A 4-Year Exercise Program in Children Increases Bone Mass Without Increasing Fracture Risk

WHAT'S KNOWN ON THIS SUBJECT: Observation studies and short-term prospective intervention studies have shown that physical activity positively affects the accrual of bone mass and size during growth; however, fracture risk has not been evaluated.

WHAT THIS STUDY ADDS: This study reports the long-term results of a prospective intervention with increased physical activity at a population-based level and for the first time evaluated the clinical relevant end point, fracture risk.

abstract

BACKGROUND: Most prospective pediatric exercise intervention studies cover <1 year and use bone traits as surrogate end points for fractures. This prospective controlled exercise intervention study therefore followed not only skeletal development but also fracture incidence for 4 years.

METHODS: Fractures were prospectively registered in a cohort of children aged 7 to 9 years, 446 boys and 362 girls in the intervention group (2675 person-years) and 807 boys and 780 girls in the control group (5661 person-years). The intervention included 40 minutes per day of school physical education for 4 years whereas the controls had 60 minutes per week. In a subsample, 73 boys and 48 girls in the intervention and 52 boys and 48 girls in the control group, bone mineral content (g) and bone width (cm) were followed by means of dual-energy radiograph absorptiometry.

RESULTS: The rate ratio for fractures was 1.11. In the dual-energy radiograph absorptiometry–measured children, there were no group differences at baseline in age, anthropometrics, or bone traits. The mean annual gain in lumbar spine bone mineral content was 7.0% higher in girls and 3.3% higher in boys and in femoral neck width 1.7% higher in girls and 0.6% higher in boys in the intervention than in the control group.

CONCLUSIONS: A population-based moderately intense 4-year exercise program in 7- to 9-year-old children increased bone mass and size without affecting the fracture risk. Pediatrics 2012;129:e1468–e1476

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KEY WORDS BMC, bone mineral content, bone size, boys, children, controlled, exercise, fracture, girls, growth, physical activity, prospective

ABBREVIATIONS

BMC—bone mineral content
CI—confidence interval
DXA—dual-energy radiograph absorptiometry
FN—femoral neck
HSA—hip structural analysis
LS—lumbar spine
Z—section modulus

Dr Löfgren was involved in the statistical analysis, the interpretation of data, and the writing of the article; Dr Dencker collected and analyzed the accelerometer data; Dr Nilsson was involved in the statistical analysis; and Dr Karlsson designed the study, worked with the analysis, and was in charge of writing the article. All authors read and approved the final manuscript.

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High physical activity induces anabolic skeletal effects, as does moderate activity during growth.\textsuperscript{1–10} The most osteogenic activities include fast dynamic loads with high magnitude and high frequency, whereas endurance activities are less effective.\textsuperscript{11,12} Physical activity during growth is also associated with high peak bone mass, and half of the variance in bone mass at age 70 is estimated to be predicted by peak bone mass.\textsuperscript{13} Because low bone mass in old age is associated with high fracture risk, exercise during growth ought hypothetically to be used as prophylaxis against osteoporosis and fragility fractures.\textsuperscript{14} The pre- and early peripubertal years are the ideal period for exercise because mechanical load preferentially affects surfaces of bone that is undergoing fast apposition.\textsuperscript{15} This is supported by studies showing that the same type of exercise confers benefit before but not after puberty.\textsuperscript{2–10,15,16} Cited studies have used bone mineral content (BMC) as the primary endpoint variables, have predominantly included volunteers, had specific programs designed to be osteogenic, and all but 3 studies used a follow-up of $\leq 1$ year.\textsuperscript{5,6,8,10,16} It is debated, however, whether skeletal benefits are achieved with general training on a population-based level and retained with longer interventions. In addition, bone mass is only a surrogate end point for the clinically relevant entity of fractures. Low bone mass in both adults and children is associated with high fracture risk; however, there is no causal relationship.\textsuperscript{17–19} For example, the fracture incidence is higher in athletes with higher than average bone mass and also in children with high physical activity levels.\textsuperscript{20} The aim of this study was therefore to evaluate whether an extended exercise intervention program in children could produce long-term skeletal benefits without increasing the fracture incidence.

