

A School-Based Exercise Intervention Elicits Substantial Bone Health Benefits: A 2-Year Randomized Controlled Trial in Girls

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ABSTRACT. *Objective.* Childhood weight-bearing physical activity is recognized as an important determinant of peak bone mass, and physical activity intervention may represent a feasible strategy for primary prevention of osteoporosis. Previous school-based exercise interventions have all been of <10 months in duration. We implemented a high-impact, circuit-based, jumping intervention (10 minutes, 3 times a week) over 2 school years and compared changes in bone mineral content (BMC) over 20 months (2 school years) in 9.9 ± 0.6-year-old intervention girls (N = 32) and controls (10.3 ± 0.4 years, N = 43).

Methods. We measured BMC for the total body, lumbar spine, proximal femur (and femoral neck and trochanteric subregions), and lean and fat mass by dual-energy radiograph absorptiometry (Hologic QDR 4500), and height, sitting height, leg length, and weight at baseline and 20 months. We assessed Tanner stage, general physical activity, and calcium intake by questionnaire.

Results. Girls were Tanner breast stage 1 to 3 at baseline. There were no significant differences in baseline or 20-month change in body size or composition, average physical activity, or calcium intake between groups. There were substantially greater gains in lumbar spine (41.7% vs 38.0%) and femoral neck (24.8% vs 20.2%) BMC in intervention than in control girls (P < .05, analysis of covariance; covariates were baseline BMC and height, change in height, physical activity, and final Tanner stage).

Conclusion. Three brief sessions of high-impact exercise per week implemented over 2 consecutive years within the elementary school curriculum elicited a substantial bone mineral accrual advantage in pubertal girls. *Pediatrics* 2003;112:e447–e452. URL: <http://www.pediatrics.org/cgi/content/full/112/6/e447>; girls, bone health, bone mineral content, exercise, intervention.

ABBREVIATIONS. LS, lumbar spine; FN, femoral neck; PE, physical education; BMC, bone mineral content; BA, bone area; TB, total body; PF, proximal femur; TR, trochanteric.

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The World Health Organization reports that lack of physical activity is a major underlying cause of death, disease, and disability and attributes >2 million deaths annually to physical inactivity.¹ The health costs of chronic diseases associated with physical inactivity are nearly \$1 trillion annually in the United States.² There is considerable evidence that strongly links physical inactivity to the increasing prevalence of osteoporosis.³ The costs of osteoporosis and related fracture continue to escalate and currently exceed \$6 billion/year in the United States² and are of considerable concern worldwide.⁴

It is increasingly accepted that the roots of adult osteoporosis are cultivated in childhood,^{5–7} and the World Health Organization agrees that the debate around noncommunicable diseases must be redirected toward prevention.¹ A recent editorial argued strongly that, of all modifiable lifestyle factors that influence bone, exercise during growth has the greatest capacity to reduce the public health burden of osteoporosis-related fractures.⁵ The author called for safe, effective, relatively simple, and inexpensive programs of activity in childhood to reduce the burden of adult osteoporosis.⁵

We previously reported a 1% to 3% bone-mass advantage at the lumbar spine (LS) and femoral neck (FN) in children who completed simple yet diverse weight-bearing exercise programs for 10 to 20 minutes, 3 times per week.^{8–11} These programs were instructed by classroom, not physical education (PE) specialist, teachers. Others have reported similar findings with more intense school programs^{12–15} and repetitive school-based box-jumping programs.¹⁶ However, all previous prospective trials of exercise interventions have been completed in 1 academic year (≤10 months). The question of whether reported short-term benefits continue to accrue with participation over a longer term has not been addressed.

Thus, we assessed bone outcomes (bone mineral content [BMC] and bone area [BA]) in girls who completed a 20-month, school-based exercise program during regular elementary school PE. We hypothesized that, over 20 months, girls in intervention schools would accrue more BMC and increase BA more than controls. If this proved to be the case, it would have substantial implications for the content of school PE classes.

MATERIALS AND METHODS

We have detailed our procedures in previous reports.^{8–10,17} All measurements took place at the University of British Columbia

Bone Health Research Laboratory, and the exercise program was conducted within intervention schools.

