Association of Depressive Symptoms and Anxiety With Bone Mass and Density in Ever-Smoking and Never-Smoking Adolescent Girls

Lorah D. Dorn, PhD; Elizabeth J. Susman, PhD; Stephanie Pabst, MEd; Bin Huang, PhD; Heidi Kalkwarf, PhD; Susannah Grimes, MSN

Objectives: To examine (1) the association of depressive and anxiety symptoms with bone mass and density in adolescent girls and (2) to examine this association in subgroups of those who have ever or never smoked.

Design: Prospective study using baseline reports.

Setting: Urban teenage health center and the community.

Participants: Two hundred seven girls (aged 11, 13, 15, and 17 years).

Outcome Measures: Bone mineral density (BMD) and content (BMC) of the hip, spine, and total body determined by dual-energy x-ray absorptiometry. Independent variables included self-report depressive symptoms, anxiety, and smoking history.

Results: Higher depressive symptoms were associated with lower total body BMC and BMD but not hip or spine BMC and BMD. Only in white adolescents was higher state anxiety associated with lower total body BMC and hip BMC and BMD. Ever-smokers were not significantly different than never-smokers in age-adjusted BMC or BMD, but they had higher depressive and anxiety symptoms. Although no significant depression or anxiety by smoking group interactions were found, subgroup analyses suggest that in ever-smokers, higher trait anxiety was related to lower total body BMC.

Conclusions: This is the first study to report that higher depressive and anxiety symptoms are associated with lower total body BMC during adolescence in girls. Knowing that this association is present at a young age is worrisome, as peak bone mass is attained in adolescence. Findings may aid in identifying girls who are at risk for low bone mass and developing intervention/prevention strategies during adolescence. Importantly, mechanisms that explain these associations and the effect of smoking on bone health need longitudinal examination.

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OSTEOPOROSIS IS A MAJOR public health problem that is experienced by more than 10 million adults.1 Osteoporosis increases risk for fractures and concomitant morbidity and mortality primarily in the elderly. Many risk factors for osteoporosis have been identified,1 though evidence for some is inconsistent.2 In part, the risk for osteoporosis is dependent on peak bone mass attained during adolescence and young adulthood.3 Maximizing accrual of bone minerals during growth may offset loss that occurs in later decades. More than 40% of bone mass is accrued during adolescence,4 primarily during the 2 years surrounding menarche. As much bone accumulates in these 2 years as is lost in the last 4 decades of life.5,6 Thus, it follows that adolescence is a critical period for facilitating optimum bone mass and density.

A strong association exists between adult depression and osteoporosis, or lower bone mineral density (BMD).7,15 There was a negative association between depression and BMD in young adult men (aged, 20-39 years), but it was nonsignificant in women.15 To our knowledge, there are no studies that examine depression, anxiety, and bone mass and density in healthy adolescents, though 1 study in girls with anorexia nervosa reports a negative effect of depression on bone.17 Lack of studies in healthy adolescents is of particular concern, as depression increases in girls during adolescence and anxiety is more common in females than males.18 Anxiety also often precedes depression.20,21 Furthermore, smoking and depression are associated in adolescence,22 and smoking is a risk factor for facilitating optimum bone mass and density.
factor for osteoporosis in adulthood. Thus, examining depression, anxiety, and smoking and their association with bone health in adolescents is warranted.

Our study examines the association of depressive symptoms and anxiety with bone mass and density in adolescent girls. Our secondary objective was to determine if this association varied in those who have ever smoked vs those who have never smoked. Smoking was thought to be a modifier of the association between depressive symptoms (or anxiety) and bone. Although smoking was not considered a mechanism for influencing bone in these cross-sectional analyses, age of initiation was included as a proxy for exposure.

METHODS

DESIGN AND SAMPLE

The study represents baseline analyses from an observational prospective study. Girls (n=207) were enrolled at ages 11, 13, 15, or 17 years and were divided into 5 defined levels of smoking experience from “not even a puff” to daily smoking. The goal was to enroll a sample in which age and smoking category were proportional to national figures on smoking.