METHODS

The Malmö Pediatric Osteoporosis Prevention Study is a population-based, nonrandomized, prospective, controlled exercise intervention study following skeletal development and fracture incidence in 7- to 9-year-old children. The study design has previously been reported in detail.\textsuperscript{7–10} In summary, 4 neighboring elementary schools that were government-funded, with the children allocated to the school according to their residential address and with a standard curriculum of physical education accepted participation in the study. One school was chosen as intervention school. The intervention included daily school physical education (200 minutes per week), whereas the control group continued with 60 minutes given in 1 or 2 lessons per week. Lessons were led by ordinary teachers and included general activities such as ball games, running, jumping, and climbing.

For the fracture epidemiologic evaluation, all school children from the 4 schools were included (100%) because physical education is a compulsory school subject and fractures were objectively registered through the archives of the city hospital, not through the questionnaires. Fractures were prospectively registered in 446 boys and 362 girls in the intervention group and 807 boys and 780 girls in the control group. There is 1 hospital in the city, so virtually all fracture patients attend the hospital, with the classification system validated during 4 decades.\textsuperscript{21} Previous evaluations have reported that $<3\%$ of all fractures in the target population are missed by this system.\textsuperscript{21} One person followed for 1 year equaled 1 person-year.

From the target population, a subcohort of children was invited for measurements of anthropometrics and skeletal traits before intervention and then annually in the same month for a period of 4 years.\textsuperscript{7,9} Children with diseases or medication known to influence bone metabolism were excluded. At baseline, 55 of 61 girls and 84 of 89 boys agreed to participate in the intervention school. One girl was excluded because she was 11 months younger than all the rest. During the 4-year follow-up period, 6 girls and 8 boys moved out of the region or declined additional participation. Two boys were excluded because they were taking medication known to influence bone metabolism, leaving 48 girls with a baseline mean age of 7.7 $\pm$ 0.6 (range 6.5–8.7) and 73 boys with a mean age of 7.8 $\pm$ 0.6 (range 6.7–8.7) to be included in the intervention group with measurements done. Sixty-four of 158 girls and 68 of 169 boys accepted participation in the control schools. At follow-up, 15 girls and 13 boys had moved out of the region or declined additional participation, 1 girl and 2 boys were excluded because they were taking medication known to influence bone metabolism, and 1 boy adopted from Colombia was excluded as being the only non-Caucasian, leaving 48 girls with a baseline mean age of 7.9 $\pm$ 0.6 (range 6.8–8.9) and 52 boys with a mean age of 8.0 $\pm$ 0.6 (range 6.7–8.9) in the control group on whom measurements were performed. The risk of selection bias seems minimal because there were no differences in anthropometrics or bone traits between children within the schools before the intervention or between the children that participated throughout the study and the dropouts.\textsuperscript{7,9} Nor were there any differences in height, weight, or BMI when data from the grade 1 compulsory school health examination were analyzed to compare the children who participated with those who refused.\textsuperscript{8,10}

A questionnaire that the children filled in annually with their parents was used to evaluate various lifestyle factors such as dietary habits, diseases, medication, and physical activity. The questionnaire included specific questions...
about time spent in organized leisure time sports activity. Total duration of physical activity was estimated as duration of school physical education and organized leisure time activity per week and mean value during the 4 years calculated. Pubertal maturity was ascertained by self-assessment of Tanner staging. Measurements were conducted annually for 4 years. Body weight and height were measured by standard equipment. BMC (g) was measured by dual-energy radiograph absorptiometry (DXA, DPX-L version 1.3z, Lunar; Madison, WI) in total body, lumbar spine (LS), femoral neck (FN), and trochanter. The width of the third lumbar vertebra and the FN were evaluated at the LS and hip scan as an evaluation of FN cross-sectional area (cm²), section modulus (Z; cm³), and cross-sectional moment of inertia (cm⁴). The method introduced by Beck et al, excluding biologically unlikely values, 3 SD beyond the mean, was advocated, resulting in the exclusion of 46 of the 1005 HSA analyses. Total body fat mass and total body lean mass were measured by total body scans. Our research technicians calibrated the machine daily with the Lunar phantom, and they performed measurements and software analyses. The coefficients of variation, evaluated by duplicate measurements in 13 healthy children was BMC 1.4% to 3.8%, bone width 1.5% to 2.2%, FN cross-sectional area 2.2%, FN Z 6.2%, FN cross-sectional moment of inertia 6.2%, total body fat mass 3.7%, and total body lean mass 1.5%

Physical activity after 2 years was objectively measured by accelerometers (model 7164 MTI; Manufacturing Technology Inc, Fort Walton Beach, FL) on 4 consecutive days with methodology described previously. Mean activity was defined as the total accelerometer cpm of monitoring, moderate-to-vigorous physical activity as time spent >3 metabolic equivalents and vigorous physical activity as time spent >6 metabolic equivalents. Cutoff points used for all children were >1000 cpm for moderate-to-vigorous physical activity and >3500 cpm for vigorous physical activity. Activity >5000, 6000, and 10 000 cpm was also registered to capture the most intense activities, known to be osteogenic.