Design

To assess school PE as a vehicle for the intervention and to avoid exercise contamination within schools, we randomized schools to either exercise intervention ($n = 7$ schools) or control ($n = 7$ schools) groups. Children were measured at the beginning (October 1999 and September to October 2000) and end (June 2000 and 2001) of 2 consecutive school years (4 measures per subject). The intervention was implemented for 7 months each year (November to May), with a break during the summer holiday (July to August). Thus, 20 months elapsed between October 1999 (beginning of baseline measures) and the beginning of June 2001 (final measures). Changes within a school year are described as 8-month changes to reflect measurement time and intervention time.

Subjects

At baseline, the year-1 cohort included 191 girls in grades 4, 5, and 6 (8.8–11.7 years old) from a previously described school district with a population of ~34% Hong Kong Chinese, 57% North American/Western European white, 5% East Indian, and 4% other ethnic origin or mixed ethnicity.⁸ Fourteen schools (of 41 total) volunteered to participate after we presented the study at a school district principals' meeting. All children in grades 4, 5, or 6 attending these schools were eligible to participate. We accepted into the study all children who, with their parents, provided informed consent. The 14 year-1 schools were stratified by race (<33% Asian or >33% Asian) and number of participants (<20 or >20) before randomization to ensure equivalence between groups. We allocated schools, by random draw, before obtaining any baseline information on schools or individual children. Each girl's parents completed a health-history questionnaire for their daughter. All girls who participated for 2 school years were healthy, and none took medications known to influence bone metabolism.

All control schools consented to participate in year 2. Attrition between years 1 and 2 occurred in 4 ways (Fig. 1). 1) In 2 intervention schools, principals declined participation for the school. This was either because target teachers were in their first year of teaching and principals felt that the intervention would be distracting, or there were too few (1 or 2) study children per classroom to warrant participation of new teachers (-29 girls). 2) Three

intervention school teachers declined to participate, although other classes from these schools continued in the program (-8 girls). 3) Sixteen girls in the intervention group and 29 girls in the control group either moved to a new school or did not respond to the consent form in year 2 (-45 girls). 4) Seventeen control girls in grade 7 were excluded, because the grade 7 girls in the intervention group were lost due to school or teacher attrition, and only grades 5 and 6 remained in the intervention schools (-17 girls). Thus, of the 87 intervention and 92 healthy control girls who completed year 1,⁸ 34 (39%) and 46 (50%) girls, respectively, participated in year 2.

In both intervention and control groups, there was a small difference in mean age (0.3 years) between girls who dropped out and those who continued as a result of the attrition (intervention group) and omission (control group) of grade-7 girls. Baseline LS BMC was higher in those girls who dropped out of the intervention group than those who continued, which reflected the difference in age. Eight-month change in LS BMC was similar between those girls who dropped out and those who continued. There were no differences in baseline or 8-month change in height, weight, lean mass, fat mass, or FN BMC between intervention or control girls who withdrew after year 1 and those who continued in year 2.

The University of British Columbia Clinical and Behavioral Sciences Research Ethics Board approved this study.

School-Based Exercise Intervention

We reported the details of the year-1 exercise intervention elsewhere.^{8,10} Briefly, this program provided a progressive, 10- to 12-minute program of diverse weight-bearing exercises during regularly scheduled PE classes (2 times per week) and on 1 other day during the week. Teachers facilitated circuit-training that included 5 different jumping activities with ground-reaction forces that ranged from 3.5 to 5 times body weight.¹⁸ Children progressed from 50 to 100 jumps per session across 3 (~10-week) levels of difficulty. In year 2, teachers used a higher proportion of high-impact jumps. The exercise stations incorporated plyometric jumps, alternating-foot jumps, and 2-foot obstacle jumps. Girls ran or skipped (alternate weeks) between stations and laps increased from 5 (55 jumps) at year 2 baseline to 12 (132 jumps) at year 2 final. "Levels" were advanced every 8 to 10 weeks, when the step height increased from 10 cm (level 1) to 30 cm (level 2) to 50 cm