Participants were recruited from an urban teenage health center and the surrounding community. A questionnaire determined eligibility. Exclusion criteria included (1) pregnancy or breastfeeding within the past 6 months, (2) primary amenorrhea (age, >16 years), (3) secondary amenorrhea (<6 cycles per year), (4) a body mass index (calculated as weight in kilograms divided by height in meters squared) of less than the 5th percentile or weight greater than 136 kilograms, (5) taking medication or having an illness that influences bone health, and (6) having psychological disabilities that impair comprehension or compliance. The study focused on mood and behavioral constructs common in adolescence. Therefore, we attempted to encompass a range of affect (few depressive symptoms to meeting diagnostic criteria) in our participants. In keeping with this representation, we did not exclude girls who were taking hormone contraceptives or most categories of psychotropic medications. However, data were collected on these variables and carefully examined and/or controlled for in the analyses when appropriate. The study was approved by the institutional review board of the Cincinnati Children’s Hospital Medical Center. Parents provided consent and the adolescents assented. Girls who were enrolled were not different from those not enrolled by race/ethnicity, height, smoking history, education using the modified Hollingshead Four-Factor Index of Social Status. Socioeconomic status was estimated by parent occupation and education using the modified Hollingshead Four-Factor Index of Social Status.

STATISTICAL ANALYSIS

The primary outcome was total body BMC (in grams). Total body BMD (in grams per centimeters squared) and hip and lumbar spine BMC and BMD were also considered for the purpose of confirming and comparing the findings for total body BMC. Ever- and never-smokers were compared using t and χ² tests for continuous and categorical variables, respectively. As age is an important confounder of smoking, 2-way analyses of variance were then used to compare ever- vs never-smokers on bone variables adjusted for age group. Generalized linear regression (for the primary aim) was used to model bone mass and density separately for depression and anxiety. Height, weight, age, race, pubertal stage, and socioeconomic status were included as key covariates. Other covariates (calcium and soda intake, hormone contraceptive use, physical activity, and menarche) were included in the model only if they remained significant after adjusting for the other covariates. Interaction effects were examined between depression and anxiety, smoking, and race.

Only significant terms (P ≤ .05) were used as key covariates. Other covariates (calcium and soda intake, hormone contraceptive use, physical activity, and menarche) were included in the model only if they remained significant after adjusting for the other covariates. Interaction effects were examined between depression and anxiety, smoking, and race. Only significant terms (P ≤ .05) were used as key covariates. Other covariates (calcium and soda intake, hormone contraceptive use, physical activity, and menarche) were included in the model only if they remained significant after adjusting for the other covariates. Interaction effects were examined between depression and anxiety, smoking, and race. Only significant terms (P ≤ .05) were included in the model only if they remained significant after adjusting for the other covariates. Interaction effects were examined between depression and anxiety, smoking, and race. Only significant terms (P ≤ .05) were included in the model only if they remained significant after adjusting for the other covariates. Interaction effects were examined between depression

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Table 1. Demographic and Anthropometric Characteristics of a Sample of Adolescent Girls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>125 (62.2)</td>
</tr>
<tr>
<td>African American</td>
<td>65 (32.3)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (5.5)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.0 (2.2)</td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>51 (23.5)</td>
</tr>
<tr>
<td>13</td>
<td>50 (24.8)</td>
</tr>
<tr>
<td>15</td>
<td>56 (27.7)</td>
</tr>
<tr>
<td>17</td>
<td>45 (22.2)</td>
</tr>
<tr>
<td>Socioeconomic status by the Hollingshead</td>
<td></td>
</tr>
<tr>
<td>Status score, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Tanner breast stage, No. (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>2</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>3</td>
<td>26 (13.1)</td>
</tr>
<tr>
<td>4</td>
<td>33 (16.6)</td>
</tr>
<tr>
<td>5</td>
<td>130 (65.3)</td>
</tr>
<tr>
<td>Postmenarcheal, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>154 (74.8)</td>
</tr>
<tr>
<td>No</td>
<td>52 (25.2)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>159.3 (8.6)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>60.55 (18.7)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>23.6 (6.3)</td>
</tr>
<tr>
<td>Overweight status, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>At risk for obesity</td>
<td>37 (18.97), 33.5 (6.2)</td>
</tr>
<tr>
<td>At risk for overweight</td>
<td>40 (20.51), 25.3 (2.1)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>118 (60.51), 19.8 (2.4)</td>
</tr>
<tr>
<td>Calcium intake, mean (SD), mg/d</td>
<td>1093 (918)</td>
</tr>
<tr>
<td>Soda intake, mean (SD), cups/d</td>
<td>1.6 (1.8)</td>
</tr>
<tr>
<td>PAQ-C score, mean (SD)</td>
<td>2.1 (0.6)</td>
</tr>
</tbody>
</table>

Abbreviation: PAQ-C, Physical Activity Questionnaire for Older Children.

[b]Calculated as weight in kilograms divided by height in meters squared.
[b]According to Centers of Disease Control and Prevention criteria using body mass index.