Informed written consent was obtained from parents or guardians of the participants, and the Lund University Ethics Committee (LU 453-98; 1998-09-15) approved the study. Data are presented as mean ± SD or mean with 95% confidence interval (CI). Gender-specific baseline group differences were tested by Student’s t test and Fisher exact test. The annual changes of all parameters were calculated by using linear regression slopes for each individual and group difference in annual changes by analysis of covariance with adjustment for Tanner stage at follow-up. All children were then divided into tertiles according to physical activity, and tertile differences were tested by analysis of variance. Fracture risk with 95% CI was estimated by Poisson distribution. P < .05 was regarded as a statistically significant difference.

RESULTS

There were 148 fractures during the study period. 30 hand, 64 distal forearm, 9 mid-forearm, 21 humerus, 6 clavicula, 5 tibia, 5 ankle, 6 foot, 1 spine, and 1 pelvis. In the intervention group, there were 51 fractures (19.1 events/1000 person-years), and in the control group 97 (17.1 events/1000 person-years), leading to a rate ratio of 1.11 (0.78–1.57), with no gender difference (Table 1, Fig 1). In 79 cases (53%), the fractures were the result of a slight trauma, in 51 cases (34%), a moderate trauma; and in 2 cases (1%), a high-energy trauma. In 16 cases (11%), there was no information about trauma mechanism. There were no differences in the trauma energy that caused the fracture between the intervention and the control group in either boys or girls (all P > .3, respectively; data not shown). In addition, we found no cases of stress fractures. In the measured children, the only difference in anthropometrics, bone parameters, and lifestyle was a higher duration of physical activity in the intervention groups (Tables 2 and 3). All children were at Tanner stage 1 at baseline, whereas at follow-up, more boys in the control group had higher Tanner stages (Table 2). The accelerometer data showed that girls and boys in the intervention group had more intense activities than children in the control group (Table 2).

Two years of intervention was associated with a higher percentage of intense activities (≥6 MET) in the intervention group than in the control group (Table 3). Boys in the intervention group showed a higher mean activity and a higher percentage of intense activities (≥6 MET) than those in the control group (Table 3).

TABLE 1 Fracture Epidemiology in Children in the Exercise Intervention Group and the Control Group

<table>
<thead>
<tr>
<th>Participants, n</th>
<th>Fractures, n</th>
<th>Person-Years</th>
<th>Fractures/1000 Person-Years, Mean (95% CI)</th>
<th>Rate Ratio, Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All individuals</td>
<td>808</td>
<td>51</td>
<td>2675</td>
<td>19.1 (14.2–25.1)</td>
</tr>
<tr>
<td>Intervention</td>
<td>51</td>
<td>1587</td>
<td>5661</td>
<td>17.1 (13.9–20.9)</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>362</td>
<td>97</td>
<td>1198</td>
<td>17.1 (10.5–28.4)</td>
</tr>
<tr>
<td>Control group</td>
<td>780</td>
<td></td>
<td>2788</td>
<td>15.8 (11.5–21.2)</td>
</tr>
<tr>
<td>Boys</td>
<td>446</td>
<td>53</td>
<td>1506</td>
<td>20.6 (14.0–29.2)</td>
</tr>
<tr>
<td>Control group</td>
<td>807</td>
<td></td>
<td>2872</td>
<td>18.5 (13.8–24.1)</td>
</tr>
</tbody>
</table>

Data presented as numbers, years, and means with 95% CI.
LS and 4.1% higher in FN bone mineral content (both $P < .01$), 8.7% higher in the trochanter and in bone width, 1.7% higher in the FN width, and 0.7% higher in the third lumbar vertebra width (all $P < .05$) than in the control group (Table 3). The mean annual gain in BMC in the boys in the intervention group was 3.3% higher in the LS and the mean gain in FN width was 0.6% higher (both $P < .05$) than in the control group (Table 3).