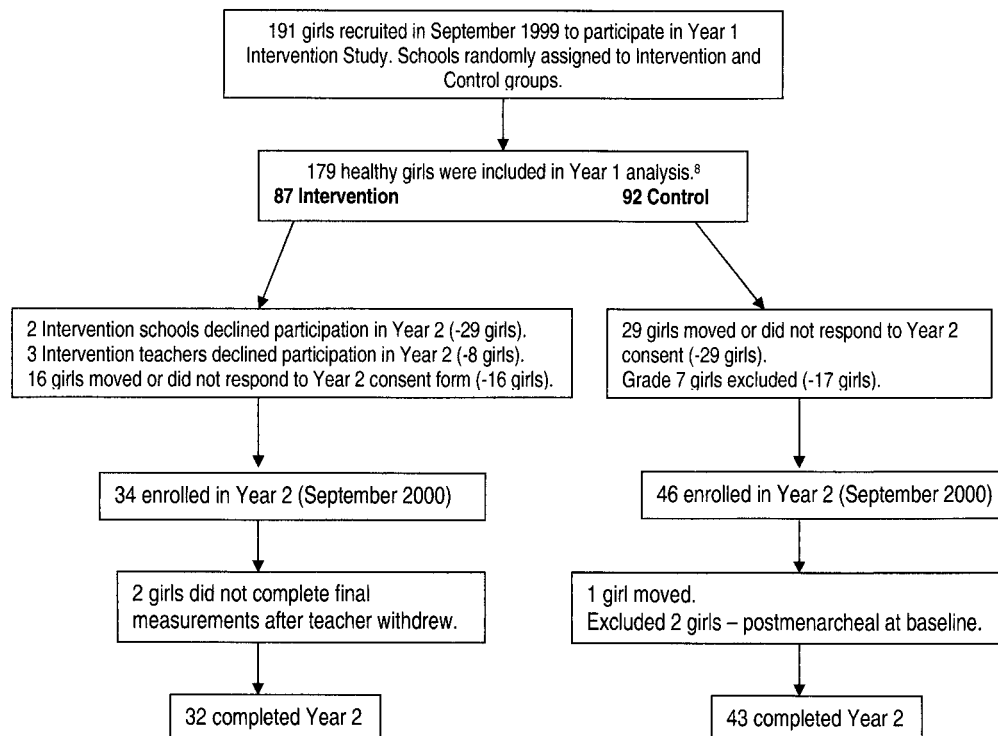


Fig 1. Trial profile.

(level 3), and the obstacle height at the 2-foot jump station was increased from 10 cm (level 1) to 20 cm (level 2) to 30 cm (level 3). On 1 other day during the week, teachers facilitated progressively more (15–50) plyometric jumps (level 1), half-tuck jumps (level 2), or full-tuck jumps (level 3).

In-school training of teachers ($N = 15$) was conducted according to a guideline manual.^{8,10} We visited each class twice during the school year to monitor the intervention, and teachers detailed exercise activities and attendance in a manual. No injuries were reported as a result of the intervention program. On average, there were 57 and 45 exercise sessions in years 1 and 2, respectively. Girls in control schools participated in 2 40-minute regular PE sessions per week as mandated by the school board. The integrated resource package for PE provided by the school board allows flexibility in the types of activities in which the students engage while specifying that the following focus areas must be included: movement in alternate environments (ie, outdoors, wilderness setting, or local park), dance, games (with an emphasis on selecting and combining locomotor and nonlocomotor skills and manipulating objects), gymnastics, and movement in individual and dual activities.

Dependent Variables

Our primary outcome was BMC (grams) for the total body (TB), LS, and proximal femur (PF), and its FN and trochanteric (TR) subregions, assessed by using a Hologic QDR 4500W bone densitometer (DXA). We also report BA (centimeters²) as a secondary outcome. Two trained and qualified technicians acquired all scans. Scans were analyzed by using standardized procedures¹⁹ by 1 researcher (K.J.M.). TB lean mass and fat mass (grams) were obtained from TB DXA scans. Our precision (0.8–3.5% coefficient of variation, depending on skeletal site and parameter) and quality assurance procedures for densitometry are reported elsewhere.^{8,17} We also assessed long and vertical²⁰ jump (to the nearest millimeter) to represent dynamic power at baseline and 20 months.