NOTE: Analyses were completed using SAS, version 9.12 (SAS Institute Inc, Cary, North Carolina). Data are presented as mean (standard deviation [SD]).

RESULTS

Participant characteristics are presented in Table 1 and Table 2. Most of the sample was either white (62.2%) or African American (32.3%). Only 5.5% of the sample was of other or mixed race. Therefore, analyses were conducted in 2 groups: white vs African American individuals and individuals of other or mixed race. Considering age and racial distribution, BMC and BMD measures are consistent with a recent national report. Specifically, the mean total body BMCs of girls in our study were generally between the 50th and 75th percentiles of the national report.

PRIMARY ANALYSIS

The final 3 models for total body BMC regressed on depressive symptoms and state and trait anxiety are reported in Table 3. All models included the following significant covariates: age, race, age by race interaction, height, weight, and Tanner breast stage. No other covariates remained significant and thus were not included in the model. The association between CDI and total body BMC is presented in the Figure, A. After adjusting for covariates, higher depressive symptoms were associated with lower total body BMC (β = -2.64; P = .03). A 1-SD increase (10 points) in the CDI T score was associated with a 26.4-g lower total body BMC. This is equivalent to a difference of 1.4% of the sample mean, or 82% of the sample SD. Neither the interaction of CDI score by smoking status nor by race was significant. The CDI T score was similarly associated with total body BMD (P = .01), but it was not associated with hip or spine BMC or BMD.

There was no significant association between trait anxiety and total body BMC (Figure, B, and Table 3) (P = .19) after adjusting for covariates. Neither the interaction of trait anxiety by smoking status nor by race was significant. Similarly, no effect of trait anxiety was found for total body BMC or for hip and spine BMC and BMD. There was no significant interaction of state anxiety and smoking status for total body BMC (Table 3). However, a state anxiety by race interaction was found (Figure, C and D). Among white participants, higher state anxiety was associated with significantly lower total body BMC (P = .04). A 1-SD increase (10 points) in state anxiety score resulted in a 36.7-g decrease in total body BMC. This is equivalent to a difference of 2.0% of the sample mean, or 82% of the sample SD. Similarly, state anxiety was associated with lower hip BMC (P = .02) and BMD (P = .03) but not lumbar spine BMC or BMD (data not shown).
SECONDARY AND SUBGROUP ANALYSES

Nearly all participants were pubertal and postmenarcheal (Table 1). Among all participants, oral contraceptive use was reported in 13%, depot medroxyprogesterone acetate in 10%; 2% reported a history of taking both estrogen and progesterone. Further, 9% of participants took over-the-counter acetaminophen. Fewer reported a history of using birth control pills (8% ever vs 4% never). For depressive symptoms, ever-smokers had higher CDI scores (data not shown). They were also more likely to have lower total bone mineral content (BMC) and that the earlier smoking onset was associated with a 120-g lower total body BMC. However, when we use the mean age at onset of smoking in our sample (13 years), the depression effect on total body BMC was found only in never-smokers in whom higher depressive symptoms were associated with lower total body BMC (β = −5.88 [1.99], 95% CI: −9.87 to −1.89). A 1-SD increase in CDI score was associated with a 58.8-g lower total body BMC. Trait anxiety was not significant among never-smokers. In ever-smokers, there was a significant trait anxiety by age at smoking onset interaction. The model suggested that higher trait anxiety was associated with lower total body BMC and that the earlier smoking onset was (eg, when the onset of smoking was at 7 ½ years [the youngest age at onset]), the stronger the trait anxiety effect was on bone health (β = −12.1, P = .03). A 1-SD increase in trait anxiety was associated with a 120-g lower total body BMC. However, when we use the mean age at onset of smoking in our sample (13 years), the β coefficient becomes nonsignificant (β = 0.24 [2-21, P = .91]. State anxiety was negatively associated with total body BMC (P = .05) in never-smokers. Neither state anxiety nor its interaction with race was significant in ever-smokers.

This is the first article to examine the association of depressive symptoms and anxiety with bone mass and density in healthy adolescent girls. We found that girls with more depressive symptoms, and in some cases anxiety, were more likely to have lower total body BMC. Subgroup analyses by ever and never having smoked either enhanced or weakened associations with bone mass or density, depending on whether depressive symptoms or anxiety remained significantly higher than those of never-smokers (P < .001).

