 (-0.33 to 0.45)	0.07
Change [‡]	-0.08 (-0.26 to 0.09)	0.22	-0.04 (-0.22 to 0.14)	0.12
Peripheral Quantitative Computed Tomography- or pQCT-Based Measures [§]				
Trabecular vBMD				
At Study Entry	-22.9 (-42.9 to -2.91)	0.64	6.0 (-14.8 to 26.8)	0.17
At Follow up	-28.6 (-53.2 to -3.9)	0.68	-5.4 (-31.8 to 21.1)	0.13
Change [‡]	-4.4 (-19.2 to 10.4)	0.22	-21.3 (-34.9 to -7.7)	1.18
Total vBMD				
At Study Entry	-26.1 (-55.9 to 3.7)	0.49	0.6 (-30.8 to 32.1)	0.01
At Follow up	-29.0 (-57.6 to -0.4)	0.60	-9.2 (-40.8 to 22.5)	0.18
Change [‡]	-13.6 (-34.3 to 7.2)	0.47	14.9 (-36.5 to 6.7)	0.51

[¶]DXA-based measurements were converted into age-sex-height-race-specific Z-scores. The analyses were adjusted for age and age-sex-specific height and body mass index (BMI) Z-scores. In addition, the "Change" analyses were also adjusted for the corresponding skeletal measurement at study entry as well as for change in height and BMI Z-scores between study entry and follow up.

[‡]Refers to change in the respective measurements between study entry and follow up.

[§]The analyses were adjusted for age, physical activity, and BMI Z-score. In addition, the "Change" analyses were also adjusted for the corresponding skeletal measurement at study entry as well as for time interval between study entry and follow up.

Significant results ($p < .05$) are bolded and results with a suggestion of significance ($p < .10$) are bolded and italicized.

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