Independent Variables

Maturity was rated^{1–5} against Tanner breast and pubic hair line drawings.²¹ The girls were either assisted by a member of the research team with each follow-up assessment or completed it with written instructions (in English or Chinese) under parental supervision at home. Menarcheal status and date of menarche were ascertained at each laboratory visit as relevant. We measured sitting height and standing height (stretch stature both) to the nearest millimeter, calculated leg length, and assessed body weight as reported previously.^{8,17}

We used a food frequency questionnaire to estimate dietary intake of calcium.^{22,23} A bilingual (Chinese-English) trained measurer assisted Chinese children. The questionnaire was administered 3 times during each school year (fall, winter, and spring, 6 times total), and we report average calcium intake across 20 months.

Moderate to vigorous physical activity during the previous 7 days was determined by a modified version of the Physical Activity Questionnaire for Children (PAQ-C).²⁴ Final general physical activity scores were calculated as an average of the PAQ-C items in a continuous range between 1 (low activity) and 5 (high activity).^{6,25} We modified the PAQ-C to include an estimate of time spent in loaded physical activity and the number of nights of extracurricular sports activities per week.^{8,17} The questionnaire was administered 3 times (fall, winter, and spring) during each school year, and the average score of 6 questionnaires is reported.

Statistical Analyses

We compared baseline age, height, and weight (body size), lean and fat mass (body composition), bone parameters (BA and BMC), and dynamic power (long and vertical jump) between control and intervention groups by using independent t tests. We similarly compared 20-month change in body size and composition, dynamic power, average physical activity, and calcium intake between intervention and control groups (Table 1). We used analysis of covariance to evaluate actual 20-month change in our primary and secondary outcomes (BMC and BA), and we provide these

TABLE 1. Baseline Characteristics and 20-Month Change for Control ($N = 43$) and Intervention ($N = 32$) Girls Who Completed 20 Months of the Study

Variables	Control ($N = 43$)	% Change	Intervention ($N = 32$)	% Change
Baseline age (years)	10.3 (0.4)		9.9 (0.6)	
Final Tanner stage (1/2/3/4/5)	1/15/21/6/0		5/13/12/2/0	
No. postmenarcheal at final	15		8	
No. Asian/Caucasian/other	10/24/9		12/14/6	
Baseline height (cm)	142.4 (6.6)		139.6 (8.6)	
Δ in height (cm)	11.1 (2.2)	7.8 (1.7)	11.1 (2.6)	7.9 (1.6)
Baseline weight (kg)	38.5 (8.6)		34.6 (8.4)	
Δ in weight (kg)	9.6 (3.2)	25.4 (7.8)	8.6 (4.0)	24.8 (9.4)
Baseline BMI (kg/m ²)	18.8 (3.3)		17.6 (3.2)	
Δ in BMI (kg/m ²)	1.5 (1.1)	7.8 (5.8)	1.2 (1.2)	7.0 (7.0)
Baseline sitting height (cm)	75.3 (3.7)		73.6 (4.2)	
Δ Sitting height (cm)	5.6 (1.5)	7.3 (2.3)	5.5 (1.9)	7.4 (2.4)
Baseline leg length (cm)	67.0 (3.6)		66.1 (5.3)	
Δ Leg length (cm)	5.6 (1.5)	8.3 (2.3)	5.5 (1.7)	8.3 (2.4)
Baseline lean mass (kg)	25.8 (4.1)		24.3 (4.2)	
Δ Lean mass (kg)	6.6 (1.8)	25.9 (6.5)	6.3 (2.7)	25.6 (9.4)
Baseline fat mass (kg)	11.3 (5.7)		9.2 (4.6)	
Δ Fat mass (kg)	2.5 (2.3)	23.2 (20.2)	1.8 (1.9)	21.9 (17.9)
Baseline long jump (cm)	123.7 (16.7)		121.8 (17.8)	
Δ Long jump (cm)	3.5 (12.4)	3.4 (10.5)	8.3 (12.9)	7.6 (11.4)
Baseline vertical jump (cm)	22.3 (4.9)		20.9 (4.7)	
Δ Vertical jump (cm)	5.4 (5.0)	25.1 (26.2)	6.7 (4.7)	35.7 (32.6)
Average physical activity score (maturity stages 1–5)	2.9 (0.5)		2.9 (0.5)	
Background variables				
Average loaded activity (hours/wk)	5.4 (3.0)		5.8 (3.6)	
Average sport nights (n /wk)	1.9 (1.4)		1.7 (1.5)	
Average calcium intake (mg/day)	907 (363)		899 (478)	

Δ indicates change; BMI, body mass index.