Subgroup analyses were conducted, stratified by ever- and never-smokers. The depression effect on total body BMC was found only in never-smokers in whom higher depressive symptoms were associated with lower total body BMC (β = −5.88 [1.99], 95% CI: −9.87 to −1.89). A 1-SD increase in CDI score was associated with a 58.8-g lower total body BMC. Trait anxiety was not significant among never-smokers. In ever-smokers, there was a significant trait anxiety by age at smoking onset interaction. The model suggested that higher trait anxiety was associated with lower total body BMC and that the earlier smoking onset was (eg, when the onset of smoking was at 7 ½ years [the youngest age at onset]), the stronger the trait anxiety effect was on bone health (β = −12.1, P = .03). A 1-SD increase in trait anxiety was associated with a 120-g lower total body BMC. However, when we use the mean age at onset of smoking in our sample (13 years), the β coefficient becomes nonsignificant (β = 0.24 [2-21, P = .91]. State anxiety was negatively associated with total body BMC (P = .05) in never-smokers. Neither state anxiety nor its interaction with race was significant in ever-smokers.
anxiety was the explanatory variable of interest. For example, trait anxiety was not significantly associated with bone mass and density in the full sample. However, among ever-smokers, a negative association between anxiety and total body BMC was noted when we controlled for age at onset of smoking. Specifically, this association was stronger in those who started smoking at a younger age. Enhancement of the negative association between anxiety and depression may reflect a dose-response relationship between age and bone health. A negative effect of smoking on BMD was reported in adults, but in the only available study of adolescents, no association was found. The current findings indicate that anxiety and depression are implicated in bone health, but they need to be replicated.

The negative association between depressive symptoms and total body BMC and BMD held for never-smokers but not for ever-smokers. Initially this finding seems counterintuitive. It may be that smoking improved depressive symptoms in girls via self-medication resulting in no significant association between depressive symptoms and total body BMC. This interpretation is consistent with a finding that smoking reduces depressive symptoms. The association of smoking with depressive symptoms and anxiety needs further exploration, even in the absence of an association in adolescents, given that smoking may predict later depressive symptoms. Yet to be confirmed is the causal direction between smoking and depressive and anxiety symptoms in adults and adolescents.

Race was an important factor in the association between anxiety and bone characteristics. Higher state anxiety was associated with lower BMC but only in white participants. Bone mineral density is lower in white children than in African American children. Thus, the effect of anxiety on bone may add to the already enhanced risk of lower BMD in white individuals. It is important to note that our minority sample was smaller than the white sample and thus power may be limited for these analyses.

Figure. Generalized linear regression models showing partial leverage plots of the associations of Children’s Depression Inventory (CDI) score with total body bone mineral content (BMC) \((P = .03)\) (A), trait anxiety with total body BMC \((P = .19)\) (B), and state anxiety with total body BMC in white \((P = .04)\) (C) and African American (D) adolescent girls \((P > .05)\). All models included the following significant covariates: age, race, age × race interaction, height, weight, and Tanner breast stage. No other covariates remained significant and thus were not included in the model. Predicted total body BMC, the corresponding 95% prediction interval (solid lines), and confidence interval for the mean (dashed lines) are shown. T scores indicate a mean of 50 and an SD of 10.
The findings that depressive symptoms and state anxiety are associated with lower total body BMC may aid in identifying girls who are at risk for low bone mass and developing prevention programs during adolescence. Depression and anxiety are already indicators to health care providers that intervention may be necessary. However, knowing that affective states may also be associated with bone alerts health care providers of the need for other types of intervention. Efforts to prevent further depression or reduce its onset may be especially important in adolescent girls, particularly at pubertal stage 3 and higher, given that depression increases around this stage of development. Thus, when a provider is caring for a depressed or anxious girl, vigilance may be needed regarding the potential role affective states along with other known factors, like smoking, may play in bone density. Furthermore, some symptoms evident in depression (eg, appetite changes and lack of physical activity) may also have negative effects on bone mass. An additional consideration is that antidepressants, specifically selective serotonin reuptake inhibitors, reduce bone density by as much as 4% in adults. However, such studies have not been carried out in adolescents; clinicians will need to consider the relative risks of treating their patient's depression and its effect on bone health.

Our objectives were not designed to examine mechanisms that affect bone in these cross-sectional analyses. We categorized adolescents into never- vs ever-smokers based on the premise that ever-smokers represented a group at risk for various negative behaviors that may in turn affect bone health. Smoking in adolescence may be a marker for an unidentified mechanism that influences BMD. Alternatively, smoking may directly influence bone health. It has been shown that nicotine was more detrimental in young, rapidly growing rats than in older rats, indicating that nicotine may suppress bone formation. A human analog study would require participation by adolescents and adults who smoke. Such a study may be performed in the future.