When the children were divided into tertiles of physical activity according to the questionnaires, there was a dose-response effect between duration of physical activity and annual gain in BMC and bone width. In girls, there was a gradually higher gain in FN BMC, trochanter BMC, and FN width (all $P < .05$) with each tertile of higher duration of physical activity, and the same pattern was found in boys, reaching significance in the LS BMC ($P < .05$) and in FN width ($P < .05$; Fig 2).

**DISCUSSION**

This study should not be misinterpreted as another study confirming that osteogenic training in motivated children improves bone mass.$^{2-6}$ The study instead adds knowledge when reporting that a moderately intense, general exercise intervention program in the peripubertal to pubertal years could improve bone mass and size on a population level, without increasing the fracture risk previously suggested to occur with high levels of physical activity in adults and children.$^{18,20,24,25}$ The reported dose-response effects strengthen a causal relationship between duration of exercise and gain in bone mass and size, visualized through the tertile comparison (Fig 2). The current study is also the longest reported intervention study, supporting the beneficial exercise-induced effects with shorter intervention.$^{2-10}$ The finding that beneficial effects remain with long intervention into the pubertal growth spurt increases the probability that the intervention will improve peak bone mass.$^{26}$

It is also interesting that not only bone mass but also bone size increased because bone structure contributes to bone resistance to fracture, independently of bone mass.$^{27-29}$ This is of clinical significance, because women with spine fractures have smaller lumbar vertebrae but normal FN size, whereas women with hip fractures have normal vertebral body size but smaller FN size than nonfractured controls.$^{28}$ Furthermore, our findings are supported by several previous reports that use the unilateral loading model in racquet players, a model of loading that is not affected by genetic, nutritional, or endocrine factors because both arms pertain to the same person but only the dominant arm is loaded during the exercise sessions, a model that convincingly shows increased BMC and bone size in the dominant and the mechanically loaded arm.$^{15,30-32}$

An unexpected finding in our study was the greater annual gain in fat mass in the intervention group compared with the controls (Table 3). This is contradictory to several previously published pediatric exercise reports,$^{2,5,33}$ but there are also previous studies that have reported similar findings to those in the current study.$^{7,9,34,35}$ The reason for the higher gain in fat in the intervention group is unclear but could possibly be due to increased appetite and food intake accompanying the increased training. Although we did not assess dietary habits, previous studies have speculated that the increased gain in fat is most likely the result of other influences besides physical activity because there has been no dose-response association between level of physical activity and gain in fat mass.$^{34}$ The finding may also be the result of chance. The gender differences in the exercise response could be due to boys in...
general being more physically active than girls outside school, and as a consequence, the extra physical education in school contributed less to the total physical activity in boys than in girls. Another possible explanation for the gender differences is that the girls were more advanced in pubertal maturation than the boys because it is generally believed that the late pre- and early peripubertal period is the one during which skeletal response to exercise is the most beneficial.15,30–32,36

Some previous studies have suggested that low-impact endurance sports such as bicycling and swimming in adults have a negative effect on BMC and a decrease in bone strength especially when these types of exercises are practiced at high volume.37–39 However, the level of exercise in the intervention group was of a moderate intensity so that all students could participate, and there was a variety of activities so that the pupils were exposed to both high- and low-impact exercise and both intensive and endurance activities. There is also an ongoing discussion about which regions should be included in pediatric exercise studies. The International Society for Clinical Densitometry position statement is that spine and total body less head are the most accurate and reproducible skeletal sites for DXA measurements in children.40 Total body BMC in our study showed a higher annual increase in girls in the intervention than in the control group but not in boys. There could, however, be a problem if only total body is used as the end-point variable because total body includes both mechanically unloaded and loaded skeletal sites. Therefore, we also included specific measurements of weight-loaded regions such as the hip and LS, the 2 most frequently used methods in clinical practice.

Finally, there are reports inferring that vigorous physical activity increases fracture risk in both children and adults caused by more exposure to trauma.18,20,24

### TABLE 2 Lifestyle Factors at Baseline and Follow-up and Accelerometer Data Collected After 2 Years in the Subsample of Children Who Were Selected For Measurements