* Control mean greater than intervention group, $P < .01$, independent t test.

adjusted changes in Table 2 and indicate adjusted percent changes in the text. Because there is considerable variability between children in a number of body-size, maturity, and lifestyle factors known to influence change in bone,^{8,11,17,22,26} we analyzed and adjusted for these differences by subject so as not to bias results by comparing school means. We adjusted for independent variables that were significantly associated with the dependent variable including baseline height and BMC, change in height, final Tanner breast stage, and extracurricular physical activity. Previous studies by our group and others^{8,10,14,27} have highlighted the relationship between change in height, final Tanner stage, and physical activity (average physical activity score) with change in bone mass. Significant correlations between independent and dependent variables were moderate to high and ranged from $r = 0.3$ ($P < .01$) for bone change versus physical activity to $r = 0.6$ ($P < .01$) for bone change versus baseline height and change in height and maturity relationships.

Statistical power was 80% to detect a 5% difference (SD 11%) in 20-month BMC change between groups. Data were analyzed with SPSS version 8.0, and significance was set at $P < .05$.

RESULTS

One control girl moved away, and 2 intervention girls withdrew after withdrawal of their classroom teacher from the study. Thus, 20-month data were collected for 45 control and 32 intervention girls in grades 5 and 6. To balance differences in maturity between intervention and control groups, we excluded the only 2 girls (controls) who were postmenarcheal at baseline. Therefore, we included 43 control and 32 intervention girls in the final analysis (Fig. 1).

Girls attending intervention schools participated in 45 ± 13 intervention sessions in year 2 and 57 ± 10 sessions in year 1. To assess the possibility of a school effect we evaluated percent change in BMC across intervention schools ($N = 87$ girls) during year 1. Seven-month percent changes (adjusted for change in body size, age, and maturity) were consistent across schools (range was 3% from highest to lowest mean school change for both LS and FN BMC).

Baseline data and 20-month change in body size, composition, and dynamic power are presented (Table 1). Control girls were 0.4 years older ($P < .01$) and tended to be slightly taller and heavier (not significant) than intervention girls at baseline. A greater percentage of control (98%; 42/43) than intervention (84%; 27/32) girls were in Tanner stages 2 through 4 at final measurement. Thirty-four percent (15/43) of controls and 25% (8/32) of intervention girls achieved menarche during the study. Intervention

girls showed a trend toward improved long jump (7.6 vs 4.3%; $P = .10$) and vertical jump (35.7 vs 25.9%; $P = .14$) compared with control girls.

Baseline and 20-month change in BMC and BA are presented (Table 2). At baseline, control girls had significantly higher unadjusted TB ($P < .05$), LS ($P < .01$), and PF ($P < .05$) BMC and FN BMC and area ($P < .05$). Adjusted 20-month change in LS (41.7 vs 38.0%; $P < .05$) and FN BMC (24.8 vs 20.2%; $P < .05$) were significantly greater in the intervention group (means adjusted for baseline BMC, final Tanner stage, baseline height, change in height, and physical activity score) (Table 2). Adding either baseline weight or 20-month weight change as covariates did not influence the results (data not shown). The adjusted differences (intervention and control) in LS and FN BMC change by interval within the 20-month study are presented in Fig. 2. BMC changes were ~2% greater for the intervention group for both intervention periods (1–8 months and 13–20 months). Bone mineral accrual rates were similar between groups during the summer holiday.