Future longitudinal analyses might profitably examine mechanisms through which smoking as well as depressive and anxiety symptoms influence bone. Smoking may influence bone by decreasing body mass and/or estrogen effects. Smoking increases irreversible 2-hydroxylation of estradiol metabolism, increases metabolizing enzymes CYP1A1 and 1A2 (primary enzymes catalyzing 2-hydroxylation of estradiol), reduces aromatization, and competes with tobacco by-products that bind to estrogen receptors, all factors that could affect bone. These mechanisms can be investigated when our sample transitions into heavier smoking stages of development.

With respect to depressive symptoms and anxiety, explanatory mechanisms for affective states that influence bone will also be important to consider in future studies. Earlier studies have implicated the stress system as a potential mechanism. In mice, chronic mild stress was associated with evidence of behavioral depression and deficits in bone when bone epinephrine levels were increased. In this case, the sympathetic nervous system likely mediated the bone effects of stress-induced depression while a β-blocker diminished bone mass. Similarly, other studies have reported an effect of the sympathetic nervous system on regulation of bone mass. Others have speculated that the mechanism of low BMD or BMC and depression in adult humans could be due to hypothalamic-pituitary-adrenal axis dysregulation, another arm of the stress system. Many adults with depression have hyperadrenocorticalism, which can reduce bone mineralization. However, literature on child and adolescent depression supports the association of depression with hyperadrenocorticalism in only a few subgroups rather than those with depression as a whole. Less evidence is available with respect to anxiety, cortisol, and bone density. Cortisol level was higher in prepubertal children with anxiety disorders around sleep onset compared with depressed children or children with no psychiatric history. Thus, in younger children, anxiety may play more of a role in inhibiting bone formation than depression.

Despite the major strengths of this study, some limitations are evident. First, the study's design was cross-sectional and causation cannot be determined. Second, activity and nutrition were based on self-report, though there is a high correlation between self-report and objective measures. Third, in our young sample, many were just beginning their smoking trajectory and its effects may not yet be evident. Adolescents who smoke even a puff are at risk for increased smoking and dependence. At follow-up, we anticipate increased smoking in the older adolescents, thus allowing for examination of the effect of different levels of smoking on bone health. Finally, hormone contraception may have influenced findings in ways that could not be statistically identified. Earlier studies reveal that depot medroxyprogesterone acetate can have a negative effect on bone associated with suppression of ovulation and a resulting hypoestrogenic state. Lower estrogen oral contraceptives may have an especially adverse effect on bone in adolescents. In 2002, nearly 47% of 15- to 19-year-old adolescent girls in the United States had sexual intercourse, and 75% used contraception during last intercourse, most commonly oral contraceptives and depot medroxyprogesterone acetate. Girls using hormone contraceptives were not excluded from this study, as this would limit generalizability to the adolescent population. In addition, hormone contraceptives were used by never- and ever-smokers and those who had high or low depressive and/or anxiety symptoms.

In conclusion, analyses that report a negative association of depressive symptoms and anxiety with bone health in adolescent girls are cause for concern and necessitate further examination. Others have echoed the necessity for such research. The percent difference (1.4%-6.5%) observed in BMD and BMC by change in depression and anxiety scores alone or by smoking status may be clinically relevant. To put this in perspective, postmenopausal women lose on average 2% (≤5%) of bone mass each year, and women of reproductive age using depot medroxyprogesterone acetate lose 2% to 3% of bone mass each year. In these scenarios, patients are monitored and in some cases interventions are instigated. Therefore, seeing a percentage difference in our sample in this range is worrisome given that these girls are at the age when peak mass is accrued. Longitudinal analyses are re-
REFERENCES


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The Archives will publish a “rolling theme issue” this year on palliative care, dying, and bereavement. We are interested in original articles, narrative and systematic reviews, and commentaries that will add to the scientific knowledge about these topics. Such articles might include observational longitudinal studies such as the effects of loss of a family member on children and adolescents; clinical trials examining specific interventions or evaluating different systems of delivering palliative, hospice, or bereavement care; and ethical analyses regarding how we decide on and enact the goals and limits of medical therapy.

Our intent is to bring these issues to the forefront of pediatrics and adolescent medicine, just as they are in the minds of those children and families who are confronted with such loss. We hope the attention of the Archives will advance science and provide help to the physicians dealing with these issues on behalf of their patients and families.

This call for papers will be an ongoing one, and we intend to publish articles on this topic throughout the year as the manuscripts are submitted and accepted. For specific guidelines on manuscript preparation and submission, please consult the author instructions on our Web site at www.archpediatrics.com. Authors should indicate in their cover letter that the manuscript is to be considered for this theme.