<table>
<thead>
<tr>
<th>Lifestyle factors at baseline</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluding dairy products</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Drinking coffee</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tried to lose wt</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Current disease</td>
<td>3 (8%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Ongoing medication</td>
<td>5 (10%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Earlier medication</td>
<td>4 (8%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Fractures</td>
<td>6 (13%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Tanner stage 1/2/3/4/5</td>
<td>48/0/0/0/0</td>
<td>48/0/0/0/0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organized physical activity (h/wk)</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>School curriculum</td>
<td>3.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Outside the school</td>
<td>0.6 (0.6)</td>
<td>1.1 (1.5)</td>
</tr>
<tr>
<td>Total physical activity</td>
<td>3.9 (0.6)</td>
<td>2.1 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accelerometer data at 2-y follow-up</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>Recording time per day (h/d)</td>
<td>11.7 (1.4)</td>
<td>11.9 (1.3)</td>
</tr>
<tr>
<td>Mean activity (cpm)</td>
<td>649 (188)</td>
<td>597 (115)</td>
</tr>
<tr>
<td>&gt;3 METS (min/d)</td>
<td>195 (46)</td>
<td>187 (58)</td>
</tr>
<tr>
<td>&gt;6 METS (min/d)</td>
<td>34 (21)</td>
<td>35 (12)</td>
</tr>
<tr>
<td>&gt;6000 mean cpm (min/d)</td>
<td>12.2 (7.3)</td>
<td>10.4 (6.2)</td>
</tr>
<tr>
<td>&gt;10 000 mean cpm (min/d)</td>
<td>2.4 (2.5)</td>
<td>1.0 (1.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lifestyle factors at 4-y follow-up</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tanner stage 1/2/3/4/5</td>
<td>4/20/14/10/0</td>
<td>1/18/21/6/1</td>
</tr>
<tr>
<td>Menarche</td>
<td>8 (17%)</td>
<td>7 (15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organized physical activity at 4-y follow-up (h/wk)</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>School curriculum</td>
<td>3.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Outside the school</td>
<td>2.6 (2.6)</td>
<td>2.6 (2.9)</td>
</tr>
<tr>
<td>Total physical activity</td>
<td>5.9 (2.6)</td>
<td>4.1 (2.9)</td>
</tr>
</tbody>
</table>

The baseline measurements were performed just before the intervention was initiated and then annually for 4 years. Questionnaire-evaluated duration of organized physical activity was estimated as hours per week. Accelerometer-measured level of physical activity is presented as minutes per day >3 or >6 metabolic equivalents (METS) or >6000 or >10 000 cpm. Data are presented as number of children with proportion (%) or as mean (SD). * significant P.

<ref>LOFGREN et al</ref>
Before exercise intervention programs can be recommended, it must therefore be shown that the intervention does not result in more fractures. This study refutes this hypothesis, at least with the power to conclude that there was no fracture reduction of ≥22% or an increase of more than 57%. However, the contradictory hypothesis supported by others, that higher BMC in physically active children would result in fewer fractures, was also refuted. The third possibility is that the exercise would lead to more traumas but the higher BMC protects against fracture, leading to no different fracture incidence in the intervention and the control groups. The findings of no increased fracture rate is important because most epidemiologic reports infer that 25% to 50% of all children will sustain a fracture during growth. Weaknesses include the power problem, so that despite including 2395
children and a 4-year follow-up period, we could not capture small group differences in fracture incidence and the data only let us state that there was at least no fracture reduction of >22% and no fracture increase of >57% in the intervention group. An individual randomization would also have been preferable but impossible to conduct because of resistance from parents, pupils, and teachers. Furthermore, the participation rate in the control schools regarding children invited for measurements was lower than in the intervention school. This may have increased the risk of self-selection bias at baseline. However, this risk must be regarded as minor because no differences between groups were seen at baseline in anthropometrics, bone parameters, ethnicity, registered lifestyle factors, or participation in organized sport activities. Also, as previously reported, no differences were seen in height, weight, or BMI between participants and nonparticipants in the invited cohort, according to an examination of data from the first health examination in school. Also, it would have been preferable to have the bone structure estimated by 3-dimensional techniques such as computed tomography and not a 2-dimensional method such as DXA and HSA. Regarding the fracture data, it would have been advantageous if the fracture incidents could have been divided into fractures occurring during physical education classes in school and fractures occurring during other activities. However, from the referrals and the reports, we could in most cases only find out the type of trauma but not whether the accident had happened during school classes or spare time.

CONCLUSIONS
The study shows that a general, moderately intense school-based exercise intervention program for 4 years in children who were prepubertal at study start improves bone mass and bone size without increasing the fracture
risk. Daily moderate physical activity ought to be initiated in prepubertal children and then continue into puberty as a strategy for population-based improvement of bone resistance to fracture.

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REFERENCES


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