DISCUSSION

We designed a safe, effective, relatively simple, and inexpensive program of diverse activities that can be implemented in elementary school PE to enhance bone mineral accrual during childhood. The nearly 5% benefit we observed at 20 months in the exercising schools was approximately double that seen in our 7-month intervention in these girls. If maintained, this advantage in bone mineral accrual represents the equivalent of 3 to 5 years of postmenopausal bone loss. This is the first study to demonstrate that a targeted exercise program during early and peripuberty has a cumulative (~2% per school year) bone benefit at 2 sites⁸ (Fig. 2) compared with accrual rates for same-aged children who are normally active.

The Exercise Intervention

The magnitude of BMC change over 2 years in the present study approximated the reported gains over 9 to 10 months in 2 studies that examined girls at a similar maturational stage (Tanner stages 1–3 at baseline).^{13,14} These after-school, weight-bearing ex-

TABLE 2. Baseline and Adjusted 20-Month Change in TB, LS, PF, FN, and TR BMC and BA (for Regions) in Girls ($N = 75$) Who Completed 20 Months of the Study

	Control ($N = 43$), baseline (SD)	Δ (95% CI)*	Intervention ($N = 32$), baseline (SD)	Δ (95% CI)*
TB BMC (g)	1121 (220)	333 (310–356)	1008 (192)	359 (332–386)
LS area (cm ²)	39.7 (4.4)	7.3 (6.7–8.0)	37.4 (5.5)	7.5 (6.7–8.2)
LS BMC (g)	26.5 (5.7)	9.3 (8.4–10.1)	22.5 (4.5)	10.9 (9.9–11.9)†
PF area (cm ²)	23.5 (3.1)	5.3 (5.0–5.7)	22.4 (3.3)	5.3 (4.9–5.7)
PF BMC (g)	16.5 (4.0)	6.7 (6.3–7.1)	14.8 (3.3)	6.8 (6.3–7.3)
FN area (cm ²)	4.2 (0.3)	0.35 (0.29–0.41)	4.1 (0.4)	0.42 (0.34–0.49)
FN BMC (g)	2.8 (0.5)	0.55 (0.48–0.61)	2.5 (0.5)	0.66 (0.58–0.73)†
TR area (cm ²)	5.8 (1.3)	2.1 (1.9–2.2)	5.3 (1.3)	1.9 (1.7–2.1)
TR BMC (g)	3.2 (1.1)	1.9 (1.8–2.1)	2.8 (0.9)	1.8 (1.6–1.9)

Δ indicates change; CI, confidence interval; SD, standard deviation.

* Adjusted for baseline bone value, baseline height, final Tanner stage, change in height, and average physical activity.

† Change is significantly greater in intervention group, $P < .05$, analysis of covariance.

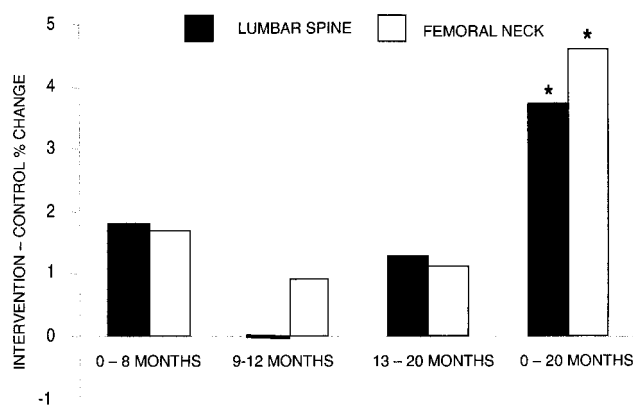


Fig 2. Difference in adjusted LS and FN BMC percent change (intervention and control group) over 1 to 8 months (first intervention period), 9 to 12 months (no intervention), 13 to 20 months (second intervention period), and 0 to 20 months (study duration). * indicates that the difference in adjusted 0- to 20-month changes were significantly greater in the intervention group ($P < .05$). Differences at other time points were not significant (adjusted for baseline BMC and height, change in height, Tanner stage at end of interval, and average physical activity; analysis of covariance).

exercise programs were implemented for 30 to 35 minutes, 3 times per week^{13,14} compared with our 10- to 15-minute, 3 times per week, school-based session. Our cohort was already active and performed, on average, 5.6 hours of recreational loaded physical activity per week. Thus, these brief sessions of high-impact activity were designed to impose diverse patterns of movement that elicited ground-reaction forces and rates of force beyond those associated with daily activities or running.²⁸ This strategy may elicit an optimal osteogenic adaptation in growing bone,^{29,30} as indicated by the larger bone mineral advantage (+4.5% at the FN) attained by prepubertal children participating in a focused, repetitive, box-jumping program,¹⁶ which was associated with much higher ground-reaction forces (8.8 times body weight) than our program. Further, our short duration program imposed minimal demands on the large team of teachers who delivered the program.

Skeletal Site Specificity of the Intervention Response

The skeletal response we observed was region- and site-specific. We previously reported significantly greater gains for LS and FN BMC after 7 months of exercise in our initial cohort.⁸ An augmented response to exercise may also be maturity-, sex-, and surface-specific. Our findings agreed with a similar site-specific response in Finnish premenarcheal, but not postmenarcheal, girls.¹³ Similarly, our 7-month intervention elicited significantly greater changes at the PF in early, but not prepubertal, girls.⁸ Either decreased endosteal expansion or increased endosteal apposition rather than increased periosteal expansion (as measured by hip structural analysis³¹) underpinned these differences in mass and structure at the PF in these girls.¹⁰ We have also reported greater gains for TB BMC and PF and TR area bone mineral density in prepubertal boys⁹ and for TR area bone mineral density in a combined group of younger (8.9 years) prepubertal boys and girls following a more moderate intervention.¹¹

Effectiveness of the School-Based Exercise Intervention

Although attrition from years 1 to 2 was high (61% of the original intervention cohort), the number of girls at the end of 20 months was comparable¹³ or greater^{12,14,16,32,33} than the sample sizes of other studies conducted over 8 to 10 months only. In our study, 70% of drop-outs were explained by new teachers who chose not to participate. Thus, success of school-based interventions depends on successful recruitment at all levels: school board, principals, teachers, students, and parents. However, to put the nature of school-based interventions in perspective, a total of ~470 grade-4 to -6 students in intervention schools performed the jumping exercises on a regular basis with their classes during years 1 and 2 but were not enrolled for measurement. Thus, school PE provides a feasible means to promote a strategy of exercise known to enhance bone-mass and bone-strength¹⁰ gains in early puberty. We suggest that an emphasis on PE training of teachers within the school systems might increase the effectiveness and long-term incorporation of physical activity initiatives within the curriculum.³⁴

There were a number of limitations in the present study. Randomization by school, as opposed to individual children, introduced bias and influenced the generalizability of results. However, this design was most feasible because it targeted a large number of children and eliminated the likelihood of contaminating the control group. In several previous studies of girls, schools^{13,14} or individuals³² self-selected to control or intervention groups. This may have introduced principal, teacher, or student bias regarding physical activity preferences. The biological variability in our results reflects the diverse ethnic group of girls at various stages of physical maturity whom we evaluated. However, because girls of the same chronological age mature at vastly different rates and at different times, our findings reside in the context of a real population. Further, despite randomization of schools within this study, there was an imbalance in maturity between the control and intervention groups, where a more advanced maturity status, on average, in the control group may have conferred different rates of bone mineral accrual. However, we recognize issues around maturity status to be a potential confound of all pediatric intervention studies and controlled for final Tanner stage statistically. Further clarity of these findings will be attained once longitudinal follow-up data are collected.

CONCLUSIONS

Our exercise intervention, implemented over 2 school years, augmented 20-month bone-mass gain at the LS and FN by 3.7% and 4.6%, respectively, in girls who were 10 years old. These results suggest that an exercise program begun in early puberty might result in a significantly greater peak bone mass compared with no involvement during these formative years. Investigations in retired, elite female dancers³⁵ and gymnasts³⁶ suggest that a bone mineral advantage, attributable to exercise training in childhood, may be maintained in adulthood. Fur-

thermore, the first published follow-up study of a high-impact, 7-month exercise program in prepubertal children provided evidence of a persistent skeletal effect at the FN after 7 months of detraining.³⁷ Follow-up of the girls in our study at full maturity is necessary to ascertain whether this maturational period represents a critical time when environmental stimuli evoke persistent adaptations in structure or function.

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